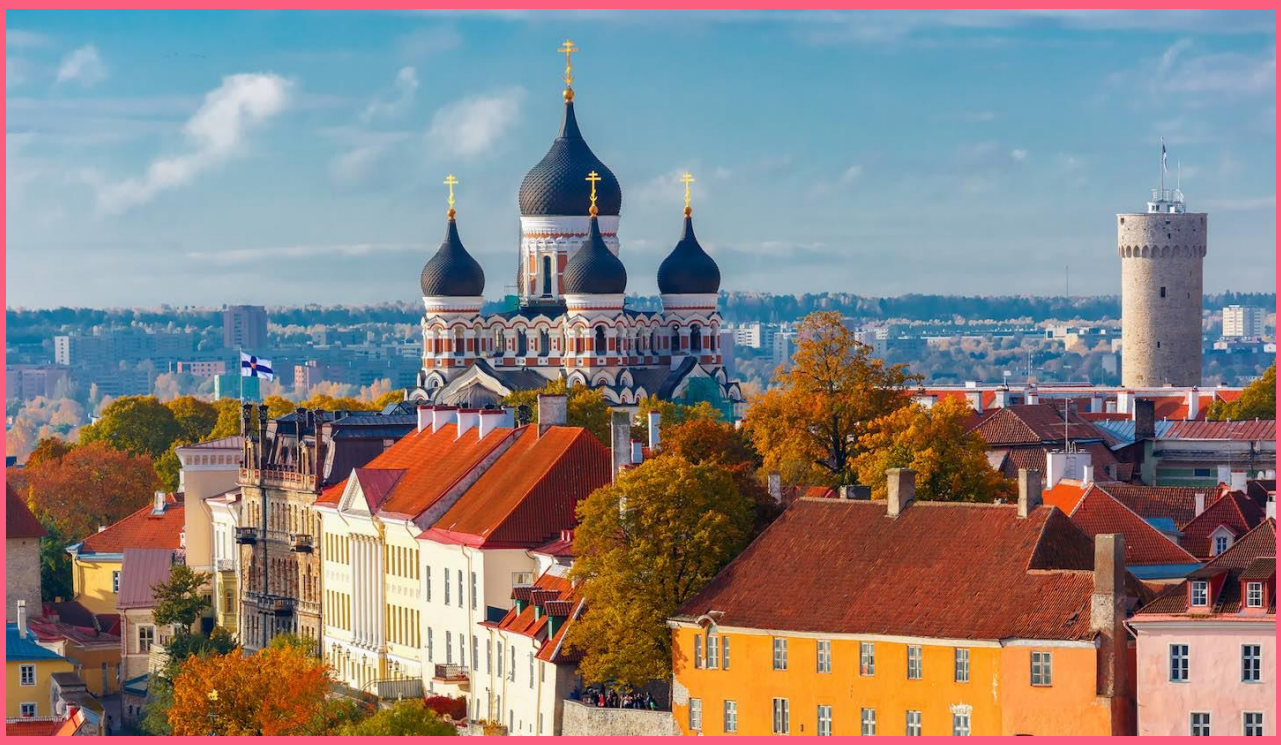


THE EIGHTH INTERNATIONAL SCIENTIFIC – PRACTICAL VIRTUAL CONFERENCE IN MODERN MEDICINE AND HEALTH: PROGNOSIS, ACHIEVEMENT AND CHALLENGES

CONFERENCE PROCEEDINGS

AZERBAİJAN-ESTONIA-KAZAKHSTAN-TURKEY

ESTONIA, TALLINN OCTOBER 21-22, 2022

THE EIGHTH INTERNATIONAL SCIENTIFIC – PRACTICAL VIRTUAL CONFERENCE IN MODERN MEDICINE AND HEALTH: PROGNOSIS, ACHIEVEMENT AND CHALLENGES

CONFERENCE PROCEEDINGS

AZERBAİJAN-ESTONIA-KAZAKHSTAN-TURKEY

ESTONIA TALLINN OCTOBER 21-22, 2022

TALLINN 2022

Organizer of the conference:

MTÜ. The International Research Education & Training Center. (Estonia, Tallinn).

LTD The Southern Caucasus International Academy of Modern Sciences. (UK, London).

LTD. Aspendos-Academy. International Academy of Medical and Social Sciences. (UK, London).

Tugay Pharmacy Company (Azerbaijan, Baku)

Invited organizations:

Azerbaijan Medical University (Azerbaijan)

Tbilisi State Medical University (Georgia).

NGO Education Support & Investment Fund (Georgia, Tbilisi)

WKMU Marat Ospanov (Kazakhstan, Aktobe)

Astana Medical University (Kazakhstan, Astana)

Alte University (Georgia, Tbilisi)

David Aghmashenebeli University (Georgia, Tbilisi)

TABLE OF CONTENTS

ORGANIZING COMMITTEE

Aytekin Hasanova
Azerbaijan Medical University. I Preventive Medicine Faculty. Deputy of Dean. PhD in Medical Biology.
Aytan Huseynova
Director. Aspendos International Academy of Medical and Social Sciences. LTD. (UK London).
Davit Tophuria
Tbilisi State Medical University. Head of International Students Academic Department, Associate Professor. PhD in HNA.
Maia Matoshvili
Tbilisi State Medical University. The First University Clinic. Dermato-Venereologist. Assistant Professor. PhD in DAPS.
Marat Sarkulov
Candidate of Medical Sciences, the chairman of Urology Department, West Kazakhstan Marat Ospanov Medical
Namig Isazade
International Research, Education & Training Center. MTÜ. PhD in Business Administration.
Nana Jikia
Rector of the Academy. Full professor. Full member and academician of Phasis Academy. Member of the Scientific Council of the Tao-Klarjeti Academy.
Nino Didbaridze
Tbilisi State Medical University. Microbiology and Immunology Department. Immunology Direction. PhD MD.
Nino Pirtskhelani
Tbilisi State Medical University. Associated Professor. Department of Molecular and Medical Genetics.
Nodar Sulashvili
Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Professor of Millennium University, Head of The International English Pharmacy Program, Head of The Division of Pharmacology.
Zhanslu Sarkulova Zhanslu Nukinovna - Doctor of Medical Sciences, Professor, Department of Anesthesiology and Reanimatology t, West Kazakhstan Marat Ospanov Medical University.
Tamar Tuphinashvili
Head of Quality Assurance Department, Professor. David Aghmashenebeli University of Georgia.
Tinatin Doliashvili
Doctor in Economics, Professor, David Aghmashenebeli University of Georgia.
Vakhtang Antia
Dean of the School of Business and Social Sciences, Professor, David Aghmashenebeli University of Georgia.
Vakhtan Nadiradze
Doctor in Economics, Assistant at David Aghmashenebeli University of Georgia.
Zhanslu Sarkulova
Doctor of Medical Sciences, Professor, Department of Anesthesiology and Reanimatology, West Kazakhstan Marat Ospanov Medical University

SCIENTIFIC COMMITTEE

Aytekin Hasanova
Azerbaijan Medical University. I Preventive Medicine Faculty. Deputy of Dean. PhD in Medical Biology.
Davit Tophuria
Tbilisi State Medical University. Head of International Students Academic Department, Associate Professor. PhD in HNA.
Elmira Aliyeva
AMU. Head of the Department of Obstetrics and Gynecology I. Doctor of Medical Sciences. Professor.
Maia Matoshvili
Tbilisi State Medical University. The First University Clinic. Dermato-Venereologist. Assistant Professor. PhD in DAPS.
Marat Sarkulov
Candidate of Medical Sciences, the chairman of Urology Department, West Kazakhstan Marat Ospanov Medical University.
Namig Isazade
International Research, Education & Training Center. MTÜ. PhD in Business Administration.
Nana Jikia
Rector of the Academy. Full professor. Full member and academician of Phasis Academy. Member of the Scientific Council of the Tao-Klarjeti Academy.
Nino Didbaridze
Tbilisi State Medical University. Microbiology and Immunology Department. Immunology Direction. PhD MD.
Nino Pirtskhelani
Tbilisi State Medical University. Associated Professor. Department of Molecular and Medical Genetics.
Nodar Sulashvili
Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Professor of Millennium University, Head of The International English Pharmacy Program, Head of The Division of Pharmacology.
Saadat Safarova
AMU. Department of Obstetrics and Gynecology I. PhD in Medicine. Associate Professor.
Saadat Sultanova
AMU. Department of Obstetrics and Gynecology I. Doctor of Medical Sciences. Professor.
Sain Safarova
AMU. Department of Internal Medicine II. PhD in Medicine. Associate Professor.
Tamar Didbaridze
Tbilisi State Medical University, First University Clinic. PhD in MD, Tbilisi, Georgia.
Tamar Tuphinashvili
Head of Quality Assurance Department, Professor. David Aghmashenebeli University of Georgia.
Tinatin Doliashvili
Doctor in Economics, Professor, David Aghmashenebeli University of Georgia.
Vakhtang Antia
Dean of the School of Business and Social Sciences, Professor, David Aghmashenebeli University of Georgia.
Vakhtan Nadiradze
Doctor in Economics, Assistant at David Aghmashenebeli University of Georgia.
Zhanslu Sarkulova
Doctor of Medical Sciences, Professor, Department of Anesthesiology and Reanimatology, West Kazakhstan Marat Ospanov Medical University

PUBLISHING COMMITTEE

EDITORIAL BOARD

PROGRAM AT A GLANCE

First day	21 October 2022
Moderators	Namig Isazade, Aytan Huseynova
Opening ceremony	Namig Isazade
19.00-19.20	**Vakhtang Antia** David Aghmashenebeli University, Georgia.
	Tamar Tuphinashvili David Aghmashenebeli University, Georgia.
	Aytakin Hasanova AMU
19.20-19.40	**Tinatin Doliashvili, Vakhtan Nadiradze** ANALYSIS OF THE CHARACTERISTICS OF THE FINANCIAL STABILITY OF THE "UNITED AIRPORTS OF GEORGIA" IN 2017-2021.
19.40-20.00	**T.A. Adaibaev, M.K. Zhanaliyeva, A.Y. Almabaeva, R. N. Zharilkassimov, O.D. Orunbek** STRUCTURAL CHANGES IN THE SPLEEN OF FETUSES AND NEWBORNS IN COMPLICATED PREGNANCY WITH GESTOSIS AGAINST THE BACKGROUND OF ANEMIA IN PREGNANT WOMEN.
20.00-20.20	**Aytakin Hasanova** FRACTIONAL RADIOFREQUENCY IN THE TREATMENT OF GENETIC SKIN AGING
20.20-20.40	**M. Matoshvili, D. Tophuria, N. Kvizhinadze, Maia Tsimakuridze, M. Kharabazde** APPLICATION OF THE MESENCHYMAL STEM CELL SECRETOME IN DERMATOLOGY: A REVIEW.
20.40-21.00	**Батыров Т.У, Пайзиева З.А.,Жаканов Т.В.,Жарилкасимов Р.Н.** ОКАЗАНИЕ ДОВРАЧЕБНОЙ МЕДИЦИНСКОЙ ПОМОЩИ ПРИ ТРАВМАХ ПОЛОСТИ РТА В УСЛОВИЯХ ЧРЕЗВЫЧАЙНЫХ СИТУАЦИИИ (ЧС).
21.00-21.20	**N. Pruidze, R. Khetsuriani, M. Arabuli, M. Matoshvili, D. Tophuria** EFFECT OF AGE-RELATED CHANGES IN MEMBRANE PROTEINS ON THE STABILITY OF HUMAN RED BLOOD CELLS.
21.20-21.40	**Rübabə Mərdanova** CİBS təlim mərkəzinin təlimçisi, beynəlxalq dərəcəli mütəxəssis. UĞURUN AÇARI - NLP. NEYRO LINQVISTIK PROQRAMLAŞDIRMA.
21.40-22.00	**Albina Kajaia, Luiza Gabunia, Nataliia Filipets, Ketevan Ghambashidze, Levan Ratiani, Manana Gongadze, Nodar Sulashvili** THE SCIENTIFIC STUDY OF THE PECULIARITIES OF UROTENSIN-2 RECEPTOR ANTAGONIST: PHARMACOLOGICAL EFFECTS OF PALOSURAN ON PLASMA RENIN CONCENTRATION AND BLOOD PRESSURE IN LABORATORY RATS WITH RENO-VASCULAR HYPERTENSION.
22.00-22.20	**Nodar Sulashvili, Nana Gorgaslidze, Luiza Gabunia, Marina Giorgobiani, Irine Zarnadze, Shalva (Davit) Zarnadze** THE SCIENTIFIC TALKS OF INVOCATIONS OF SPECIFICITIES OF PHARMACIST PROFESSIONAL AND HIGHER MEDICAL-PHARMACEUTICAL EDUCATIONAL CHALLENGES OUTLOOKS AND ACHIEVEMENTS IN GEORGIA**.**
22.20-22.40	**Ulviyya Samadli, Shafaq Asadova, Sharifa Vahabova, Rena Gurbanova, Feride Abbasova** MODERN APPROACH TO THE CLINICAL VIEW, PATHOGENESIS, AND TREATMENT METHODS OF ENDOMETRIOSIS.
22.40-23.00	**Nodar Sulashvili, Kakhaber Robakidze, Irma Buchukuri, Lela Grigolia Veriko Khundzakishvili** FEATURES OF THE MANIFESTATION OF THE INFLUENCE OF DIABETES MELLITUS ON THE MUCOUS MEMBRANES AND SKIN OF THE MOUTH.

Second day	22 October 2022
Moderators	Namig Isazade, Zamina Akhundova
19.00-19.20	**Билал, Асадов, Насими Вагабов, Гюльшан Джабраильзаде** К ПРОБЛЕМЕ ОГРАНИЧЕННОЙ ВМЕНЯЕМОСТИ В УГОЛОВНОМ ЗАКОНОДАТЕЛЬСТВЕ АЗЕРБАЙДЖАНСКОЙ РЕСПУБЛИКИ.
19.20-19.40	**M. Matoshvili, D. Tophuria, M. Tsimakuridze, N. Durglishvili** CELL THERAPY FOR CUTANEOUS DISEASES.
19.40-20.00	**M. Matoshvili, D. Tophuria, N. Adamia, M. Tsimakuridze** HEMATOPOIETIC STEM CELLS
20.00-20.20	**M. Matoshvili, D. Tophuria, M. Arabuli, N. Kvizhinadze** REVIEW OF DRUGS ISSUES OF CELL PRODUCTS DURING SKIN REPAIR.
20.20-20.40	**M. Matoshvili, D. Tophuria, Maia Tsimakuridze, N. Adamia, I Amiranashvili** THE ROLE OF MESENCHYMAL SECRETOME ON THE SKIN DURING WOUND HEALING.
20.40-21.00	**M. Matoshvili, D. Tophuria, M. Tsimakuridze, M. Kharabadze, S. Kandelaki, I. Amiranashvili** THE ROLE OF MESENCHYMAL SECRETOME ON THE SKIN DURING PHOTOPROTECTION, HAIR GROWTH, AND PSORIASIS.
21.00-21.20	**Nodar Sulashvili, Nana Gorgaslidze, Luiza Gabunia, Marina Giorgobiani, Irine Zarnadze, Shalva (Davit) Zarnadze** THE SCIENTIFIC BULLETIN OF SPECIFICITIES OF TRENDS, DIVERSITY, INCLUSION AND DISTINCTIVE OF THE CLINICAL PHARMACISTS IN MONDIAL.
21.20-21.40	**Nana Gorgaslidze, Nodar Sulashvili, Marina Giorgobiani** THE MANIFESTATION OF FEATURES ON VERIFICATION FOR THE OUTLOOK OCCUPATIONAL HEALTH AND HEALTHY SAFETY SYSTEMS, DESTITUTION DEFIANCES CONSEQUENTLY TO THE COVID-19 PANDEMIC IN GEORGIAN PHARMACEUTICAL ESTABLISHMENT FRAMEWORK.
21.40-21.50	Closing ceremony

ARTICLES AND PAPERS

FEATURES OF THE MANIFESTATION OF THE INFLUENCE OF DIABETES MELLITUS ON THE MUCOUS MEMBRANES AND SKIN OF THE MOUTH

Nodar Sulashvili[1], Kakhaber Robakidze[2], Irma Buchukuri[3], Lela Grigolia[4]
Veriko Khundzakishvili[5]
[1]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Associate Professor of Pharmacology and Pharmacotherapy at Alte University; Associate Professor of Pharmacology and Basics of Medicine Direction at Sulkhan-Saba Orbeliani University, Invited Professor/Lecturer, Tbilisi State Medical University, Tbilisi-Georgia.
[2]MD, PhD, Doctor of Medical Sciences, Professor, Caucasus International University, Invited Professor of Millennium University, Tbilisi, Georgia.
[3]MD, PhD, Doctor of Medicine, Professor, Petre Shotadze Medical Academy, Tbilisi, Georgia.
[4]MD, PhD, Doctor of Medical Sciences, Professor, Caucasus International University, Tbilisi, Georgia.
[5]MD, PhD, Doctor of Medical Sciences, Professor, Caucasus International University, Tbilisi, Georgia.
Email: n.sulashvili@ug.edu.ge

ABSTRACT

Aim of the research was to study and analyzed the effects of diabetes on the skin and mucous membranes of the mouth. Skin pathology is registered in vast majority of patients with diabetes mellitus (DM). Despite the abundance of publications on dermatological problems in DM, there is still a number of gaps to be discussed in terms of pathophysiological mechanisms. The goal of this review was to assess the mechanisms of development of different skin pathologies under DM. One of the key pathogenic mechanisms of skin lesions in diabetes is hyperglycemia and the effects of the advanced glycation end products, inducing oxidative stress, endothelial dysfunction and inflammation; that in its turn can accelerate the mechanisms of skin aging, the development of diabetic dermopathy and scleroderma diabeticorum. Imbalance of growth factors, cytokines and hormones under insulin resistance, is associated with increased proliferation of keratinocytes, fibroblasts and sebocytes, mast cell dysfunction and melanogenesis disorders in acanthosis nigricans, acrochordons, acne and inflammatory dermatitis in diabetic patients. In addition, authors discuss the role of dendritic cells and macro- phages dysfunction in impairment of peripheral tolerance and diabetic wounds pathogenesis in patients with DM.
Keywords: diabetes mellitus, hyperglycemia, advanced glycation end products, insulin resistance, skin.

Introduction

The effect of diabetes mellitus on the dynamics of the intensity of apoptosis of neurocytes and gliacytes in the cortex of the frontal, parietal and temporal lobes of the cerebral hemispheres under conditions of ischemia injury -reperfusion has been studied. It has been established that the level of apoptotic processes in the neuro- and gliacytes of the frontal cortex does not change after a 20-minute carotid ischemia followed by a 1-hour reperfusion according to the parameters studied in animals without diabetes mellitus. Neurocyte apoptosis is activated in the parietal lobe cortex, while

neuro- and gliacyte apoptosis is activated in the temporal lobe cortex. Three-month diabetes mellitus enhances apoptosis of neurons and glial cells in the cortex of the frontal and temporal lobes, neurons in the cortex of the parietal lobe, and reduces the apoptosis of gliacytes. At the beginning of the ischemia-reperfusion period, the activity of apoptotic processes in the cortex of the frontal and temporal lobes does not change in animals with diabetes mellitus, but decreases in the cortex of the parietal lobe due to glial cells. On the 12th day of observation, the activity of apoptotic processes in the neurocytes of the cortex of the temporal lobe in rats without diabetes mellitus increases, while it decreases in glial cells. Reduced p53 protein content in neurons and increased density of p53+ cells were revealed. During this period of observation, in rats with diabetes mellitus, the activity of apoptotic processes in neurons and glial cells of all lobes generally decreases. The results obtained indicate the presence of regional differences in the dynamics of the reaction of the lobes of the cerebral hemispheres in response to an ischemia-reperfusion injury, characterized by the intensity of apoptosis of neurons and glial cells.

According to the data of the World Health Organization (WHO) for 2014, the number of patients with diabetes mellitus (DM) among the adult population of the planet was about 422 million [5]. Among the complications of DM, diabetic angiopathy, polyneuropathy, retinopathy, nephropathy, and diabetic foot syndrome have clinical and social significance. [5,16]. Diabetic dermopathy also plays an important role, which clinicians should pay attention to. According to different authors, dermatological problems are observed in 40-70% of patients with DM [8,14]. Moreover, the risk of developing skin pathology in DM inversely correlates with the efficiency of correction of metabolic disorders, varying within 30-60% with adequate glycemic control, up to 94% with its inefficiency [9].

When discussing the clinical aspects of skin pathology in DM, it is worth noting some dualism: on the one hand, dermatological changes can be the first clinical manifestation of DM [14], on the other hand, the skin, as the largest organ, is the springboard for the implementation of key pathogenetic mechanisms for the development of diabetes [15].

As is known, DM can lead to the development of diabetes-specific skin lesions (diabetic dermopathy, diabetic scleroderma, diabetic bullae, diabetic wounds) [8]. On the other hand, the presence of DM predetermines a higher incidence of other dermatological lesions (infections of the skin and appendages, inflammatory dermatoses, benign and malignant neoplasms, etc.) [12,14]. Dermatological problems in DM are based on key systemic disorders, including microangiopathy, polyneuropathy, metabolic disorders (hyperglycemia, glycosylation end products, dyslipidemia), impaired immunological reactivity [3,9,15]. One of the earliest and most frequent nonspecific manifestations of skin involvement in the pathological process in DM is the development of xerosis and pruritus, the appearance of which is considered to be a consequence of microangiopathy, leading to impaired trophism and hydration of the skin, dysfunction of mast cells, and also linear pathology [1,8,12,24]. The latter is associated not only with impaired sensory function of the skin and regulation of vascular tone, but also with changes in the balance of neurotransmitters and neurotrophic factors that modulate microcirculation, proliferation, and differentiation of epidermal and dermal cells [14,15,18]. No less typical variant of skin lesions in DM are skin infections (bacterial or fungal), which are detected, according to different authors, in 30-42% of patients, and are a reflection of a violation of the barrier properties of the skin and immunological reactivity in DM [8 ,21]. Although the modern literature presents a sufficient number of works devoted to the study of dermatological problems in DM, it should be noted that they are more focused on describing the epidemiology and clinical picture of skin lesions in DM [9,14,19]. But at the same

time, there are a number of gaps in the interpretation of the pathogenetic mechanisms that determine the development of skin pathology in DM.

Aim of the research

The purpose of this review is to analyze the mechanisms of development of various types of skin pathology in diabetes mellitus.

Results and Discussion

Prevention of the development of these changes- the effects of diabetes on the skin and mucous membranes of the mouth, is based on the knowledge of the key pathophysiological mechanisms, which are given below.

Hyperglycemia and the effects of glycosylation end products (AGEs) underlie the development of most variants of skin lesions in DM. Hyperglycemia inhibits the proliferation and migration of keratinocytes, protein synthesis, causes apoptosis of endothelial cells, stimulates the synthesis of nitric oxide in phagocytes, leads to impaired chemotaxis and phagocytic activity of neutrophils [4,21]. The result of these changes is a decrease in the number of cells in the basal layer, smoothing of the epidermal-dermal border, restriction of the expression of the corresponding keratins, and a decrease in the total concentration of DNA in the epidermis [21,27]. However, at the same time, opposite changes can be observed in the skin of patients with DM - increased proliferation of keratocytes and the development of acanthosis, which is associated with the effects of hyperinsulinemia and insulin resistance (IR) [11,16]. In addition, in the epidermis of the skin of patients with DM, a violation of the keratinization process is determined, accompanied by an increase in the number and area of corneocytes - terminally differentiated keratinocytes [12]. The consequence of this is the development of hyperkeratosis, which is recorded in the early stages of diabetic dermopathy, with acanthosis nigricans, etc. [14,19]. In the stratum corneum of the epidermis of diabetic skin, a change in the lipid composition was also noted: a decrease in the level of triglycerides and an increase in the level of ceramides, cholesterol, and fatty acids, compared with the control [21].

Hyperglycemia also leads to the development of significant morphological and biochemical changes in the dermis, which are largely associated with an imbalance in the processes of synthesis and degradation of the extracellular matrix, followed by a violation of histoarchitectonics [27]. As recently as 40 years ago, Moczar et al. [18] demonstrated a violation of the ultrastructure of fibroblasts isolated from diabetic skin biopsies. AGEs directly change the properties of collagen, reducing its solubility and elasticity, increasing rigidity and resistance to enzymatic degradation during remodeling [28]. The latter may explain the role of AGEs in the development of fibrosis in diabetic dermopathy and scleroderma. An equally important mechanism of sclerotic changes in diabetic skin is a change in the differentiation of subcutaneous fat adipocytes into myofibroblasts, followed by the production and accumulation of collagen in the deep layers of the skin, which leads to an increase in its thickness and rigidity, for example, in diabetic scleroderma. [17]. In a number of patients with DM, these changes lead to impaired mobility of the joints of the hands and feet. On the other hand, diabetes is accompanied by fragmentation and disappearance of elastic fibers in the subepithelial zone of the dermis, a change in the thickness, quantity, and architectonics of collagen fibers, which is caused by an increase in the amount of matrix metalloproteinases (MMPs), which ensure the degradation of the components of the intercellular substance of the dermis [10.28]. The latter fact (in particular, an increase in the levels of MMP2 and MMP9 in the skin with DM) plays a

critical role in reducing the volume of hyaluronic acid and remodeling the microvasculature, especially in the thin skin of the face, scalp and forearms [17,27]. These changes are largely similar to those during aging, and therefore DM is considered one of the key promoters of skin aging [10].
Another mechanism for promoting skin aging in DM2 is the development of pro-inflammatory events [3]. The end products of glycosylation formed as a result of glycation of proteins, lipids and nucleic acids [10] are powerful stimulators of the formation of active oxygen radicals (AOR), while they disrupt the functioning of antioxidant systems, inhibiting the elimination of ARC [10,21]. This ultimately leads to disruption of the functioning of intracellular and extracellular proteins that induce the activation of inflammatory cytokines through the pathway triggered by nuclear factor κβ (NF-κβ) [21]. Receptors for AGEs (RAGEs) belong to the multiligand receptors of the immunoglobulin family encoded by a gene located on chromosome 6 near the genes of the major histocompatibility complex class I and II [6], i.e. pattern-recognition receptors that bind, in addition to AGEs, a number of other molecules, including S-100/calgrnulin, amphoterin (high motility group protein B1 – HMGP-B1), and β-amyloid peptides. In the skin, this type of receptor is expressed by various cells, including: keratinocytes, dendritic cells, endotheliocytes, fibroblasts, macrophages [2,6,14]. This determines the pro-inflammatory activation of both immune cells (macrophages, lymphocytes) and skin residents - keratinocytes and fibroblasts, in which the expression of pro-inflammatory factors and chemokines that stimulate the recruitment of leukocytes is enhanced [8,24]. The binding of RAGE to the ligand involves several signaling cascades, in particular, mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinases (ERKs) 1 and 2, phosphatidyl inositol 3 kinase, p21Ras, stress-activated kinase/c-Jun- N-terminal kinase and Janus-kinases involved in the regulation of cell growth and death [10]. In addition, stimulation of RAGE in cells leads to the activation of the transcription factor NF-κB, followed by transcription of a number of pro-inflammatory genes [10,28]. The consequence of this is an increase in the number of cells in the dermis that initiate inflammation - macrophages with a predominance of the M1 phenotype [3,29].
Despite the fact that hyperglycemia and AGE are a common pathogenetic mechanism of type 1 and 2 DM, a certain specificity of dermatological disorders in different types of DM has been identified. So, lipoid necrosis, vitiligo and diabetic bullae are considered specific for type 1 diabetes [18]. Although these variants of skin lesions are also described in type 2 diabetes [1,9]. For the latter, acrochordons (fibroepithelial polyps), black acanthosis (acanthosis nigricans), eruptive xanthomas, diabetic scleroderma, androgenetic alopecia, acne, psoriasis, etc. are more characteristic [12,16]. This association is due to the presence of systemic changes due to the metabolic syndrome (dyslipidemia, IR) in patients with DM2. The main part of patients with obesity and DM2 suffer from secondary IR, which is characterized by combined variants of changes in the functioning of insulin receptors and post-receptor signal transmission. It is believed that IR is the result of the accumulation and dysfunction of visceral adipose tissue [6]. Adipocyte hypertrophy is accompanied by a change in the spectrum of secreted adipokines, accumulation of M1 macrophages and lymphocytes [4]. The consequence of these disorders is a systemic increase in the levels of monocyte chemotaxis factor (MCP-1), tumor necrosis factor (TNF-α), interleukins (IL-6, IL-8 and IL-18), leptin, activator inhibitor plasminogen (PAI)-1 [16]. At the same time, skin cells are in conditions of a double imbalance: insulin deficiency and an excess of inflammatory cytokines [28]. Insulin plays an important role in maintaining homeostasis and skin function. Normally, insulin regulates the balance between the processes of proliferation and differentiation of keratinocytes [11]. Insulin receptors belong to the family of receptor tyrosine kinases. This family also includes receptors for numerous growth factors, including insulin-like growth factor (IGF), epidermal growth

factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and colony-stimulating factor receptors. and some cytokines [25]. It has been shown that hyperinsulinemia increases the production of IGF-1 and 2 in the liver, which leads to an increase in the systemic level of these growth factors [16]. In addition, the possibility of insulin cross-activation of IGF-1 receptors, which are expressed by keratinocytes and fibroblasts, has been proven, which leads to an increase in the proliferation of these cells [25]. IGF-1 activity is regulated by the level of IGF-binding proteins (IGFBPs), which increase the half-life of IGF-1 and regulate the pool of metabolically "free" IGF-1. In obese patients with hyperinsulinemia, the levels of IGFBP-1 and IGFBP-2 are reduced, which contributes to an increase in the plasma concentration of free IGF-1. An increase in bioactive IGF-1 stimulates cell growth and differentiation [14]. This explains hyperkeratosis, papillomatosis in acanthosis nigricans, as well as the formation of benign skin neoplasms - acrochordons [11]. Often, intensification of proliferative processes in the skin is accompanied by a violation of pigment metabolism, usually with hyperpigmentation [7,30]. This phenomenon is associated with the effect of activation of E3 receptors for prostaglandin E2 [30]. The production of the latter increases due to increased expression in keratinocytes and dermal cells of NF-kB and COX-2 (cyclooxygenase) [15]. Activation of the E3 receptors of melanocytes is associated with an increase in their proliferation, an increase in the local formation of MSH from the precursor, proopiomelanocortin, which ultimately leads to the accumulation of melanin [7,22,30].

An equally significant mechanism of association between IR and skin pathology in T2DM is the effects of insulin on the production of sex hormones. Insulin and IGF-1 have a powerful stimulating effect on the activity of 17-hydroxylase in the ovaries, which determines the excessive production of androgens, especially 17-hydroxyprogesterone [11]. In addition, an increase in insulin levels contributes to a decrease in the production of SHBG (sex hormone-binding globulin) in the liver, which determines more pronounced effects of free testosterone on target cells [25]. In the skin, the target of androgens is the pilosebaceous unit. An increase in the level and intensity of androgen signal transduction leads to an increase in the proliferation of sebo cytes, an increase in lipogenesis and their secretory activity, cell proliferation in the area of the funnel of the hair root, hyperplasia of the sebaceous glands, promoting the development of acne [11]. IGF-1 has a similar effect on the sebaceous glands [25]. IGF-1 is a potent growth promoter during puberty and plays a central role in the development of acne and the induction of hyperandrogenism [19] and, in fact, is a factor in signaling the relationship between insulin resistance and the development of acne vulgaris. In addition, in vitro studies have shown that insulin and IGF-1 can also stimulate the growth of hair follicles, which, in all likelihood, leads to the development of hirsutism [21,35]. However, an alternative effect of excessive insulin levels on hair growth is also possible. Thus, it has been shown that hyperinsulinemia leads to an increase in the activity of 5-alpha-reductase in the cells of the hair papilla, which leads to an increase in the conversion of testosterone to dihydrotestosterone, resulting in the development of androgenetic alopecia [8].

The spectrum of dermatological problems in patients with DM has a certain paradox - on the one hand, patients with DM are more susceptible to the development of an opportunistic infection, and on the other hand, they are more likely to develop hypersensitivity reactions, various types of inflammatory dermatosis and autoimmune pathology [11, 16]. This is associated with a dysfunction of one of the key moderators of maintaining the immunological homeostasis of the skin - dendritic cells (DC). Today, among the skin DCs, it is customary to distinguish between typical (stable) DCs that are normally present in the skin, and plasmacytoid DCs (pDCs), which appear in the skin only during inflammation [2]. According to localization, typical DCs are divided into epidermal

Langerhans cells and dermal DCs (dDCs). After receiving a signal about damage, DCs are activated, capture the antigen, and its process is accompanied by cell migration through the system of lymphatic vessels of the skin to regional lymph nodes [2]. At the same time, the activation of different DCs has different consequences. It is assumed that the main effect of activation of Langerhans cells is the development of tolerance to antigens through stimulation of Treg (T-suppressor cells) [20]. Whereas the maturation of dermal DCs can lead to the activation of various variants of the immune response through the activation of Th1, Th2, or Th17 [2,35]. It is assumed that different dDC subtypes are capable of activating different types of immune response. The most important factor in the activation and determination of the DC phenotype is the microenvironment in which these antigen-presenting cells are located [20]. The latter fact is of particular importance in the conditions of DM, which provides a combination of a complex of pathogenetic factors in the skin, including: hyperglycemia, endothelial dysfunction, oxidative stress, cytokine imbalance, mast cell dysfunction [10,24].

The study of the DC status in DM showed very conflicting data. On the one hand, it has been found that the number of both myeloid and plasmacytoid DCs decreases in the peripheral blood of patients with DM [23]. However, experimental studies revealed the parallelism of the processes of peripheral nerve degeneration and the development of polyneuropathy, the accumulation of mature DCs in the cornea of the eye [13]. Similar results were obtained by other authors who proved the association between diabetic neuropathy and DC dysfunction in peripheral tissues and organs in DM, reflecting the specifics of neuro-immune relationships in DM in different tissues. Similarly, in the skin of patients with diabetic foot syndrome, an increase in the number of DCs, primarily Langerhans cells, was revealed. At the same time, the authors showed a direct relationship between the number of Langerhans cells and the likelihood of developing diabetic wounds [25,33].

Factors stimulating DC activation, in addition to the classical stimulant, bacterial lipopolysaccharide, include reactive oxygen radicals, the formation of which, as already mentioned, is increased under conditions of hyperglycemia. It has been shown that ARCs stimulate myeloid DCs, stimulate their activation and maturation, which can contribute to the promotion of inflammatory events. In addition, insulin and IGF-1 are also stimulators of DC maturation, activating the expression of scavenger receptors (SR-A) in them and the uptake of oxidized low-density lipoproteins [20]. This determines the enhanced activation of dendritic cells, including those in the skin, under T2DM conditions. DC activation can stimulate the recruitment of monocytes and the accumulation of macrophages [2,26], which is associated with the development of diabetic complications. Previous studies have shown that a similar pattern is also characteristic of the skin - an increase in the number of macrophages is associated with the development of diabetic wounds and impaired healing [4,29]. This phenomenon is determined by a violation of metabolic processes in cells: dyslipidemia is associated with the accumulation of lipids in macrophages, which leads to special variants of inflammation, for example, in eruptive xanthoma and granuloma annulare, associated with accumulation of lipids in histiocytes, a delay in the mechanisms of resolution of inflammation and chronic inflammation [20,32]. In addition, there was a violation of the metabolism of L-arginine with enhanced activation of iNOS with the development of pro-inflammatory events, oxidative and nitroxyl stress, impaired mechanisms for resolving inflammation, progressive alteration and fibrosis [3,17,29]. An increase in the number and dysfunction of DCs and macrophages in diabetic skin may explain the higher likelihood of developing inflammatory dermatoses, such as psoriasis, although to this day the interpretation of the association between psoriasis and DM is based mainly on the role of IR. First, the skin manifestations of IR are in many respects similar to the disorders in the epidermis

observed in psoriasis (hyperproliferation with impaired differentiation of keratinocytes). Secondly, the revealed close association of the development of psoriasis and metabolic syndrome with IR can be explained by the already discussed factor of chronic inflammation that develops as a result of dysfunction of visceral adipose tissue [14]. Thus, in patients with psoriasis, a decrease in the level of anti-inflammatory adiponectin was shown with an increase in such pro-inflammatory agents as omentin, resistin, vasfatin, interleukin-6, and TNF-α [11]. The latter is considered one of the most significant cytokines involved in the development of psoriasis [15]. On the other hand, the role of TNF-α in impaired insulin sensitivity through inhibition of the tyrosine kinase activity of insulin receptors is no less known [11,25].

Conclusion

Thus, DM2 is characterized by a high frequency and variability of skin lesions. The key mechanisms for the development of skin pathology in T2DM are hyperglycemia, microangiopathy, insulin resistance, changes in the balance of growth factors and sex hormones, as well as dysfunction of antigen-presenting cells and skin macrophages. The complex of these factors determines the violation of the barrier function of the skin, the imbalance of the processes of proliferation, differentiation and cell death, the change in the skin aging program, the violation of peripheral mechanisms of tolerance to antigens, which is accompanied by an increased risk of developing infections, inflammatory dermatosis and neoplasia.

REFERENCES

1. Kochet K.A. Clinical evaluation of the effectiveness of complex pathogenetic treatment of patients with lipoid necrobiosis. Dermatovenereology. Cosmetology. Sexopathology. 2017; 5(1-2): 19-22.
2. Aliyeva EG, Sulaieva ON. Role of dendritic cells in main- tenance of the skin structural homeostasis. Morphologia. 2016;10(3):14-8.
3. Barinov EF, Sulaieva OM, Barinova ME. Molecular mechanisms of the iNOS regulation disorders in monocytes of patients with diabetic foot syndrome. Klin khirurhiia. 2010;4:40-4.
4. Barinov EF, Sulaieva ON, Barinova ME. Blood monocytic L-arginine metabolic changes in diabetic foot syndrome. Klin- icheskaia laboratornaia diagnostika. 2010;5:16-9.
5. Centers for Disease Control and Prevention. National diabe- tes fact sheet, 2014. http://www.cdc.gov/diabetes/pubs/statsre- port14/national-diabetesreport-web.pdf.
6. Lan CE, Wu CS, Huang SM et al. High-Glucose Environment Enhanced Oxidative Stress and Increased Interleukin-8 Secre- tion From Keratinocytes: New Insights Into Impaired Diabetic Wound Healing. Diabetes. 2013; 62(7):2530-8.
7. Costin GE, Hearing VJ. Human skin pigmentation: mela- nocytes modulate skin color in response to stress. Faseb J. 2007;21(4):976-94.
8. De Macedo GM, Nunes S, Barreto T Skin disorders in diabetes mellitus: an epidemiology and physiopathology review. Diabe- tol Metab Syndr. 2016;8(1):63.
9. Duff M, Demidova O, Blackburn S. et al. Cutaneous mani- festations of diabetes mellitus. Clin Diabetes. 2015;33:40-48.
10. Gkogkolou P, Bahm M. Advanced glycation end prod- ucts: Key players in skin aging? Dermatoendocrinol. 2012;4(3):259-70.

11. Gonzalez-Saldivar G, Rodriguez-Gutiarrez R., Ocampo- Candiani J. Skin Manifestations of Insulin Resistance: From a Biochemical Stance to a Clinical Diagnosis and Management. Dermatol Ther (Heidelb). 2017;7(1):37-51.
12. Horton WB, Boler PL, Subauste AR. Diabetes Mellitus and the Skin: Recognition and Management of Cutaneous Manifestations. South Med J. 2016;109(10):636-646.
13. N. Sulashvili, M. Beglaryan, T. Tsintsadze, N. Mdinaradze, L. Grigolia, M. Sulashvili, T. Khmaladze; The study of novel trends of pharmaceutical actual vocational activities and pharmacists' professional work development issue aspects; УДК 615.1:339.188 ISSN 2415-8593 MATERIALS OF IX INTERNATIONAL SCIENTIFIC-PRACTICAL CONFERENCE- "MANAGEMENT AND MARKETING IN THE MODERN ECONOMY, SCIENCE, EDUCATION AND PRACTICE". MINISTRY OF HEALTH OF UKRAINE; MARCH 18, 2021, KHARKIV-2021. Pp 69-81.
14. Leppin K, Behrendt AK, Reichard M et al. Diabetes mellitus leads to accumulation of dendritic cells and nerve fiber damage of the sub basal nerve plexus in the cornea. Invest Ophthalmol Vis Sci. 2014;55(6):3603-15.
15. Levy L, Zeichner JA. Dermatologic manifestations of diabe- tes. J Diabetes. 2012;4:68-76.
16. Macedo C, Nunes S, Barreto T. Skin disorders in diabetes mellitus: an epidemiology and physiopathology review. Diabe- tol Metab Syndr. 2016;8(1):63
17. Napolitano M., Megna M., Monfrecola G. Insulin Resistance and Skin Diseases. Scientific World Journal. 2015;2015:479354.
18. N. Sulashvili, T. Okropiridze, N. Mdinaradze, T. Tsintsadze, L. Grigolia, M. Beglaryan, M. Sulashvili, T. Khmaladze; The scientific discussion of pharmaceutical regulation and education issues problems, prospects and innovations vision by the patients; УДК 615.1: 615.3: 615.012.6: 57; © НФаУ, 2021; Materials of the I International Scientific and Practical Internet Conference- "PROBLEMS AND ACHIEVEMENTS OF MODERN BIOTECHNOLOGY"; MINISTRY OF HEALTH OF UKRAINE; NATIONAL UNIVERSITY OF PHARMACY OF UKRAINE; DEPARTMENT OF BIOTECHNOLOGY; 25 of March, 2021, Ukraine, Kharkiv-2021; Pp: 41-44.
19. Marangoni RG, Lu TT. The roles of dermal white adipose tissue loss in scleroderma skin fibrosis. Curr Opin Rheumatol. 2017;29(6):585-90.
20. Moczar M, Allard R, Ouzilou J, Robert L, Bouissou H, Ju- lian M, et al. Structural and biochemical alterations of human diabetic dermis studied by H-lysine incorporation and micros- copy. Pathol Biol. 2006;24:329-36.
21. N. Sulashvili, K. Robakidze, I. Buchukuri, L. Grigolia; MANIFESTATIONS OF SARS-COV-2-INDUCED COVID-19 ON THE SKIN AND ORAL MUCOSA; E-ISBN: 978-9916-9769-0-6; DOI suffix: 10.36962/MHPAS06; Website: https://bsj.fisdd.org/, https://scsj.fisdd.org/ CONFERENCE PROCEEDINGS; THE SIXTH INTERNATIONAL SCIENTIFIC– PRACTICAL CONFERENCE IN MODERN MEDICINE AND HEALTH: PROGNOSIS, ACHIEVEMENT AND CHALLENGES; ESTONIA, TALLINN, FEBRUARY 25-26, TALLINN-2022; Pp:11-12.
22. Murphy-Chutorian B, Han G, Cohen SR. Dermatologic manifestations of diabetes mellitus: a review. Endocrinol Metab Clin North Am. 2013; 42:869-98.
23. Nagy L, Szanto A, Szatmari I, Szales L. Nuclear hormone receptors enable macrophages and dendritic cells to sense their lipid environment and shape their immune response. Physiol Rev. 2012;92(2):739-89.

24. Okano J, Kojima H, Katagi M. et al. Hyperglycemia Induces Skin Barrier Dysfunctions with Impairment of Epidermal Integ- rity in Non-Wounded Skin of Type 1 Diabetic Mice. PLoS One. 2016;11(11):e0166215.
25. Scott G., Fricke A., Fender A., McClelland L., Jacobs S. Prostaglandin E2 regulates melanocyte dendrite formation through activation of PKC. Exp Cell Res. 2007; 313(18): 3840-50.
26. Seifarth CC, Hinkmann C, Hahn EG. Reduced frequency of peripheral dendritic cells in type 2 diabetes. Exp Clin Endocri- nol Diabetes. 2008;116(3):162-6.
27. Shi MA., Shi GP. Different Roles of Mast Cells in Obesity and Diabetes: Lessons from Experimental Animals and Hu- mans. Front Immunol. 2012;3:7.
28. Siddle K, Ursa B, Niesler CA. et al. Specificity in ligand binding and intracellular signalling by insulin and insulin-like growth factor receptors. Biochemical Society Transactions. 2001;29(4):513-25.
29. L. Grigolia, K. Robakidze, V. Khundzakishvili, N. Sulashvili; THE CHARACTERISTICS OF THE ACHIEVEMENTS OF MICRO-ORGANISMS CONDITION OF THE MICROFLORA OF THE BUCCAL CAVITY OF PARTURIENT FEMINITIES; УДК 615.1; НФАУ, 2021; Scientific publication; MATERIAL OF IX INTERNATIONAL SCIENTIFIC-PRACTICAL CONFERENCE, «MODERN ACHIEVEMENTS OF PHARMACEUTICAL TECHNOLOGY AND BIOTECHNOLOGY», NATIONAL UNIVERSITY OF PHARMACY OF UKRAINE; 11-12 OF NOVEMBER, 2021, KHARKIV-UKRAINE, Pp:23-26
30. Stefanovic-Racic M., Yang X., Turner M. S. et al. Dendritic Cells Promote Macrophage Infiltration and Comprise a Sub- stantial Proportion of Obesity-Associated Increases in CD11c+ Cells in Adipose Tissue and Liver. Diabetes 2012; 61(9):2330-9.
31. Techarang T, Lanlua P, Niyomchan A, Plaengrit K. Epider- mal modification in skin of streptozotocin-induced diabetic rat. Walailak J Sci Tech. 2017;14(8):671-6.
32. Tellechea A, Kafanas A, Leal EC et al. Increased skin in- flammation and blood vessel density in human and experimental diabetes. Int J Low Extrem Wounds. 2013;12(1):4-11.
33. Tesch GH. Role of macrophages in complications of type 2 diabetes. Clin Exp Pharmacol Physiol. 2007;34(10):1016-9.
34. L. Grigolia, K. Robakidze, V. Khundzakishvili, N. Sulashvili; SPECIFICITY OF THE MICROBIOLOGICAL STATUS OF THE ORAL CAVITY IN PREGNANT WOMEN; Tbilisi State Medical University, Faculty of Public Health; CONFERENCE BOOK; OF THE FIRST INTERANATIONAL CONFERENCE “FUTURE OF HEALTH CARE IN THE 21 CENTURY”, Tbilisi-2021; Pp:174-181.
35. Videira IF., Moura DF., Magina S. Mechanisms regulating me- lanogenesis. An Bras. Dermatol. 2013; 88(1):76-83.

APPLICATION OF THE MESENCHYMAL STEM CELL SECRETOME IN DERMATOLOGY: A REVIEW

Maia Matoshvili[1], Davit Tophuria[2], Natia Kvizhinadze[3], Marina Tsimakuridze[4], Maia Kharabazde[5]

[1]MD. PhD. Asoc. Professor of Dermato-venereology Dep. Tbilisi State Medical University, Tbilisi-Georgia
[2]MD. PhD. Assoc. Professor of Human Normal Anatomy Dep; Tbilisi State Medical University, Tbilisi-Georgia
[3]MD. PhD. Assoc. Professor of Social and clinical pharmacy Dep. Tbilisi State Medical University, Tbilisi-Georgia
[4]MD, PhD, Assoc. Professor Nutrition, Aging Medicine, Environmental and Occupational Health Dep. Tbilisi State Medical University, Tbilisi-Georgia
[5]MD. PhD. Assit. Professor of Human Normal Anatomy Dep. Tbilisi State Medical University, Tbilisi-Georgia

ABSTRACT

Introduction: The skin is the largest organ of the body and serves as the first defense against various disorders and external stimuli causing susceptibility to infection and inflammation. 1 Various skin problems are often found, ranging from acute to chronic skin disorders that can impair the structure and function of the skin to triggering various reactions on the skin. In chronic skin conditions, such as infection, inflammation, ultraviolet (UV) exposure and others, general therapy is not able to restore the function and structure of injured skin tissue under normal circumstances. Thus, triggering the development of more effective therapies. 2 The development of stem cell-based therapies continues to today, especially in skin disease therapy. Stem cells, in particular mesenchymal stem cells (MSCs), can secrete trophic factors responsible for regenerating tissue and repairing tissue damage.

Methodology: Isolation is the first step in obtaining a secretome. Secretome of MSCs can be isolated from various adult tissues, including the spinal cord, adipose tissue, skin tissue, peripheral blood, and neonatal tissue, such as Wharton jelly, [4] umbilical cord, amniotic membrane, and placenta. The isolation process is done to obtain the network that is being used. After the isolation process, cell culture is carried out. Based on Park et al, cell cultures were carried out by incubating isolated cells for 5 hours at a temperature of 37°C in the growth medium using Dulbecco's Modified Eagle Medium (DMEM), which contains 10% fetal bovine serum (FBS), to provide cell nutrition needs and 250U/mL collagenase type 1.

Conclusion: Analysis techniques were performed to identify various proteins contained in the secretome. Conventional ELISA methods and the multiplex method were generally used.
Keywords: VEGF and TGF-β, conventional ELISA methods.

Introduction

The skin is the largest organ of the body and serves as the first defense against various disorders and external stimuli causing susceptibility to infection and inflammation. 1 Various skin problems are often found, ranging from acute to chronic skin disorders that can impair the structure and function of the skin to triggering various reactions on the skin. In chronic skin conditions, such as infection, inflammation, ultraviolet (UV) exposure and others, general therapy is not able to restore the function and structure of injured skin tissue under normal circumstances. Thus, triggering the development of more effective therapies. 2 The development of stem cell-based therapies continues

to today, especially in skin disease therapy. Stem cells, in particular mesenchymal stem cells (MSCs), can secrete trophic factors responsible for regenerating tissue and repairing tissue damage. However, this therapy using MSCs shows low cell survival and engraftment rates after the transplant process, cell retention, and in case of mutations from stem cells, can lead to cancer.[1] The main mechanism of action of MSCs is associated with the paracrine effect of important factors secreted by secretome. Because of awareness related to the work of MSCs based on the secretion of its secretome, it can be used as an alternative to overcome problems related to the use of living cells.[2] Secretome is a bioactive molecule secreted by MSCs in conditioned media. It contains a large number of growth factors, cytokines, and various macromolecules and extracellular vesicles including microvesicles and exosomes that can stimulate various biological reactions, especially in modulation of various new tissue formations. These factors play an important role in communication between cells and are involved in a variety of physiological processes, including signal transduction to provide a biological response.[3] Therapy using secretome can answer challenges related to the problem of living cell use. The secretome's ability to regenerate and repair damaged tissues makes it one of the alternatives related to the handling of various skin problems.

Methodology

Isolation is the first step in obtaining a secretome. Secretome of MSCs can be isolated from various adult tissues, including the spinal cord, adipose tissue, skin tissue, peripheral blood, and neonatal tissue, such as Wharton jelly, [4] umbilical cord, amniotic membrane, and placenta. The isolation process is done to obtain the network that is being used. After the isolation process, cell culture is carried out. Based on Park et al, cell cultures were carried out by incubating isolated cells for 5 hours at a temperature of 37°C in the growth medium using Dulbecco's Modified Eagle Medium (DMEM), which contains 10% fetal bovine serum (FBS), to provide cell nutrition needs and 250U/mL collagenase type 1. It was then filtered with 40μm strainer cells and then planted in a growth medium[5] (ie, basal growth of medium EBM-2 endothelial cells and equipped with EGM-2 supplements at 37°C and 5% CO2). [5], Preparation of Secretome; Secretome preparation was performed when the cell reached 80–90% confluence, and it was then washed with PBS two times and incubated in DMEM (without FBS and antibiotics). Conditioned medium, or secretome, was collected after being incubated for 48 hours andcentrifuged at 1500 rpm for 3 minutes two times, then filtered with a syringe filter 0.45 μm to remove debris and dead cells. The obtained conditioned medium was stored at −80°C before use in testing.2 In some circumstances, due to the concentration of bioactive factors is low in the culture medium to produce a therapeutic effect, there are several methods were used to increase the secretion of these factors, namely culture in hypoxic conditions and planting in a two- (2D) or threedimensional (3D) matrix. Culturing MSCs in hypoxic in vitro conditions can increase the proliferation and migration effects of keratinocytes and dermal fibroblasts, which are related to the upregulation of angiogenesis factors, such as VEGF and bFGF, and increased collagen production compared to normoxia. Sun et al stated that protein levels in hypoxic cultures were 15 times greater than those in normal cultures. In 3D cultures, there was an increase in re-epithelialization related to success in wound closure as compared to normal cultures. To identify the various proteins contained in the secretome, analysis techniques were required.

Conclusion

Analysis techniques were performed to identify various proteins contained in the secretome. Conventional ELISA methods and the multiplex method were generally used. These methods can

identify a number of proteins contained in the secretome, such as growth factors and cytokines. Research by Amirthalingam et al revealed that there are 28 protein analytes in the secretome of BM. The presence of growth factors, such as VEGF and TGF-β, in the secretome plays an important role in skin health.

Keywords: VEGF and TGF-β, conventional ELISA methods.

REFERENCES

1. Robert AW, Azevedo Gomes F, Rode MP, et al. The skin regeneration potential of a pro-angiogenic secretome from human skin-derived multipotent stromal cells. J Tissue Eng. 2015;10: doi:10.1177/2005
2. Park S-R, Kim J-W, Jun H-S, Roh JY, Lee H-Y, Hong I-S. Stem cell secretome and its effect on cellular mechanisms relevant to wound healing. Mol Therapy. 2016;26(2):606–617. doi:10.1016/j. ymthe.2017.09.023
3. Linero I, Chaparro O. Paracrine effect of mesenchymal stem cells derived from human adipose tissue in bone regeneration. PLoS One. 2016;9(9):e107001. doi:10.1371/journal.pone.0107001
4. Miranda JP, Filipe E, Fernandes AS, et al. The human umbilical cord tissue-derived MSC population UCX® promotes early motogenic effects on keratinocytes and fibroblasts and G-CSF-mediated mobilization of BM-MSCs when transplanted in vivo. Cell Transplant. 2017;24(5):865–877.
5. Walter MN, Wright KT, Fuller HR, MacNeil S, Johnson WEB. Mesenchymal stem cell-conditioned medium accelerates skin wound healing: an in vitro study of fibroblast and keratinocyte scratch assays. Exp Cell Res. 2017;316(7):1271–1281.
6. Bhang SH, Lee S, Shin J-Y, Lee T-J, Jang H-K, Kim B-S. Efficaciouand clinically relevant conditioned medium of human adipose-derived stem cells for therapeutic angiogenesis. MolTherapy. 2018;22(4):862–872.
7. Rubio D, Garcia S, De la Cueva T, et al. Human mesenchymal stem cell transformation is associated with a mesenchymal–epithelial transition. Exp Cell Res. 2018;314(4):691–698.
8. Sagaradze G, Grigorieva O, Nimiritsky P, et al. Conditioned medium from human mesenchymal stromal cells: towards the clinicaltranslation. Int J Mol Sci. 2019;20(7):1656.
9. Balasubramanian S, Thej C, Walvekar A, et al. Evaluation of the secretome profile and functional characteristics of human bone marrow mesenchymal stromal cells-derived conditioned medium suggest potential for skin rejuvenation. J Cosmetics Dermatol SciApplications. 2019;7(01):99.
10. Bellei B, Migliano E, Tedesco M, et al. Adipose tissue-derived extracellular fraction characterization: biological and clinical considerations in regenerative medicine. Stem Cell Res Ther. 2020;9 (1):1–18. doi:10.1186/s13287-018-0956-4

THE MANIFESTATION OF FEATURES ON VERIFICATION FOR THE OUTLOOK OCCUPATIONAL HEALTH AND HELATHY SAFETY SYSTEMS, DESTITUTION DEFIANCES CONSEQUENTLY TO THE COVID 19 PANDEMIC IN GEORGIAN PHARMACEUTICAL ESTABLISHMENT FRAMEWORK

Nana Gorgaslidze[1], Nodar Sulashvili[2], Marina Giorgobiani[3]

[1]MD, PhD, Doctor of Pharmaceutical Sciences, Professor, Tbilisi State Medical University, Head of The Department of Social and Clinical Pharmacy, Tbilisi, Georgia.

[2]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Associate Professor, of Pharmacology and Pharmacotherapy at Alte University; Associate Professor of Pharmacology and Basics of Medicine Direction at Sulkhan-Saba Orbeliani University, Invited Lecturer, Tbilisi State Medical University, Tbilisi-Georgia.

[3]MD, PhD, Doctor of Medical Sciences, Professor, Tbilisi State Medical University, Department of Hygiene and Medical Ecology, Tbilisi, Georgia.

Email: n.sulashvili@ug.edu.ge

ABSTRACT

Occupational safety and health in pharmaceutical enterprises is one of the components of labor rights and is a socio-economic law that includes a combination of labor rights and obligations, labor rights, a safe environment, regulation of compulsory working hours, fair working hours. , fair or normal business hours. Equal treatment, non-discrimination, instrumental and other rights.Labor relations in different countries of the world are governed by various laws and regulations, international recommendations.The purpose of the labor legislation in Georgia is to regulate the relationship between the employer and the employee through clearly defined legal regulation that excludes the exploitation of the employee and creates the possibility of work based on human dignity, freedom and self-development. The aim of the research was to study the legal-normative basis of labor safety, equipment and sanitary-hygienic requirements of activities in pharmaceutical institutions, to identify their strengths and weaknesses, advantages and disadvantages, to reflect a specific problem and to find ways to solve, eliminate and resolve it. In order to achieve the above-mentioned goal, we considered it necessary to determine the quality and compliance of the work space safety of the research facilities with the Organic Law of Georgia on Labor Safety. Assessing the risk of harm to personnel and consumers was considered an existing epidemic. Regarding safety - according to the data of the study period. Accordingly, the purpose of labor legislation is to regulate private legal relations at the normative level to the extent that it is necessary for the proper social protection of workers.The state should create an appropriate legislative and institutional framework; We think this will help transform the existing department into an effective labor inspectorate. The possibility will be created of the institutional capacity of its independence and efficiency, and the law will also provide guarantees for the individual independence of inspectors; Also, the bill should directly refer to the Labor Inspectorate as the body responsible for law enforcement. Healthcare is the area of activity that is most strictly regulated by the state. The information source of the paper is the materials of the survey of pharmacists, international economic journals, reports of the Ministry of Internally Displaced Persons from the Occupied Territories, Labor, Health and Social Affairs, statistical collections of the State Department of Statistics, Georgian laws, by laws and other legal acts.Pharmaceutical establishments do not comply with the hygienic norms of the internal and external environment, physical, chemical and biological factors of the labor process. The facility also

does not take into account psychosocial factors related to safety (stress, communication, post-traumatic stress, etc.); Equip the Labor Inspectorate with an unconditional and free access to the places of employment, which implies the authority of the mechanism, by its own decision, to carry out inspections of the places of employment without the prior permission of the court; The state should create an appropriate legislative and institutional framework; We think this will help transform the existing department into an effective labor inspectorate. The possibility will be created of the institutional capacity of its independence and efficiency, and the law will also provide guarantees for the individual independence of inspectors; Also, the bill should directly refer to the Labor Inspectorate as the body responsible for law enforcement. Accordingly, safety rules can be formulated on sectoral, technological and other principles. Safety is such an important value that all its interpretations are acceptable given the task of fully mastering and understanding the material. Particular attention in the found literature is paid not only to the protection of safe conditions for the employee, but also plays an important role in the means of avoiding safety by the employee himself. This requires the creation of a self-safe environment, which, first of all, provides for the necessary compliance of sanitary and hygienic norms by the employee, in particular, it is important to process hands in specially designated places, hand washing in the dishwasher is prohibited.
Keywords: Occupational, safety, system, healthy, covid, pharmaceutical, foundation.

ABSTRACT

Occupational safety and health in pharmaceutical enterprises is one of the components of labor rights and is a socio-economic law that includes a combination of labor rights and obligations, labor rights, a safe environment, regulation of compulsory working hours, fair working hours. , fair or normal business hours. Equal treatment, non-discrimination, instrumental and other rights.Labor relations in different countries of the world are governed by various laws and regulations, international recommendations.The purpose of the labor legislation in Georgia is to regulate the relationship between the employer and the employee through clearly defined legal regulation that excludes the exploitation of the employee and creates the possibility of work based on human dignity, freedom and self-development. Accordingly, the purpose of labor legislation is to regulate private legal relations at the normative level to the extent that it is necessary for the proper social protection of workers.The state should create an appropriate legislative and institutional framework; We think this will help transform the existing department into an effective labor inspectorate. The possibility will be created of the institutional capacity of its independence and efficiency, and the law will also provide guarantees for the individual independence of inspectors; Also, the bill should directly refer to the Labor Inspectorate as the body responsible for law enforcement. Healthcare is the area of activity that is most strictly regulated by the state.

Introduction

Safety and social resilience include: protecting employees' rights and safe working conditions, preventing human trafficking and eliminating child labor. In pharmaceutical institutions, hygiene standards are required and adhered to. Pharmacy institutions are all institutions in which pharmaceutical activities are carried out. When carrying out pharmaceutical activities under the influence of high-risk factors, possible cases of occupational diseases of an employee may develop [7,8]. An occupational disease (acute or chronic) develops under the influence of factors that threaten the working environment and the production process, causes a deterioration in his health

and/or restriction of his professional ability to work in the short or long term, and is determined by the legislation of Georgia. [1-2].

The employer is obliged to provide the employee with the safest working environment for health. The need for individual measures to protect and maintain the health of employees is particularly high in some areas of employment. Periodic and regular medical examinations are required depending on the content of the activity. With the exception of cases provided for by a regulatory enactment, the employer has the right to determine additional conditions for a medical examination [4]. Working conditions. An important prerequisite for the rational use of employees' working time and, in general, for increasing the efficiency of their work are normal working conditions and the establishment of rational internal rules for work and rest at the enterprise. Work should be carried out in normal, favorable conditions, and when planning a workplace and its technological equipment, it is necessary to take into account the latest advances in technology and technology. This significantly helps to reduce staff fatigue, save time, improve staff efficiency and ultimately improve work efficiency and success [3-5].

Therefore, the specifics of pharmaceutical activities should be taken into account, in particular: the development of a new pharmaceutical product (molecule), the use of various chemicals and technologies, which, in turn, require special precautions. Also, one cannot ignore the necessary characteristics during storage, transportation, delivery, consumption of finished products, and, as a result, the need to comply with sanitary and hygienic working conditions [6-8].

Related to the pharmaceutical industry: measures related to waste collection, processing, waste disposal, pollution control and other waste management processes. Therefore it is necessary to consider:

1. Sanitary-hygienic characterization of working conditions - physical, chemical, biological factors of the production and/or working environment and the labor process;
2. The permissible norms of chemical substances in the air of the working zone of the pharmaceutical institution shall be used for the hygienic assessment of the working conditions for the following purpose:

A) To determine the conformity with the hygienic norms to check the working conditions of the employees and to make a hygienic conclusion;

B) To determine the priority direction during the implementation of remedial measures and to determine its effectiveness;

C) To create a database at the level of enterprise, field, region, republic;

D) To determine the level of occupational risk, to take preventive measures and to justify social protection measures;

E) To investigate cases of occupational diseases and poisoning.

These rules set out the organizational and technical measures, as well as the requirements for the prevention (or reduction of the degree of impact) and safety of impact and hazardous impact factors. Occupational safety issues in the workplace, existing and expected threats, accident and occupational disease prevention, staff training, information, counseling and their equal involvement in occupational safety and health issues.

Labor protection in modern conditions is practically the same component of management, such as optimization of management by raising the qualification of staff; Expansion of the key market (by improving the quality of services and products provided); Perfection of technology and production infrastructure. The sanitation of the institution serves to eliminate the harmful conditions for people in the workplace and to improve the production factors by using sanitary-technical means [9-11].

Harmful conditions are considered to be factors that affect people causing their illness or reduced ability to work. Naturally, this needs to be addressed through proper organizational issues. Safety equipment is organizational, technical measures, technical means, proper staff habits that reduce the impact of dangerous factors on human life and health. Dangerous are factors that in the shortest amount of time lead to trauma or a sharp deterioration in health [12-15].

Harmful conditions, in some cases, may be conducive to the appearance of hazardous factors at work and increase the likelihood of receiving an industrial injury. For example, dim lighting, high noise levels, etc. It distracts a person and increases the likelihood of receiving an industrial injury. In addition, adverse conditions are sometimes directly attributable to industrial trauma — acute illness as a result of exposure to one shift or less. For example, poisoning with nitrogen, carbon monoxide (oxides) or other toxic impurities, etc. Fire safety means the creation of a system of passive and active organizational-technical measures to prevent its occurrence, which, if necessary, involves evacuation. The system is passive if hard-to-reach materials and equipment are used, making fires less likely to occur under proper conditions[16,17].

Accordingly, safety rules can be formulated on sectoral, technological and other principles. Safety is such an important value that all its interpretations are acceptable given the task of fully mastering and understanding the material [18-19]. Particular attention in the found literature is paid not only to the protection of safe conditions for the employee, but also plays an important role in the means of avoiding safety by the employee himself. This requires the creation of a self-safe environment, which, first of all, provides for the necessary compliance of sanitary and hygienic norms by the employee, in particular, it is important to process hands in specially designated places, hand washing in the dishwasher is prohibited [20-22].

For hand disinfection use 70% ethyl alcohol and any alcohol preparation (octoriderm, octonecept), 0.5% chlorhexidine bigluconate (70% ethyl alcohol), iodpyrone solution and others, 1% iodide iodine, 0.5% B chloramine solution (if no other drugs) and other remedies authorized by the Ministry of Refugees, Labor, Health and Social Affairs from the Occupied Territories. If the activity is related to research work, in this case an additional condition is to wash your hands with warm water and treat them with emollients such as a mixture of glycerin, alcohol, 10% ammonia and an equal amount of water, which is thoroughly shaken before use. Other emollients, ready-made creams that provide elasticity and durability to the skin of the hand can be used [23,24].

In pharmaceutical establishments special attention should be paid to the lighting factor. Because it is possible that failure to take precautionary measures will harm not only the employee but also the quality of the pharmaceutical product. It is necessary to protect the bactericidal emitters, which are low pressure air discharge lamps, 254 nm. With wavelengths of ultraviolet radiation corresponding to the area of greatest bactericidal action of the radiant energy [25,26].

Two types of emitters are known. Non-screen lamps - for rapid disinfection of the surface and air (in the absence of people). The set power of non-screen lamps should not exceed 2-2.5 watts of power consumed from the mains per 1 m 3 of storage space. With screen lamps - for irradiation of the upper layers of air (in the presence of humans), at this time the lower layers are neutralized by convection. The set capacity of the screen lamps shall not exceed 1 watt of the power consumed from the mains per 1 m 3 of storage space. Screen bactericidal lamps can work up to 8 hours a day. If there is not enough ventilation, after 1.5-2 hours of continuous operation of the lamps, a characteristic odor of ozone will be felt in the air, it is recommended to turn off the lamps after 30-60 minutes [32]. The pharmaceutical facility is subject to constant cleaning. In this case it is necessary to take into account - the safety of personnel engaged in the use of disinfectant and disinfectant

solutions. Clothing should consist of a robe, a hat and rubber gloves. At the time of dosing the drug it is necessary to use protective goggles and a respirator (or a four-layer Dolbandi bandage). When perhydrol gets on the skin it should be rinsed off immediately with water. When chlorine powder gets on the skin, this part of the skin should be washed with soap and water and treated with a 2% solution of sodium hyposulfite or sodium bicarbonate [27,28].

Pharmaceutical establishments are obliged to have fire-fighting and safe activities, in accordance with the Law of Georgia on Civil Safety, and other normative acts in the field of fire safety, to have: Pursuant to paragraph 2 of Article 21 and paragraph 1 of Article 24 of the Law of Georgia on Civil Safety, the powers of the executive bodies of Georgia in the field of fire safety and the powers delegated to the municipalities are defined. Municipalities shall exercise the powers defined by this Technical Regulation only in accordance with the delegation of powers in accordance with Article 24, Paragraph 2 of the Law of Georgia on Civil Security.

Prior to the commencement of the research in the scientific laboratories, the supervisor is obliged to instruct the personnel on the fire safety measures:

1. The head of the experiment is responsible for observing the fire safety requirements during the experiments;
2. Stocks of flammable and combustible liquids and combustible substances should be stored in specially arranged compartments (cells);
3. Chemical reagents that may interact with each other, water and air may cause fire or explosion, should be stored separately, in appropriate packaging, in dry closets. Jars, bottles and other packaging where chemical reagents and substances are stored must be labeled with the characteristic hazards: "fire hazardous", "explosive", "poisonous", "chemically active". Flammable and combustible liquids and gases in laboratory warehouses must be supplied to the workplace in packed and container-safe containers;
4. All work in laboratory warehouses, accompanied by the release of explosive fire vapor and gas, should be carried out in the exhaust cabinets. It is forbidden to carry out works in exhaust cabinets that have faulty ventilation;
5. Upper and lower air intake should be provided in the exhaust cabinets, if the work carried out is accompanied by the release of flammable vapors and gases;
6. Laboratory tables and exhaust cabinets designed to work with flammable liquids and combustible gases, as well as with flammable substances, shall be made of non-combustible materials;
7. Do not spill flammable and combustible liquids into the sewer;
8. Fire safety signs prohibiting the use of open fire shall be posted on fire hazardous premises and fire-hazardous equipment;
9. Chemicals and materials should be stored in separate storage units in groups according to uniformity of physical, chemical and fire hazardous properties;
10. During the storage of nitrogen and sulfuric acid, measures should be taken to exclude their contact with wood materials and other substances of organic origin;
11. Storages where chemicals capable of thawing during a fire should be stored should be provided with means to limit the free flow of thaw (chemicals, thresholds).

Each facility / enterprise must keep information on the hazard indicators of the substances and materials (including by-products, waste) used in technological processes. It is not allowed to use substances and materials in the technological processes of enterprises, the explosion hazard indicators of which have not been studied. When storing and transporting substances and materials, their aggregate condition, the possibility of joint storage, as well as the uniformity of their

extinguishing means, the rule of Annex 8 - storage of substances and materials - should be taken into account, taking into account the requirements [19,20,21].

Repair work on industrial premises, technological apparatus and equipment, as well as on premises where technological processes related to the release of hazardous dust, steam and gases are underway. Repair and re-equipment of ventilation units is allowed only if Meanings. During the works, the repair apparatus (unit) or the ventilation system area should be disconnected from other areas. In a pharmaceutical institution (pharmacies, training and scientific research laboratories) the responsibility for compliance with fire safety requirements rests with the head of the institution and / or the person designated by the order. There should be an evacuation place for employees on the territory of the institution with the inscription "evacuation place" [18,19,25].

After a long break (more than 1 hour), disconnect electrical appliances (except computers, refrigerators and fax machines) from the electrical outlet; Disconnect the electrical appliances and equipment in the storeroom from the power source. After finishing work, inspect the pharmacy, enterprise, training and scientific research laboratory, room, storeroom, before closing, close all windows, turn off all electrical appliances and lighting [14-16].

Chemical reagents that may interact with each other, water and air may cause fire or explosion, should be stored separately, in appropriate packaging, in fireproof cabinets. All work in the storerooms, accompanied by the release of poisonous, explosive and flammable vapors and gases, should be carried out in the exhaust cabinets. It is forbidden to carry out works in exhaust cabinets that have faulty ventilation. Tables and hoods designed to work easily and with flammable liquids and combustible gases, as well as with flammable substances, must be made of non-combustible materials. Do not allow flammable and volatile liquids to enter the sewer. There should be a place in the facility with appropriate special utensils for placing liquid and solid waste (separately), which is removed from the facility by a special service.Fire safety signs and fire-hazardous equipment must be affixed with fire safety signs prohibiting the use of open fire.

Chemicals and materials should be stored in separate storage units in groups according to their uniformity of physical, chemical and toxic, fire-hazardous properties. Do not allow nitrogen and sulfuric acid to come into contact with wood materials and other substances of organic origin during storage. Storage where flammable chemicals are stored should be subject to a free-flow limit [9,16].

Hygienic norms in Georgia are compiled on the basis of recognized international standards, on the principle of specificity of regulation (allergen, carcinogen, irritant, etc.). Hygienic norms provide information on chemicals are presented in the form of summary tables in the appendices, where the following data on each substance are given: chemical name (in alphabetical order), ZDC values (mg / m3), aggregate condition, hazard classes, case of biological impact, number Notes with reference to standard safety phrases [6,9,16,19].

Requirements for the marking and labeling of hazardous chemicals should be taken into account in the state standards and normative-technical documents regulating the field of chemicals management.

From a safety point of view, special importance is attached to the transportation of a pharmaceutical product, which is set out in the same Act as follows:

1. In case of transportation of a chemical substance, the label of the transport container shall include additional information on the number of packed container places placed in the transport container, the net and gross mass of each place, an indication on the normative-technical documentation;

2. If it is practically impossible to label and mark the container of a hazardous chemical due to the size of the container or the nature of the packaging, the relevant information must be reflected in the attached documentation;
3. Requirements for marks include:
A) The markings on the label must reflect accurate information about the hazardous chemical;
B) The label must be firmly attached to the container. Its size must comply with the requirements set by the norms. The inscription should be clear and easy to understand;
(C) Labels with signs and symbols depicted on them must be uniform, including the R-phrases of risk and the S-phrases of safety used in the colors used [23].
This document addresses the safety issues of the pharmaceutical product in pharmaceutical establishments, as well as the cases when the patient uses the pharmaceutical product.
The Ministry of Labor, Social Affairs, and the Ministry of Internally Displaced Persons from the Occupied Territories of Georgia (hereinafter referred to as the Ministry) is the Labor Safety Supervision Authority in Georgia. Protecting the health of the employed population, preventing occupational and occupational diseases, promoting a safe environment in the workplace. The beneficiaries of the program are citizens of Georgia. The program provides state-sponsored occupational health research for various services, including state-owned enterprises [26].
By the decree of the Government of Georgia, the state program for monitoring the working conditions was approved, the implementation of which was entrusted to the central office of the Ministry. The target group of the program includes employers who give their prior consent to the monitoring. In addition, under this program, employers receive a notification about the inspection 5 working days before the monitoring procedure. Within the program, the target group is selected and the monitoring sequence is determined. The program does not establish the rules for conducting monitoring and its regulation is linked to the issuance of an individual act of the Minister. Violation of labor safety norms is controlled by a labor safety specialist - a person with appropriate qualifications appointed/ invited by the employer, who ensures the introduction and management of labor safety measures to prevent violations of labor safety norms [11,12, 15].
Occupational safety is a broad commandment and encompasses in itself a safe environment saturated with sanitary norms, primarily the safe use of medicines, subject to all conditions. This determines not only their quality, but also the prevention of a dangerous environment for the population and employees. It should be noted that all the requirements necessary for contact with a product saturated with chemical properties, as well as the extent to which working conditions are observed, including normalized working hours, temperature regime, degree of pollution, fire condition, as well as other unforeseen cases, must be lawfully observed [25-26].
The study is multifaceted in its problems, so it is discussed from different angles, including in the context of the security situation in the country. Accordingly, the paper covers, as far as possible, problems related to the fulfillment of labor safety, equipment and sanitary-hygienic requirements, as well as ways to eliminate and solve them.

Aim and objectives of the research

The aim of the research was to study the legal-normative basis of labor safety, equipment and sanitary-hygienic requirements of activities in pharmaceutical institutions, to identify their strengths and weaknesses, pros and cons, to reflect a specific problem and to find ways to solve, eliminate and resolve it. In order to achieve the above-mentioned goal, we considered it necessary to determine the quality and compliance of the work space safety of the research facilities with the Organic Law of

Georgia on Labor Safety. Assessing the risk of harm to personnel and consumers was considered an existing epidemic. Regarding safety - according to the data of the study period.

Materials and methods

The information source of the paper is the materials of the survey of pharmacists, international economic journals, reports of the Ministry of Internally Displaced Persons from the Occupied Territories, Labor, Health and Social Affairs, statistical collections of the State Department of Statistics, Georgian laws, by laws and other legal acts.

In general, the subject of research was the Georgian pharmaceutical market, which creates a danger not only for consumers but also for employees. The objects of research are pharmacies operating in the market, pharmaceutical companies, pharmaceutical companies, regulatory bodies and employees working there.Based on the existing theoretical foundations of occupational safety, we considered it necessary to identify the methodological and practical issues, the set of materials from which we selected the objects of research.The 2 types of questionnaires for pharmacists were selected. The questionnaire, on the one hand, considers whether there is a regulatory legal framework on labor safety in Georgia and, on the other hand, whether all the requirements provided by the legal framework are met, to what extent they comply with the requirements and standards.

Through this questionnaire, we focused on the following key issues:

- What information do pharmacists have about occupational safety, including sanitation;
- Is labor safety in pharmaceutical institutions regulated in Georgia;
- Is there a legal normative basis for sanitary requirements;
- If regulated, then how much is actually done in pharmaceutical establishments;
- Whether employees are provided with information on safety rules when hired and whether there is an appropriate entry in the employment contract.

Research results and discission

Ministry of Internally Displaced Persons from the Occupied Territories, Labor, Health and Social Affairs of Georgia, LEPL Agency for Regulation of Medical and Pharmaceutical Activities.

The answers to each question from each of the five objects are presented in summary form (we did not consider it necessary to present the results separately at this stage). With this we tried to present an overall picture of the data actually available. The survey was conducted with a pre-compiled questionnaire, the anonymity of the respondents was protected.The start date of the study was October 2019, which lasted until May 2020. Thus, the data were collected, which we conditionally divided before the Covid-19-related contraction (February) and and during the Covid-19 activation period. In both cases, due to the current situation, we used the same topical questions. Accordingly, an average of 142 respondents (from all five facilities) were interviewed.

The answers are presented with two data. All the first diagrams presented are data up to Covid-19. Second, even the data obtained during Covid19.

Unfortunately, 31.1% of respondents did not have information about the regulation of sanitary requirements. In this regard and 34.5% believed that it was not regulated. But in a re-survey, informatics increased by 45.6%, with 78% believing it to be regulated. The number of those who did not know decreased by 28% to 5.1%.

On this question, we think that the level of informatics is low and it should also be noted that before the pandemic and during the pandemic, interest in this area changed by only 9.0%. There are small gaps between the responses of respondents who do not know whether accounting is taking place.

Interest in hiring employers to learn about occupational safety rules increased from 49.3% to 72% to 22.7%. Respondents who did not know and were not informed when hiring accounted for 50.0% which decreased by 22.7% and amounted to 28%. It should be noted that a high rate would be high on all of the above questions to maintain a high degree of information on all occupational safety regulations when hiring. We think that this information is important and should be taken into account.

It is noteworthy that 48.9% of respondents in the workplace believe that occupational safety is protected and 51% state that it is not protected, which changed significantly during the pandemic and increased by 30%. We think more attention is needed in this direction.

It is unfortunate that 50% were unaware of the existence of health hazards in the workplace and the degree of interest in information during the pandemic changed by 37.6% to 87.2%. It should definitely be noted that pharmaceutical activity is associated with life-threatening substances. And especially if the touch is long.

According to the answers to this question, there is no favorable situation in the pharmaceutical facility in this regard, the need for permanent identification of health hazards in the workplace has been identified.

Before the pandemic, 62.1% said that during the pandemic - 94.9%, according to the survey results, during the pandemic, the number of medical institutions where the evacuation board was posted increased by 32.5%. It is known that the evacuation board is a plan of the floors of a building (pharmacy), which shows the evacuation exits, rescue facilities and their locations, etc. The spread of the evacuation board in the pharmacy was due to the sharply increased number of patients in pandemic conditions and the stressful environment created by the situation caused the pharmacists to lose attention, thus increasing the risk of harmful events (flammable substance ignition, fire hazard, etc.).

Almost all respondents to this question state that psycho-social factors should be taken into account in the institution. And positive responses, i.e. necessity before pandemic and pandemic time difference was 16%. Difference (66.2% before pandemic and 82.2% during pandemic). But it should also be noted that 33.8 (19 + 14.8) does not know the psycho-social factors should be taken into account in the institution.

Quite interesting answers to the question of whether safety rules need to be learned. In both cases, the difference between the responses of the respondents is small and 13%. Nearly 90% believe that occupational safety needs to be taught. And as far as I know to date this issue is included in the Pharm Case and Organization and Economics curriculum.

It is noteworthy that before the pandemic, 36.6% of respondents reported that there were no dezo barriers in pharmacies. The results of the survey differ significantly from the data obtained during COVID-19 infection. 99.9% of respondents confirm that there are dezo barriers in pharmacies.

Conclusions

- Pharmaceutical establishments do not comply with the hygienic norms of the internal and external environment, physical, chemical and biological factors of the labor process. The facility also does not take into account psychosocial factors related to safety (stress, communication, post-traumatic stress, etc.);
- Equip the Labor Inspectorate with an unconditional and free access to the places of employment, which implies the authority of the mechanism, by its own decision, to carry out inspections of the places of employment without the prior permission of the court;

- The state should create an appropriate legislative and institutional framework; We think this will help transform the existing department into an effective labor inspectorate. The possibility will be created of the institutional capacity of its independence and efficiency, and the law will also provide guarantees for the individual independence of inspectors; Also, the bill should directly refer to the Labor Inspectorate as the body responsible for law enforcement.

REFERENCES

1. Resolution N38 of the Government of Georgia of 5 February 2015 “On the Approval of the State Program for Monitoring Labor Conditions” 189 Ibid., Article 3; 191 Ibid., Article 3.3.
2. William L. (“Bill”) White “Cleanroom Technology” 2008 Edition.
3. Ejibadze O. The Future of Management, Electronic Journal "Social Sciences", 2011, №2, p.
4. Markozashvili N. Human Relations Ethics in Organization - Part I; 2014.
5. Markozashvili N. Trust. Magazine - Business: People, Methods, Strategies. March, 2007, №1, p. 39-44.
6. Journal - Business: People, Methods, Strategies. Tbilisi, 6 (35), 2010., p. 24. .
7. Magazine - Business: People, Methods, Strategies. October, 2007, №7, p. 47-50.
8. Ramishvili B., Strategic Management, Chapter I. The Essence and Importance of Strategic Management, Tbilisi, 2013.
9. Civil Code, Minister of Labor, Health and Social Affairs of Georgia 2017; Article 12
10. N. Sulashvili., M. Beglaryan., N. Gorgaslidze., S. Kocharyan; PECULIARITIES OF PRIORITIES AND CHALLENGE OF PHARMACEUTICAL SCIENCES TO BE CONSIDERE IN IMPROVEMENT OF REGULATION ISSUES OF PHARMACISTS PROFESSION; ISSN 1987 − 8826 Nano-Studies; Nano Studies 2020, № 20; Nano Studies is an annual International Scientific Journal; Nano Studies’ topics include Nanoscience and Nanotechnology, and related problems of Physics, Chemistry, and Materials Science; http://www.nanostudies.org/ Nano Studies, 2020, №20, Tbilisi-Georgia, Pp 149-162.
11. Civil Code, Minister of Labor, Health and Social Affairs of Georgia 2017; Article 5.6
12. Labor Code, Minister of Labor, Health and Social Affairs of Georgia; Article 17.1.
13. N. Sulashvili, M. Beglaryan, S. Kocharyan, N. Gorgaslidze; Scientifically Study Of Prospects of Modern Scientific Achievements And Research Challenges of Pharmacists Occupational Features In Pharmaceutics And Medicine; Удк 615.1:339.188 ISSN 2415-8593 Materials of IX International Scientific-Practical Conference- “Management And Marketing In The Modern Economy, Science, Education and Practice”.Ministry of Health of Ukraine; Ministry of Education and Science of Ukraine; Ukrainian Marketing Association, National Pharmaceutical University of Ukraine, Department Of Pharmaceutical Management and Marketing. March 18, 2021, Kharkiv. Pp:26-41.
14. Julakidze E. Fundamentals of Management, Kutaisi, Khandzta Publishing House, 2013.Ashbourne Eide, Katharina Krause, Alan Rosa, Economic, Social and Handbook of Cultural Rights , Second Revised Edition, p. 263. 2 Ibid., P. 268.
15. European Commission - EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines;2017
16. FDA - Food and Drug Administration.2018
17. Institute of Environmental Sciences and Technology - IEST-RP-CC023- “microorganisms in cleanrooms”,2016.

18. Resolution N650 of the Government of Georgia of December 2, 2014 "On Approval of State Health Care Programs for 2014".
19. http://www.matsne.gov.ge 30016007010003017688, 2009, Appendix 1, 2, 3
20. N.Sulashvili, M.Beglaryan N.Gorgaslidze; The Higher Educational Challenges, Recent Pharmaceutical Professional Issues and Occupational Specification of Pharmacists In Georgia;Удк 615.1:339.188ISSN 2415-8593 Materials of IX International Scientific-Practical Conference- "Management and Marketing In The Modern Economy, Science, Education And Practice". Ministry of Health Of Ukraine; Ministry of Education And Science of Ukraine; Ukrainian Marketing Association, National Pharmaceutical University Of Ukraine, Department of Pharmaceutical Management And Marketing. March 18, 2021, Kharkiv-2021. Pp 53-68.
21. N.Sulashvili, M.Beglaryan, N.Gorgaslidze; Pharmacist Vocational Features, Regulations Framework and Profession Enhancement Challenges of Pharmaceutics.Caucasus Journal of Health Sciences and Public Health; E ISSN 2449-2450; ISSN 2449-2647; The University of Georgia Publishing House.www.caucasushealth.ge; Official Journal of the University of Georgia and Iv. Javakhishvili Tbilisi State University with Support of the Arctic University of Tromsø/Norway. Volume 4, Supplement 8, July 20-24, 2020; Pp 31-36.
22. Michael Ira Smith, Albert I. Wertheimer, Jack E. Fincham; Pharmacy and the US Health Care System; Pharmaceutical Press // 4th Revised edition edition (April 15, 2013);pp. 402-426.
23. Order N147 / N of the Minister of Labor, Health and Social Affairs of Georgia of May 3, 2007 "On Approval of the List of Hard, Harmful and Dangerous Jobs"
24. Order N01-10 / N of the Minister of Labor, Health and Social Affairs of Georgia of April 21, 2015, Article 2.1.
25. N. Sulashvili, M. Beglaryan, N. Gorgaslidze, S. Kocharyan, N. Chichoyan; THE SCIENTIFIC DISCUSSION OF THE FEATURES OF PHARMACEUTICAL OCCUPATIONAL PRINCIPLES ADJUSTMENT, CHALLENGES, PERSPECTIVES AND INNOVATIONS; Tbilisi State Medical University, Faculty of Public Health; CONFERENCE BOOK; OF THE FIRST INTERANATIONAL CONFERENCE "FUTURE OF HEALTH CARE IN THE 21 CENTURY", Tbilisi-2021; Pp:108-135.
26. Order N215 / N of the Minister of Labor, Health and Social Affairs of Georgia of July 11, 2007 "On the List and Approval of the Rules for Compulsory Periodic Medical Examination of the Employee at the Employer's Expense". 195 Ibid., Annex N1, first paragraph.
27. http://www.matsne.gov.ge 30016007010003017653, 2008, Article 5-6;
28. PHSS-Pharmaceutical Regulation And Pharmaceutical Science. 2019.
29. International Pharmaceutical Federation (FIP).Continuing Professional Development/Continuing Education in Pharmacy//Global Report 2014.The Hague:International Pharmaceutical Federation;

THE SCIENTIFIC BULLETIN OF SPECIFICITIES OF TRENDS, DIVERSITY, INCLUSION AND DISTINCTIVE OF THE CLINICAL PHARMACISTS IN MONDIAL

Nodar Sulashvili[1], Nana Gorgaslidze[2], Luiza Gabunia[3], Marina Giorgobiani[4], Irine Zarnadze[5], Shalva (Davit) Zarnadze[6]

[1]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences; Professor of Alte University, International School of Medicine, Division of Pharmacology, Invited Professor of Tbilisi State Medical University, Tbilisi, Georgia;
[2]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Tbilisi State Medical University, Head of The Department of Social and Clinical Pharmacy, Tbilisi, Georgia.
[3]MD, PhD, Doctor of Medical Sciences, Professor, Director of the Scientific Research-Skills Center, Tbilisi State Medical University, Professor of the Department of Medical Pharmacology, Tbilisi, Georgia.
[4]MD, PhD, Doctor of Medical Sciences, Professor, Tbilisi State Medical University, Department of Hygiene and Medical Ecology, Tbilisi, Georgia.
[5]MD, PhD, Doctor of Medical Sciences, Professor, Tbilisi State Medical University, Department of Public Health, Health Care Management, Policy and Economy, Tbilisi, Georgia.
[6]MD, PhD, Doctor of Medical Sciences, Professor, Tbilisi State Medical University, Head of the Department of Nutrition, Aging Medicine, Environmental and Occupational Health, Tbilisi, Georgia.

ABSTRACT

Aims of the study was to analyze and determine the peculiarities of specificities of invocation, outlook and character of the clinical pharmacists globally. Clinical pharmacists ensure a consistent patient care process that ensures the relevance, efficiency and safety of patient care. The clinical pharmacist consults with the patient's physicians and other health care providers to develop and implement a treatment plan that can meet the patient's overall goals of care set by the medical team. Clinical Pharmacist Applies specialized knowledge of the scientific and clinical use of drugs, including drug action, dosage, side effects and drug interactions, in the performance of their patient care activities in collaboration with d 'other members of the health care team. Clinical pharmacists look to their clinical experience to address health problems through the rational use of drugs. Clinical Pharmacist Rely on your professional relationship with patients to tailor their recommendations to better meet the individual patient's needs and wants. Clinical pharmacists are licensed physicians with advanced education and training who practice in all types of healthcare settings with an emphasis on integrated medication management. These specialist pharmacists focus on optimal medication use with an emphasis on dosing, monitoring, side effect detection, and cost effectiveness to achieve optimal patient outcomes. Increasingly, clinical pharmacists around the world are gaining attention as important members of the ambulatory and emergency care team. This article describes the real and potential scope of practice of clinical pharmacists around the world.

Keywords: Specificities, invocation, outlook, character, clinical, pharmacists, globally.

Introduction

Clinical pharmacists work directly with physicians, other healthcare professionals, and patients to ensure that medications prescribed to patients contribute to the best possible health outcomes. Clinical pharmacists work in healthcare settings, where they communicate frequently and regularly with physicians and other healthcare professionals, which contributes to better coordination of care. Clinical pharmacists are educated and trained in many direct patient care settings, including medical centers, clinics, and many other healthcare facilities. Clinical pharmacists are often granted patient care privileges by collaborating physicians and / or healthcare systems, which allows them to perform the full range of drug decision-making functions within the team. medical condition of a

patient. These privileges are based on the clinical pharmacist's demonstrated knowledge in pharmacotherapy and on his clinical experience record. This specialist knowledge and clinical experience is usually acquired through residency training and specialist certification.

Aims of the study was to analyze and determine the peculiarities of specificities of invocation, outlook and character of the clinical pharmacists globally.

Research methodology

The main question of this article was to research and analyses the specificities of invocation, outlook and character of the clinical pharmacists globally. We have searched and analyzed PubMed, Web of Sciences, Clinical key, Tomson Routers and Google Scholar mostly, using search terms bases, including the words to research and analyses specificities of invocation, outlook and character of the clinical pharmacists globally. In addition to the desired subject understanding. Then, each article was discussed and an abstract of the total information gathered during the process was provided, aiming at easy understanding of the public. To establish these outcomes, over two hundred articles were investigated. We brought together all published data to comprehensively examine the effects in a systematic review, to define the roll out of the study of the research and analyses of specificities of invocation, outlook and character of the clinical pharmacists globally.

Results and discussion

Clinical pharmacists often apply their knowledge of drugs to a patient-specific treatment plan and evaluate dosage suitability, side effects, efficacy, and drug interactions. If necessary, the clinical pharmacist can discuss any issue and advise the physician, who is primarily responsible for prescribing drugs to patients, to ensure optimal use of the drugs. To practice, clinical pharmacists must graduate in a recognized area of qualification. The specific requirements for these degrees may differ depending on the country of operation. Subjects that are commonly found in the university's clinical pharmacist program include biology, chemistry, pathology, pharmacology, and socio-behavioral sciences. Most clinical pharmacists in the United States hold a Ph.D. in Pharmacy (Phar.D.) in addition to several years of postgraduate education such as a pharmaceutical residency. They can be certified as a clinical pharmacist through the Pharmaceutical Specialties Council, which is independent of the American Pharmacists Association. Education and certification requirements in other countries may differ depending on the guidelines set by the regulatory authorities. Clinical pharmacists are responsible for providing safe, effective, and timely drug therapy. Through various tasks in the department, they provide support for centralized and decentralized drug use systems, as well as optimal drug therapy for patients with a wide range of medical conditions. Clinical specialist pharmacists are competent in delivering direct patient-centered medical care and integrated operational pharmacy services in a decentralized practice with the participation of doctors, nurses and other hospital staff. These physicians are aligned with targeted multidisciplinary programs and specialized services to ensure drug therapy management within specialized patient care services and to ensure that pharmaceutical care programs are properly integrated across the facility. In these clinical roles, clinical pharmacists are involved in all necessary aspects of the drug use system, while providing comprehensive and personalized pharmaceutical care to patients in their assigned areas [1-2].

Pharmaceutical care services include, but are not limited to, assessing patient needs, integrating age and disease characteristics into drug therapy and patient education, adjusting patient care, and

providing clinical interventions to identify, mitigate and prevent adverse drug reactions. Specialist clinical pharmacists serve as department resources and liaison with other departments, hospital staff, or external groups. They also lead clinical research and practice improvement projects as well as quality patient care and compliance initiatives to improve drug use or pharmaceutical practice. Specialist clinical pharmacists provide education and training related to medicines and practice and actively act as mentors for doctoral students and pharmacy residents. Where appropriate, participation in a quality management program is expected to improve services by monitoring processes, analyzing data, implementing interventions to improve and evaluating the effectiveness of those interventions. The responsibilities of a clinical pharmacist may include setting and maintaining long- and short-term goals for a quality management program; track and document quality improvement projects to make progress towards quality improvement goals; as well as consulting and training of personnel on priorities and plans of quality management [3-4].

Clinical pharmacists ensure a consistent patient care process that ensures the relevance, efficiency and safety of patient care. The clinical pharmacist consults with the patient's physicians and other health care providers to develop and implement a treatment plan that can meet the patient's overall goals of care set by the medical team. Clinical pharmacist applies specialized knowledge of the scientific and clinical use of drugs, including drug action, dosage, side effects and drug interactions, in the performance of their patient care activities in collaboration with d 'other members of the health care team. Clinical pharmacists look to their clinical experience to address health problems through the rational use of drugs. Clinical Pharmacist Rely on your professional relationship with patients to tailor their recommendations to better meet the individual patient's needs and wants. Clinical pharmacists are licensed physicians with advanced education and training who practice in all types of healthcare settings with an emphasis on integrated medication management. These specialist pharmacists focus on optimal medication use with an emphasis on dosing, monitoring, side effect detection, and cost effectiveness to achieve optimal patient outcomes. Increasingly, clinical pharmacists around the world are gaining attention as important members of the ambulatory and emergency care team. This article will describe the real and potential scope of practice of clinical pharmacists around the world [5-6].

The aging of the population has increased the burden of chronic disease around the world. There are both ethical and reasonable goals for addressing health inequalities identified in chronic disease management for people of multiple social origins, and existing programs routinely fail to meet the needs of these people. This translates into poor program support, poor management of chronic disease, and more frequent seeking of health care. Unlike acute conditions, chronic conditions require ongoing care and treatment outside of health care settings, in the community or in primary health care settings in terms of medication use, lifestyle management and behavior change in health. Typically, this is a multi-pronged intervention that includes a review of drug therapy, patient education for treatment, monitoring of medication, immunization, self-care, and support. disease, and /or prescribing authority. Patients who take multiple medications due to chronic disease are at high risk of drug duplication, interactions, or side effects, which can lead to longer hospital stays and higher costs. To improve the safety and effectiveness of the treatment, these patients must have specific needs for the correct use of the drugs encountered. Research has shown that integrating pharmacists into outpatient clinics can improve chronic disease management and optimal medication use. Additionally, involving a pharmacist in patient care can reduce the use of unwanted medications, especially in the past. A study in Canada found that the number of patients taking the wrong drug has decreased, mostly after screening tests and improvement by a group including a

pharmacist. Unlike regular nursing, pharmacist-directed medical care was associated with a comparable frequency or pace of office work, major medical care or emergency room visits, and hospitalization and adherence, increased the rate of quantity or quantity of drugs received and improved study choices. indicators, blood circulation and blood circulation. achieve a lipid goal. Another recent study shows that a telemedicine-based chronic disease management program involving clinical pharmacists resulted in statistically significant improvements in diabetes and hypertension outcomes, as well as clinically significant improvements in lipid control. and smoking cessation [7–8].

Clinical pharmacists are specialized medical practitioners who provide direct patient care and holistic treatment. While this practical model has proven itself best in the United States, there are clinical pharmacists around the world who are improving the care of patients of all ages in all areas of emergency and outpatient care. This article discusses training standards, expected skills, and contributions from clinical pharmacists. Clinical pharmacists practice across all healthcare settings and use in-depth knowledge of drugs and medical conditions to manage drug therapy as part of a multidisciplinary team. Clinical pharmacists are responsible for drug treatment and patient outcomes. They are the primary source of scientifically reliable information on the safe, correct and economical use of medicines. Whereas pharmacists may be involved in the management of specific drugs or individual medical conditions the standard of care that ensures that each patient's drugs (prescription, over-the-counter, supplements, or herbal medicines) are individually assessed to determine if they are appropriate whether they are for the patient, effective for the disease, safe for use in concomitant diseases and concomitant therapy, and whether the patient can take them. An individualized care plan defines goals, monitoring and expected outcomes The patient is actively involved in developing the plan with other members of the care team. The impact of conventional medical management provided by clinical pharmacists on an outpatient basis is being studied to identify efficient processes and measure overall patient outcomes. Disease-specific drug management programs have shown a reduction in the incidence of some drug-related problems, including non-adherence, and have reduced some health care costs [9–10].

Clinical pharmacists are pharmacists, physicians who specialize in direct patient care. Although they are expected to follow the steps outlined in the pharmacist's POC, Standards of Practice (SOP) help clinical pharmacists comprehensively assess drug needs and often manage complex and specialized regimens. Documentation requirements are more detailed and, where applicable, should be consistent with billing requirements. The clinical pharmacist can exercise his practice more independently in certain contexts, in particular according to organizational privileges. Clinical pharmacists who have received the appropriate qualifications and certifications should now enjoy hospital privileges such as doctors and providers of excellence. They are required to maintain a valid license, but have additional certification requirements. SOP for the clinical pharmacist also includes educational, research and quality improvement activities [11-12].

Pharmaceutical education varies across the world. In the United States (USA), a pharmacist is eligible for a license after 6 years of training in pharmacy. While not required, many of these graduates already have a Bachelor of Science degree in another field. Pharmacists interested in direct patient care may receive additional training in postgraduate residency programs in Emergency or Outpatient Care. It is a large-scale accredited expertise in clinical care, drug information, administration, teaching methods projects/research. Those interested in specialization can complete their second year of postgraduate study in areas as diverse as any medical specialty (outpatient care, intensive care, infectious diseases, internal medicine, oncology, and many others). Additional

research grants may follow, especially for those interested in an academic or research role. Pharmacists licensed in the United States have received formal training, and many universities are partnering with pharmaceutical schools outside of North America to create clinical pharmacy training opportunities for international students. Additional clinical practice sessions were included in the training programs. Clinical pharmacists may practice under a formal collaborative practice agreement with physicians in their area of practice or under hospital conditions. For example, a pharmacist can change the dose, frequency, or way of taking medications that are covered by a collaborative practice agreement. They may also initiate serum concentration monitoring or other applicable laboratory tests to monitor the effects of therapy. Quality assessments have demonstrated the value of these programs. Hospitals may require people to provide periodic quality assessments or evidence of minimum activity. Pharmacists' laws are governed by the ordinances of state and local hospitals [13-14].

Clinical pharmacists are already part of many medical teams. Most are part of a multidisciplinary emergency or ambulatory care team, but some are in private practice with a wide range of physicians. There are many examples of the influence of clinical pharmacists and this article will highlight some of the recent publications. Since the emphasis is on taking medication, most measures reflect the optimal use of medications and the prevention of adverse events. Widespread use of antihypertensive drugs can cause side effects if the doses are not correctly titrated. The benefits of training, monitoring and intervention by clinical pharmacists have been demonstrated in a prospective randomized trial involving heart failure or hypertensive patients treated in a large public hospital. Patients who received clinical pharmacist intervention had a lower risk of any adverse drug event or medication error, preventable side effects, potential side effects and medication errors compared to control patients treated in the same clinics. Patients with a complicated cardiovascular history took the most drugs and events. The interaction, training and regular communication of pharmacists with the rest of the team improved treatment adherence, patient satisfaction, and reduced the use of medical services and the direct costs of treatment. A systematic review of randomized trials on the impact of a clinical pharmacist on patients with heart failure showed similar benefits with reduced hospitalization rates for all causes and hospitalization rate for heart failure. Other reviews describe additional benefits clinical pharmaceutical monitoring and interventions for various treatment evaluation criteria (blood pressure, lipid profile, weight and glycemic control), a collective care strategy including clinical pharmacists [15–16].

Clinical pharmacists in inpatient emergency teams have been shown to reduce the preventable side effects of drugs. The clinical pharmacist surrounding himself with the intensive care team identified and prevented more drug side effects more effectively than the pharmacists involved in order entry and verification, and avoided potential costs. A review of studies describing the impact of clinical pharmacists on inpatients suggests that adding a clinical pharmacist to the emergency team resulted in improved treatment without any evidence of harm. Teamwork during rounds, patient interviews, outpatient and inpatient coordination, discharge education and follow-up have all improved outcomes. Patients at greatest risk, such as the very old and very young, have been shown to benefit from the presence and input of clinical pharmacists [17].

A clinical pharmacist is trained to work directly with patients in a healthcare system such as hospitals or clinics. Because the clinical pharmacist has detailed knowledge of drugs and their effects, and because the clinical pharmacist has extensive experience with patients, physicians often give clinical pharmacists significant control over prescribing drugs and monitoring patients. Among other things, clinical pharmacists are responsible for selecting the right drugs, monitoring patients,

diagnosing potentially untreated illnesses, consulting with the patient about the effects of drugs, and ensuring patients adhere to prescribed drug regimens. Clinical pharmacists are people who help patients recover from illness or lead healthy lives. The doctor diagnoses and prescribes medications in general terms, but the clinical pharmacist helps make specific decisions. For example, if a patient has an adverse reaction to a particular drug, the clinical pharmacist will recommend alternative treatments. The clinical pharmacist will also help select the best drug combinations for the patient's condition [18].

The clinical pharmacist manages for critical care pharmacist residency program and oversees the resident's progress and interactions with other mentors in our healthcare system. The clinical pharmacist participates in multidisciplinary book club discussions, thematic conferences, and quality assessment meetings. Like other professionals, the clinical pharmacist strives to maintain its role in scientific publishing in the literature, maintain skills, and keep abreast of the growing literature. As a certified critical care pharmacist, a clinical pharmacist must undergo continuing education and maintain certification, and as a licensed pharmacist, a clinical pharmacist must also pursue continuing education. As clinical pharmacy programs around the world are at different stages of development, the need for specialists who specialize in drugs and their optimal use is universal. Clinical pharmacists have supported these training programs and provided training to individuals and groups. Their publications are used by pharmacists around the world to prepare and maintain the certification board. This awareness is expected to continue as more partners are involved and more pharmacists and their multidisciplinary teams recognize the power of clinical pharmacists to improve patient care [19].

The name clinical pharmacy describes the work of pharmacists whose main job is to communicate with other healthcare professionals, to meet, interview, interview and assess patients, to follow up specific pharmacotherapeutic recommendations, to monitor and control a patient's response to pharmacotherapy, and to provide drug information. Clinical pharmacists, mainly working in clinics, hospitals, health insurance funds and emergency services. They provide patient-centered services rather than production-centered services. The clinical pharmacist must know the pharmaceutical sciences, medicine, pharmacology, pharmacotherapy, clinical pharmacology, pharmaceutical care, clinical pharmacy and all pharmacy to be treated with rational pharmacotherapy, which includes the cost of minimum economic conditions for achieve maximum therapeutic effect and ultimately patient health and safety of care. Although the number of pharmaceutical industries is increasing around the world, the approach to life-saving drugs is still inadequate in most parts of the universe. The emerging costs of medical services, limited financial sources, a lack of human potential in the health system, an inept, inefficient and incompetent health sector, a large number of diseases and changes in the technological, social, d emigration, social, political and economic environment. common or different in many countries, countries and regions. Thus, the evolution of the psychological, mental, social, technological, human, political and economic environment has necessitated the transformation and reorganization of health care in the world. Modern therapies are needed at the personal and community level to ensure modern, effective, safe and reliable drug therapy services for patients in extremely difficult situations [20].

Because in parallel with the development of the pharmaceutical infrastructure and the creation of jobs, we are seeing the growing prominence of the pharmaceutical specialties. Most pharmaceutical specialties are clinical pharmacists. For many years, after a successful, helpful and helpful demonstration of clinical pharmacy services, planning, schema and design in Western countries such as Europe, Canada, UK, USA, Japan, Australia, South Africa and New Zealand, and still part of the

universe continued to adapt to changing pharmaceutical practices and services. Along with the adoption of these new projects, these regions and states also require transformation and modification of the existing curriculum for pharmaceutical higher education in order to provide the necessary teaching, education, training and training so that future specialists and practitioners in pharmaceutical departments have the required evidence, knowledge, knowledge and knowledge in clinical skills. The impact of these changes was strong enough that even countries that lacked or lacked the development of appropriate health infrastructure and types of training equipment were eager to prepare future pharmacists trained in these intentions [92–94]. Bachelor's degrees in Pharmacy are multi-certified, such as Bachelor of Pharmacy, Master of Pharmacy (Pharm M), and Doctor of Pharmacy (Pharm D) offered to developing countries. In Western countries such as the European Union, Canada, Australia, USA, Japan, South Africa, New Zealand and many developed countries, the profession of a clinical pharmacist is considered to be successful. Further education programs in pharmaceuticals in developing countries differ significantly from similar degree programs offered in Western countries such as the European Union, United Kingdom, Canada, USA, Japan, Australia, Iceland and New Zealand. The main reasons for the differences in Western countries are differences in need, requirements for specialists, pharmaceutical practice and health care system [21-22].

A hospital pharmacy is a specialized area of a pharmacy that is integrated with a medical center. These include centers such as a hospital, polyclinic, narcological hospital, poison control center, and drug information center in a residential facility. This occupation includes the selection, preparation, storage, preparation and distribution of drugs to patients in a medical environment. Another important area is counseling patients and other healthcare professionals on the safe and effective use of drugs. The main task of a hospital pharmacy is to manage the use of drugs in hospitals and other health centers. The goals include the selection, prescribing, purchasing, delivery, administration and validation of drugs to optimize patient outcomes. When using any medication, it is important to ensure that the correct patient, dose, route of administration, timing, medication, information, and documentation are followed. Hospital pharmacists are responsible for preparing many pharmaceutical products for patient use. Some of these formulations must be sterile, for example when administered with total parenteral nutrition (PN) or for other drugs administered intravenously, such as certain antibiotics and chemotherapeutic agents. This process is complex and requires high qualifications on the part of pharmacists in producing quality products in addition to properly equipped premises [23].

In many cases, the clinical pharmacist works directly with patients to help them understand the drugs they are taking and to encourage them to take the drugs as directed; The Clinical Pharmacist manages patient lines, clinical areas, and therapeutic programs; Promotes pharmacy services, direct patient care programs, drug use systems in designated wards and areas of care to ensure that drug use activities meet patient needs, evidence-based best practices and regulatory standards. Develops and implements control measures and restriction / monitoring programs; The clinical pharmacist monitors and evaluates the prescribed pharmacy programs in terms of operational, quality and financial efficiency and regularly compares himself with the best local and national practices; The clinical pharmacist proactively identifies practice issues that need to be assessed and promotes clinical research projects, quality improvement initiatives, or the training of healthcare professionals as needed to advance the practice; Develops and oversees policies and procedures for drug procurement, drug use, drug distribution and drug control; The clinical pharmacist ensures that the pharmacy is an integral part of the health care delivery system and contributes to the improvement

and expansion of pharmacy services / programs; Provides direct patient care and clinical practice, including decentralized and service-oriented programs; The clinical pharmacist is well versed in decentralized pharmacy services and clinical pharmacy programs; Works as an active member of a multidisciplinary team and collaborates with healthcare providers in decentralized patient care areas to provide patient-centered care; Identifies high-risk patients and implements measures to improve quality and safety; Makes appropriate, evidence-based, patient-centered drug recommendations; The clinical pharmacist is involved in the management of emergency medical care; Providing a review of medication intake at discharge, approval and counseling as needed; Provides pharmaceutical services throughout the medical center; Owns hospital IT systems and drug ordering systems; Provides accurate, safe, timely and appropriate drug therapy in accordance with the age and needs of the patient; The clinical pharmacist performs critical patient monitoring and reviews the patient profile / chart to identify, prevent, or mitigate drug-related problems, wrong drug or dose selection, sub-therapeutic dose, overdose, drug adverse reactions, drug interactions, drug missing, no indication to treatment, the use of drugs without indications and treatment failure; The clinical pharmacist communicates effectively and appropriately with healthcare providers and caregivers (doctors, nurses, etc.), and ensures the continuity of pharmaceutical care between shifts and between staff; The clinical pharmacist is actively involved in drug management and restriction programs; Participate in the work of pharmacies and distribution of medicines; Clinical Pharmacist maintains competence and actively participates in operations programs, central pharmacies, subsidiary pharmacies and specialty pharmacy areas, as required by the work assignment; Facilitates the process of purchasing, ordering and dispensing specialized drugs, including but not limited to chemotherapy, parenteral nutrition, controlled substances, etc., as appropriate [24-25].

Pharmaceutical care and clinical pharmacology are a professional discipline that combines fundamental pharmacology and clinical medicine. The Clinical Pharmacist offers invaluable support in developing the final prescription with improved patient care and increased safety. Its development began in the early 1950s, largely thanks to the efforts of Harry Gold. The introduction of pharmacists into hospital services began as early as 1957. Pharmacotherapy became more and more complex. The clinical pharmacist has pioneered a new role for pharmacists in hospital services. The role of clinical pharmacists underwent significant changes from the 1960s to the 1990s as their involvement in direct patient care improved. In the early 1970s, federal funding helped significantly expand the clinical pharmacy teaching staff at pharmacy colleges. Pharmaceutical Education has discussed the place of clinical pharmacy in pharmaceutical education. With clinical pharmacists overwhelmed with patient numbers and the emergence of new drugs, doctors are increasingly turning to pharmacists for drug information, especially in institutions [36-37]. The clinical pharmacist often takes a slightly different approach to drug use and can provide valuable additional information, such as interactions, in the clinician's decision-making process for potential drug changes and monitoring. The concept of pharmaceutical care emphasizes the responsibility of pharmacists to seek the best possible outcomes for patients from a therapeutic regimen. They possess an in-depth knowledge of medicines that is combined with a fundamental understanding of the biomedical, pharmaceutical, socio-behavioral and clinical sciences. Clinical pharmacists follow evidence-based treatment guidelines, advancing science, the latest technology, and appropriate legal, ethical, social, cultural, economic and professional prescriptions to achieve their desired therapeutic goals. Consistently, clinical pharmacists take responsibility and accountability for the management of drug therapy in a direct patient care setting, whether they practice on their own, in consultation, or in collaboration with other healthcare professionals. Their functions include comprehensive drug management (ie,

prescribing, monitoring and adjusting drugs), non-drug counseling, and coordination of care. Interdisciplinary collaboration enables pharmacists to provide direct patient care or telecommuting in a variety of clinical settings, including disease management, primary care, or specialty care. A clinical pharmacist can take responsibility for chronic or acute diseases related to the endocrine, cardiovascular, respiratory, gastrointestinal, or other systems. Clinical pharmacist researchers generate, disseminate and apply new knowledge to drive improvement. In the healthcare system, clinical pharmacists are experts in the therapeutic use of drugs. A clinical pharmacist usually provides patients and healthcare professionals with drug treatment reviews and approvals. Clinical pharmacists are the primary source of scientifically reliable / scientifically logical information and advice on the safe, appropriate and economical use of medicines. They obtain a medical history and medication history, check for medication errors including prescribing, dosing and administering errors, identify drug interactions, track adverse reactions, suggest individual dosing regimen, advise patients, etc. They also provide information on medication use. and medical devices such as an inhaler, insulin pen, eye drops, nasal sprays, etc. [26-27].

There are both ethical and practical imperatives to addressing health inequalities associated with chronic disease management for people with social difficulties, and existing programs often do not adequately meet the needs of these people. This leads to low participation rates, suboptimal chronic disease management and higher utilization of health services. Unlike acute conditions, chronic conditions require ongoing care and treatment outside of health care settings, in the community or in primary health care settings in terms of medication use, lifestyle management and behavior change in health. Typically, this is a multi-pronged intervention that includes a review of drug therapy, patient education for treatment, monitoring of medication, immunization, self-care, and support. disease, and / or prescribing authority. Patients who take a lot of medications due to chronic disease are at high risk for drug duplication, interactions, or ADRS, which can lead to longer hospital stays and higher costs. To improve the safety and efficacy of therapeutic agents, these patients must meet special needs for appropriate drug use. Research has shown that integrating pharmacists into outpatient clinics can improve chronic disease management and optimal medication use. Additionally, involving a pharmacist in patient care can help reduce inappropriate medication use, especially in the elderly. The study shows that the proportion of patients receiving the wrong drug drops considerably after review and optimization of the drug by a team including a pharmacist. Compared to conventional treatment, pharmacist-directed care was associated with a similar frequency or frequency of office visits, emergency room or emergency department visits, as well as hospitalizations and adherence, increases in the amount or dose of drugs received and improvements in study glycemic choices, blood pressure, and lipid target achievement. Another recent study shows that a telemedicine-based chronic disease management program involving clinical pharmacists resulted in statistically significant improvements in diabetes and hypertension outcomes as well as clinically significant improvements in lipid control and withdrawal smoking [28-29].

The practice of the pharmacy has changed a lot in recent years. Professionals can directly contribute to patient care to reduce drug-related deaths, promote health and prevent disease. Medical organizations around the world are under tremendous pressure from the growing demand for patients. Unfortunately, cure is not always possible, especially in this era of chronic disease, and the role of doctors is limited to controlling and relieving symptoms. The growing number of patients with chronic conditions is associated with high morbidity, health care costs and the burden on physicians. The clinical pharmacy took over the medical care, which the doctors partly refused. Overwhelmed by the number of patients and the emergence of new drugs, doctors are increasingly

turning to pharmacists for information about drugs, especially in institutions. After the pharmacists were transferred to the counting and dispensing of drugs, they carried out institutional reviews of drug use and acted as consultants for all types of healthcare facilities. In addition, when clinical pharmacists are active members of the healthcare team, they increase efficiency by: Providing the necessary feedback on drug use and dosage. Work with patients to resolve medication problems and improve adherence [30-31].

Clinical care team in the form of health professionals - physicians, advanced practice registered nurses, other registered nurses, medical assistants, clinical pharmacists and other health professionals - with the training and skills to provide coordinated care high quality, specific to the patient's clinical condition ... needs and circumstances. The clinical pharmacist also provides support for group practice. Although the composition of the teams may vary, the responsibility and authority for specific aspects of the treatment rests best with the person best suited to the task. The effectiveness of a team of clinical pharmacists depends on a culture of trust, shared goals, effective communication and mutual respect. The best interests of the patient should be the driving force behind teamwork. The clinical pharmacist does not need to be in the same place as a member of the medical team and therefore the large group of health professionals certainly includes general practitioners in hospitals, clinics and stores. Although this is only an example, patients benefit from collective management through better BP control, and a large proportion of patients achieved controlled BP when the pharmacist was part of the clinic. the team. The composition of dynamic clinical teams is reflected in the multidisciplinary nature of large professional organizations such as the Society for Resuscitation, the Society for Hospital Medicine, the Nutrition Society, and the Society for Neurocritical Physicians. Most of these organizations include clinical pharmacists in leadership positions, including the chair [32-33]

Pharmacists in the Netherlands have significantly reduced prescribing errors and patient-related harm while on the ward compared to basic central pharmacy services. Children's pharmacists in China have shown significant reductions in adverse drug reactions, length of hospital stay, and drug costs compared to a control group of similar patients without a pharmacist. While these are just a few examples, pharmacists around the world, including in Chile, offer patient-centered services. Clinical pharmacy is gaining popularity, and some universities offer training programs for pharmacists to become specialists in clinical pharmacy and pharmaceutical services, which is more focused on patients and medical personnel and differs from the academic degree of the Master of Pharmaceutical Sciences or PhD in Pharmacology [34-35].

The statements have been developed to define the core competencies of pharmacists in a number of countries, as well as the International Pharmaceutical Federation. The Pharmacist Training Proposal for Basic Pharmacist Education and Skills includes provisions that are applicable to clinical pharmacists, in particular for documenting patient information and drug therapy management and follow-up. The skills of clinical pharmacists or advanced and specialized practitioners were also described and summarized. Although in many countries the clinical pharmacist has not compiled a uniform list of competencies for medical practitioners, the statement describes a general framework and training criteria for hospital pharmacists who have completed residency training, which form the basis of the knowledge and skills expected from the medical practitioner and also for clinical pharmacists. ... Intensive care pharmacists have developed a peer review process and career program that has resulted in the accreditation of an increasing number of medical practitioners. Referral support, interviews, thematic discussions and peer reviews have been incorporated into this rigorous process that serves as a model for other specialized practices [19-20].

The health systems of many other countries have developed similar claims of competence for pharmacists. As a critical care pharmacy specialist, it is difficult to describe a typical day, but usually busy with the elements of a pharmacist's support process during the day. It is believed that the clinical pharmacist will be responsible for all aspects of the administration of the drug. Every day, the clinical pharmacist assesses and evaluates new patients and updates the progress of previous patients, identifies drug-related issues and potential problems, develops a problem list and treatment plan for optimal dosage based on the renal and hepatic function, potential drug interactions and serum concentration. The clinical pharmacist joins the multidisciplinary rounds with the intensive care team and applies the treatment plan by teaching the medical residents the correct order of entry or by entering the orders themselves according to a collaborative practice agreement and by them. documenting in an electronic health record. A major contribution to medication management is identifying therapies that are no longer needed, reducing the cost and risk of adverse events, and supporting antimicrobial stewardship programs with infectious disease physicians and pharmacists. The clinical pharmacist also supervises the performance of quality measures such as the appropriate prevention of venous thromboembolism, the appropriate use of drugs to prevent stress gastritis, the addition of aspirin to increase the levels of troponin associated with l coronary ischemia, and discussing the need for central tubing and urinary catheters. The clinical pharmacist educates the team on drug-related topics and related literature through tours and didactic discussions. A clinical pharmacist is always available for emergencies and resuscitation, and to answer questions related to mediation [21-22].

For each new patient, a member of the pharmacy team compiles a medication history from electronic records, family, patient, local doctors or pharmacies and documents it in the EMR. The clinical pharmacist will then cross-check this list to determine medication-related reasons for hospitalization, such as non-adherence or overdose, and advise on which medications to choose to avoid withdrawal reactions or other adverse events. While the clinical pharmacist has a more limited role in verifying drug orders in the EMR and has little role in the actual distribution of drugs, the clinical pharmacist serves as a liaison with technicians and pharmacists specializing in parenteral products and drugs. Distribution systems to ensure medications are present when needed. Nurses have a formidable task of prescribing drugs, and the clinical pharmacist facilitates this process by providing information on intravenous injection compatibility and teaching unknown treatments [23-24].

Other aspects of my role include developing quality assessment tools and data evaluation. EMR is made more efficient by properly designing control systems that are effective and make it easier to make quality measurements and select preferred treatments. Clinical pharmacists make important contributions to these drug therapy control and surveillance systems. They also report the side effects of medications. Many side effects or incidents are related to systemic problems, and the clinical pharmacist regularly provides advice on possible process improvements when programming intravenous pumps, drug safety systems, or other processes [25].

Hospital pharmacists are drug experts who work in multidisciplinary medical teams to manage drug use in hospitals. Hospital clinical pharmacists are integrated into services and departments and provide clinical pharmacy services to patients at the bedside, with each clinical pharmacist (or team) being responsible for patient care in a specific medical ward or department. Hospital pharmacists provide clinical pharmacy services to patients hospitalized at the bedside as well as in other clinical areas such as emergency departments and outpatient clinics, as well as physicians and nurses. Most of them work in hospitals, however, innovations in the practice of hospital pharmacy have led pharmacists to work in community health services, nursing homes, rehabilitation centers and medical

clinics. general. Roles may vary depending on the organization and clinical needs of the hospital pharmacy. Most hospital pharmacists provide clinical services in their area of specialization; however, they can apply their skills to other roles including pharmacy managers, purchasing managers, hospital pharmacy consultants. Educational roles are also prevalent, such as giving lectures to pre-registered trainees, making presentations to other medical staff, or providing educational support to pharmacy students [26].

Clinical pharmacists play a key role in drug delivery and patient health monitoring in various healthcare settings. They dispense prescribed medicines to patients and help doctors and other healthcare professionals with medicines. Their responsibilities include helping diagnose, selecting appropriate drugs, monitoring patients' health, checking for side effects of drugs, etc., making appropriate vaccinations, etc. Since these specialists are experts in the clinical effects and composition of drugs, including their chemical, biological and physical properties, they protect the health of the population, ensuring the purity of drugs and the correct dosage of drugs. They use special protective equipment such as masks, gloves, etc. when handling sterile or potentially hazardous pharmaceuticals. Clinical pharmacists work in a variety of environments such as hospitals, clinics, nursing homes, community health centers, pharmacies, pharmacies, etc. They work full time. They may need to work evenings, nights, weekends and holidays [27].

The European Association of Clinical Pharmacy defines that as the health specialty that characterizes the activities of clinical pharmacists and the provision of health services, clinical pharmacists promote and develop rational and appropriate pharmacotherapy, the rational use of pharmaceutical manufacturing and medical devices. Although the American College of Clinical Pharmacy abbreviated it describes and reports that clinical pharmacy is a problem area of modern pharmacy with the knowledge, evidence and practical skills of rational drug therapy using drugs. The practice of clinical pharmacy includes knowledge of pharmacotherapy, pharmaceutical care and first aid; it combines leadership in health care with specific therapeutic knowledge, understanding, cognition, learned habits and assessment to ensure rational and optimal treatment outcomes for patients. Pharmaceutical care and clinical pharmacy are closely related concepts, although there are differences between professional development structures that determine specificity. For example, the British Clinical Pharmacy Association states that clinical pharmacy includes the theoretical knowledge and understanding, practical skills, values and attitudes needed by pharmacists to promote healthcare and pharmaceutical services to individual patients and populations [28].

Conclusions

Clinical pharmacists are people who help patients recover from illness or lead healthy lives. The doctor diagnoses and prescribes medications in general terms, but the clinical pharmacist helps make specific decisions. For example, if a patient has an adverse reaction to a particular drug, the clinical pharmacist will recommend alternative treatments. The clinical pharmacist will also help select the best drug combinations for the patient's condition. A clinical pharmacist is trained to work directly with patients in a healthcare system such as hospitals or clinics. Because the clinical pharmacist has detailed knowledge of drugs and their effects, and because the clinical pharmacist has extensive experience with patients, physicians often give clinical pharmacists significant control over prescribing drugs and monitoring patients. Among other things, clinical pharmacists are responsible for selecting the right drugs, monitoring patients, diagnosing potentially untreated illnesses, consulting with the patient about the effects of drugs, and ensuring patients adhere to prescribed drug regimens.

REFERENCES

1. Sulashvili N., Beglaryan M. Shashiashvili G. Medical Professional's job Satisfaction and pharmaceutical organization issues viewed by Drug Dispensers in Georgia// ISSN 1987-863X, 8th Eurasian Multidisciplinary Forum, EMF 2018, 6-7 September. Tbilisi, Georgia. pp.42-55.
2. National Matching Services. Summary results of the match for positions beginning in 2014. https://www.natmatch.com/ashprmp/ stats/2014applstats.html. Accessed March 24, 2014
3. Hassell K. Centre for Pharmacy Workforce Studies (CPWS) briefing paper: GPhC register analysis2011.http://www.pharmacy.regulation.org/sites/default/files/Analysis%20of%20GPhC%20Pharmacist%20Register%202011.pdf. Accessed April 9, 2014.
4. Pharmacist's professional features and work gratification/ N. Sulashvili; M.Beglaryan // Black sea scientific journal of academic research multidiscipline journal. (Medicine, Pharmacy sciences) Volume 29. March-April 2016. Tbilisi, Georgia, p.62-68.
5. Pharmacists' professional features, viewed by the customer's (customer's) eyes in Georgia/ N. Sulashvili, M. Beglaryan // Scientific-Practical Journal. Experimental and Clinical Medicine, №4, 2017. Tbilisi, Georgia, p. 22-25.
6. Krass I. Ways to boost pharmacy practice research. The Pharmaceutical Journal 2015;(2). Pp-15-41.
7. ParthasarathiG. A Textbook of Clinical Pharmacy Practice: Essential Concepts and Skills // Universities Press India Private Limited; 2 edition (January 18, 2017); pp. 26-37.
8. Franklin B. D.& van Mil J. W., Defining clinical pharmacy and pharmaceutical care // Pharm World Science 2005;27(3): p. 137-144.
9. Sulashvili, N., Beglaryan M. Characteristics of pharmacist activity, viewed by the customer's//
   International Science and Innovation Festival 2017. Conf.-es "Healthy Lifestyle-Scientific Evidence and Controversial issues" and "Innovation in Medicine" Tbilisi State Medical University. September 2017. Tbilisi, Georgia. pp. 30-31.
10. N. Sulashvili, M. Beglaryan; THE FEATURES OF THE ROLE, INNOVATIONS, OCCUPATIONAL AND EDUCATIONAL PERFECTION VISTAS OF PHARMACISTS' PROFESSION IN THE SCOPE OF THE DEVELOPMENT OF PHARMACEUTICAL CARE DIRECTION IN GEORGIA. ISSN 2521-3261 (Online); ISSN 2521-3253 (Print); DOI 10.37057/2521-3261; https://journalofresearch.eu/index.php/jreu; (EJR) European Journal of Research, Volume 7, Issue 1, 2022; Published 19-01-2022. Pages 14-25.
11. N. Sulashvili, M. Beglaryan, J. Cheishvili, I. Zarnadze, Sh. Zarnadze, T. Tsintsadze; CURRENT SCIENTIFIC RESEARCH DISCOVERY OUTCOMES OF HIGHER PHARMACY EDUCATIONAL PERSPECTIVES AROUND ON MULTIPURPOSE PHARMACIST' OCCUPATION TOWARDS MEDICINE, PHARMACEUTICS AND PUBLIC HEALTH;УДК [37:61]:001.895(063); MATERIALS OF THE ALL-UKRAINIAN SCIENTIFIC AND PRACTICAL CONFERENCE- "INNOVATIONS IN MEDICAL EDUCATION: PERSPECTIVES, CHALLENGES AND OPPORTUNITIES" WITH INTERNATIONAL PARTICIPATION; MINISTRY OF HEALTH OF UKRAINE ZAPORIZHZHYA STATE MEDICAL UNIVERSITY, 21 of January, 2022. ZAPORIZHZHYA, UKRAINE-2022; Pp:194-212.

12. N. Sulashvili, A. Aznauryan, A. T-Markosyan, N. Gorgaslidze, S. Kocharyan, I. Zarnadze, B. Yenokyan, T. Chikviladze, N. Chichoyan, L. Gabunia, Sh. Zarnadze, M. Beglaryan; MODERN SCIENTIFIC DISCUSSION OF SPECIFICITES OF THE ROLE, ACHIEVEMENTS, INNOVATIONS, PROFESSIONAL AND ENHANCEMENT PROSPECTS OF PHARMACISTS IN THE CONTEXT OF THE DEVELOPMENT OF HEALTH CARE SECTOR GLOBALLY.ISSN 1512-0392; E-ISSN 2667-9736; SCIENTIFIC-PRACTICAL JOURNAL of Experimental and Clinical Medicine №5-6; 9 of October, 2021, Tbilisi-Georgia. Pp: 38-42.
13. Thomas R. Brown; By Thomas R. Brown - Handbook of Institutional Pharmacy Practice//4th (fourth) Edition; American Society of Health-System Pharmacists (December 1, 2006); pp. 65-71.
14. Ashley W. Ells (Author), Justin Sherman; Community and Clinical Pharmacy Services // A step by step approach.; McGraw-Hill Education/Medical; 1 edition (April 30, 2013); pp. 45-156.
15. Kenneth R. Baker; Medication Safety: Dispensing Drugs Without Error // Delmar Cengage Learning; 1 edition (May 10, 2012); pp. 12-35.
16. Moore T.J., Furberg C.D., Mattison D.R., Cohen M. R. Completeness of serious adverse drug event reports received by the US Food and Drug Administration in 2014. // Pharmacoepidemiology, Drug Safety. 2016; 25(6): pp. 713–718;
17. Robert P. Navarro; Managed Care Pharmacy Practice 2nd Edition // Jones & Bartlett Learning; 2 edition (December 25, 2008); pp. 336-389.
18. World Health Organization; Quality Assurance of Pharmaceuticals 2017: WHO Guidelines, Good Practices, Related Regulatory Guidance and GXPs Training Materials // World Health Organization; 2017 edition (January 11, 2018); pp. 51-59.
19. Jeri J. Sias and Susana V. James; Spanish for the pharmacy professional (English and French Edition) // American Pharmacists Association; 1st edition (January 30, 2009); pp. 35-79.
20. N. Sulashvili; Peculiarities of professional and career improvement strategy for pharmacists' republic of Armenia ministry of education and science; Yerevan state medical university; Dissertation; Dissertation for the Scientific Degree of PhD in Pharmaceutical Sciences; On specialty 15.00.01 – Pharmacy; YEREVAN – 2019; Pp 1-175;
21. N. Sulashvili, M. Beglaryan, N. Alavidze, L. Gabunia, I. Pkhakadze, T. Okropiridze, M. Sulashvili, G. Pkhakadze; Legal and regulatory scope, and identify the main challenges and opportunities of Georgian pharmacists.REPUBLIC OF ARMENIA ISSN 1829-040X, ORCID: 0000-0001-9263-6791, BULLETIN OF THE MEDICAL INSTITUTE AFTER MEHRABYAN, VOL. 9 TOM, YEREVAN 2020, Pp 88-104.
22. Graf J, von den Driesch A, Koch K-C, Janssens U. Identification and characterization of errors and incidents in a medical intensive care unit. Acta Anaesthesiol Scand 2005;49(7):930—9.
23. Kane-Gill SL, Jacobi J, Rothschild JM. Adverse drug events in intensive care units: risk factors, impact, and the role of team care. Crit Care Med 2010;38(6 Suppl.):S83—9.
24. Société franc¸aise d'anesthésie-réanimation et Société franc¸aise de pharmacie clinique. Préconisations 2020 Prévention des erreurs médicamenteuses en A-R en période de crise sanitaire aiguë; 2020 https://www.sfpc. eu/erreurs-medicamenteuses-et-crise-sanitaire-aigue1er-retour-dexperience-covid-19/.

25. Ricard J-D, Montravers P, Langeron O. Préconisations ventilation —– Gestion du circuit d'un ventilateur de réanimation; 2020 https://www.srlf. org/wp-content/uploads/2020/03/Ventilation gestiondes-circuits rea 20032020 valide.pdf.
26. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers Y-M. Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. Drug Saf 2018;41(10):919—31.
27. García-Gil M, Velayos-Amo C. Hospital pharmacist experience in the intensive care unit: plan COVID. Farm Hosp 2020;44(7):32—5.
28. Shane P. Desselle, David P. Zgarrick, Greg Alston; Pharmacy Management: Essentials for All Practice Settings // Fourth Edition; 2016,pp. 329-347.
29. Sulashvili N. The Features of Professional Career Improvement Strategy and Job Satisfaction among pharmacists // Business-Engineering Journal. - Business Engineering in Pharmacy. №2, 2014. Tbilisi, Georgia, pp. 195-199.
30. Sulashvili N., Kvizhinadze N., Maisuradze I. Pharmacist professional features in Georgia. // Conference of young scientists. Thesis collection. Georgian National Academy of Sciences. 18-19 May 2015. Tbilisi, Georgia, pp. 81-82.
31. Sulashvili N., M Beglaryan. Pharmacist mission gratification and profession improvement strategy. // Black sea scientific journal of academic research conference newsletter. (Medicine, Pharmacy sciences). Volume 26. November 2015. Tbilisi, Georgia, pp. 10-12.
32. Sulashvili, N., Beglaryan M. Pharmacist's professional features and work gratification. // Black sea scientific journal of academic research multidiscipline journal. (Medicine, Pharmacy sciences) Volume 29. March-April 2016. Tbilisi, Georgia, pp. 62-68.
33. Sulashvili, N., Beglaryan M. Pharmacists' professional features, viewed by the customer's (customer's) eyes in Georgia. // Experimental and Clinical Medicine, Scientific-Practical Journal, №4, 2017. Tbilisi, Georgia, pp. 22-25.
34. Sulashvili, N. Peculiarities of professional for pharmacists, viewed by the health-care specialists in Georgia// Experimental and Clinical Medicine, Scientific-Practical Journal. №4 2017. Tbilisi, Georgia, pp.47-51.
35. Sulashvili, N., Beglaryan M. Professional features for employed pharmacy faculty students' in Georgia. // The New Armenian Medical Journal Supplement. YSMU Science Week 2017 Conference. November 27-December 1, Vol.11, №3, 2017, Yerevan, Armenia, p. 40.
36. Sulashvili, N., Beglaryan M. Vocational peculiarities of young pharmacist professionals// International scientific journal Intellectual. №35, 2018. Tbilisi, Georgia. pp. 96-104.
37. Sulashvili, N., Beglaryan M., Gogashvili M., Matoshvili M. Occupational particularities and strategy of Pharmacy faculty students. // Experimental and Clinical Medicine, Scientific-Practical Journal. №3, 2018. Tbilisi, Georgia. pp. 15-24.

THE SCIENTIFIC STUDY OF THE PECULIARITIES OF UROTENSIN-2 RECEPTOR ANTAGONIST: PHARMACOLOGICAL EFFECTS OF PALOSURAN ON PLASMA RENIN CONCENTRATION AND BLOOD PRESSURE IN LABORATORY RATS WITH RENO-VASCULAR HYPERTENSION

Albina Kajaia[1], Luiza Gabunia[2], Nataliia Filipets[3], Ketevan Ghambashidze[4], Levan Ratiani[5], Manana Gongadze[6], Nodar Sulashvili[7]

[1]MD, PhD Student of Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia;
[2]MD, PhD, Doctor of Medical Sciences, Professor, Director of the Scientific Research-Skills Center at Tbilisi State Medical University, Professor of the Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia;
[3]MD, PhD, Doctor of Medical Sciences, Professor of the Department of Pharmacology, Bukovinian State Medical University, Chernivtsi, Ukraine;
[4]MD, PhD, Doctor of Medical Sciences, Professor of Department of Pathological Physiology at Tbilisi State Medical University, Tbilisi, Georgia;
[5]MD, PhD, Doctor of Medical Sciences, Professor, General Director of the First University Clinic of Tbilisi State Medical University, Head of the Department of Emergency Medicine, Reanimatology and Anesthesiology at Tbilisi State Medical University; Tbilisi, Georgia;
[6]MD, PhD, Doctor of Medical Sciences, Assistant Professor of Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia,
[7]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Invited Professor-Lecturer of Scientific Research-Skills Center of Tbilisi State Medical University, Tbilisi, Georgia; Associate Professor of Pharmacology and Pharmacotherapy of International Medical School at Alte University, Tbilisi, Georgia;

ABSTRACT

Our aim is to investigate the effect of palosuran, an antagonist of urotensin-2 receptors, on blood pressure and plasma rennin concentration in laboratory rats with renovascular hypertension (2 kidneys + 1 clamp). Blood pressure was measured using the non-invasive tail-cuff method. Studies have shown that palosuran (10 mg/kg/day for 4 weeks) has an antihypertensive effect in test rats. The blood pressure also decreased after administration of the NO synthase inhibitor L-NAME (10 mg/kg, single dose), presumably due to its antagonistic properties against urotensin-2 receptors. In hypertensive rats, the renin concentration in the blood plasma increased progressively compared to the data from healthy rats. Renin concentrations were significantly lower in hypertensive rats treated with palosuran than in hypertensive rats that received no treatment. The decrease in renin concentration persisted after administration of L-NAME, with the exception of late initiation of treatment. From this it can be concluded that in experimental rats with renovascular hypertension the vasodilation effect of palosuran outweighs the inhibitory effect of L-NAME on NO production and the endothelium-independent vasoconstrictive effect induced by urotensin, especially in the early stages and at the beginning of hypertension treatment. The study was carried out on male Wistar rats weighing 200-250 g after an adaptation period of at least 1 week. All rats were housed in a laboratory with eight people per cage under controlled climatic conditions with a 12-hour light-dark cycle and free access to regularly pelleted rat food and drinking water. The protocol used in this study for the use of rats as an animal model for the study was monitored and approved by the Ethics Committee on Animal Welfare and Use of the Tbilisi State Medical University (N39 - 08/17/2019). For experimental modeling of hypertension, we used the Reno-vascular (the two-kidney, one-clip -

2K1C) H. Goldblatt model. Under general anesthesia (Nembutal - 50 mg/kg), after separation of the renal artery from the vein and nerve, the silver clip (0.2 mm internal diameter) was placed on the left renal artery close to the aorta. The experimental animals were divided into 3 groups: Group I - healthy, intact rats; Group II - hypertensive rats; Group III - hypertensive rats, subjected to treatment with palosuran, started after 4 weeks of disease modeling; Group IV - hypertensive rats, subjected to treatment with palosuran, started after 8 weeks of disease modeling. In the group's II and III rats, NO-synthase inhibitor - L-NAME (10 mg/kg, single dose) was administered intraperitoneally also after the completion of the treatment with palosuran. Systemic arterial pressure (systolic pressure, diastolic pressure) was measured once a week for 12 weeks using arterial pressure measurement system " Systole " (non-invasive tail-cuff method for BP measurement). The mean arterial pressure was calculated. Plasma renin concentration was determined using ELISA (HumaStar HS).
All statistical tests were conducted using IBM SPSS Statistics. Differences between control and treated animals were determined by using the Independent-Samples T-test. The criterion for significance was set to $P < 0.05$.
Palosuran was injected intraperitoneally with the dose of 10 mg/kg, daily, for 4 weeks. Palosuran could represent a new therapeutic option for people with essential hypertension. Based on the study results Palosuran significantly reduced PR compared to untreated hypertensive rats that persisted with L-NAME except for late initiation of treatment. Palosuran may represent a new treatment option for people with essential hypertension. Palosuran reduced serum Na^+ concentration and increased K^+ concentration in hypertensive rats. Concentrations of Na^+ and K^+ were maintained within normal limits even after administration of L-NAME, except for late initiation of treatment. From the results of the experiments, it can be concluded that Palosuran exhibits an antihypertensive effect in healthy and hypertensive rats. The vasodilatory effect of palosuran is superior to the inhibitory effect of L-NAME on NO and the endothelial-independent vasoconstrictor effect induced by urotensin, particularly in the early stages of hypertension. With stable arterial hypertension, PR gradually increases from the norm.
Keywords: Urotensin-II receptors, antagonist**,** renin, palosuran, L-NAME, renovascular hypertension.

Introduction

It has been known that the urotensin system plays an important role in the pathophysiology of high blood pressure. Urotensin II, as the strongest known vasoconstrictor in mammals [1,2], is activated in high blood pressure. Plasma urotensin II was increased in hypertensive patients compared to normal blood pressure controls and was directly related to systolic blood pressure. These data increase the likelihood that Urotensin II (U-II) could play an etiological role in hypertension and its complications [3,4]. High blood pressure is a serious condition that significantly increases your risk of heart, brain, kidney, and other diseases. Today, high blood pressure is considered to be the most common cause of cardiovascular diseases worldwide. An estimated 1.13 billion people worldwide have high blood pressure, most (two-thirds) of whom live in low- and middle-income countries [5,6]. Despite the effectiveness of currently available antihypertensive drugs, there is always a need for new treatment strategies that are more effective in certain groups of hypertensive patients [7,8].
U - II is a cyclic oligopeptide with vasoactive potential. By activating the urotensin II receptor (UTR), U-II could influence different signaling pathways depending on the cell and vascular compartment in which the receptor is located [9,10]. The interaction between U-II and UT leads to the activation of phospholipase C and the release of inositol (1,4,5) triphosphate [Ins (1,4,5) P3].

Interact with Ins (1,4,5) P3a receptor located in the endoplasmic / sarcoplasmic reticulum for the release of Ca^{2+} from intracellular deposits, leading totissue-dependent reaction [11,12,13]. In the cardiovascular system, yesthe receptor is located in the cardiomyocytes, increasedContractility is expected. In the vascular system,Constrictor and expander responses were re-recorded.the receptor is located on a vascular or smooth muscle cellEndothelium or endothelial activationNitric oxide synthase Ca2-dependent increaseNitric oxide, which penetrates the blood vessels gently [14,15]. Vasodilation muscle. In contrast to most transport moleculesthe binding of U-II to its receptor is essentially irreversible;this has been reported for recombinants and native UT [16,17]. This restrictive irreversibility is probably related toin the presence of a highly conserved cyclic hexapeptideBasic[18]. The irreversibility of the link has important consequencesfor regulating receiver-controlled signals. Under "normal"Under certain conditions it is likely that the receptor peptide systemfunctionally noiseless[19,20,21].

U-II has been shown to act as a vasodilator: this effect was endothelial-dependent, suggesting that vasodilation is mediated via UTR on the endothelium, while vasoconstriction is mediated via UTR on smooth muscle cells. Activation of the endothelial UTR leads to relaxation via NO formation, while activation of UTR on vascular smooth muscle cells leads to contraction via RhoA/Rho kinase activation [22,23,24].

U-II also plays a role in the regulation of body fluids in lower vertebrates, and this is now being found to extend to mammals as well. The kidneys appear to be the main source of U-II synthesis in mammals. U-II is found in both the proximal tubules and the collecting ducts. UTR is mainly localized in the renal medulla with the greatest expression in the collecting ducts of the internal medulla [25,26].

The goals of antihypertensive therapy are to prevent the occurrence / progression / recurrence of cardiovascular disease associated with persistent hypertension, reduce mortality, and help hypertensive patients lead healthy normal lives [27]. Prescribing antihypertensive drugs to achieve the recommended blood pressure goal remains the most important step in the management of high blood pressure patients [28]. Drugs that target blood pressure must be well tolerated, affordable, and easy to take to promote long-term persistence [29,30].

Administration of palosuran to rats that received streptozotocin improved survival, increased insulin levels and decreased the progression of kidney damage [31,32]. In a rat model of diabetes, treatment with palosuran increased kidney blood flow and delayed the development of proteinuria and kidney damage. Similar effects were not seen in preliminary studies in patients with diabetic nephropathy, but more studies are being conducted to refine the dosage regimen to improve the outcome [33,34]. Recent studies on the therapeutic potential of UTR antagonists have shown that UTR in the kidneys influences sodium and water excretion as well as the glomerular filtration rate [35,36]; U-II can act as a chronic regulator of basal vascular tone rather than in the short term. The term "vascular resistance regulator" has yet to be fully understood, but it is likely that they will find clinical use in the treatment of high blood pressure, heart failure and kidney disease [37,38].

Our experiments showed the antihypertensive potential of palosuran in laboratory rats with renovascularhypertension, which can be explained by its direct effect on UTR, and we thought it would be interesting to investigate the effect of palosuran on serum electrolytes, which play an important role in blood pressure regulation [39]. When treatment was started relatively late, the antihypertensive effect of palosuran was less pronounced. The damaging effect of high blood pressure on blood vessels is said to increase the production of U-II and enhance the endothelial-independent vasoconstrictor effect of U-II [40].

Arterial hypertension is a serious condition that can increase your risk of heart, brain, kidney, and other diseases. About 26% of the population die from arterial hypertension each year. It is the leading cause of premature death worldwide. An overview of current trends shows that the number of adults with high blood pressure rose from 594 million in 1975 to 1.13 billion in 2015. According to WHO estimates, 54% of strokes and 47% of coronary heart disease are a direct consequence of high blood pressure, which is one of the main risk factors for cardiovascular morbidity and mortality [41,42,43].

The goals of antihypertensive treatment are to prevent the onset/progression/recurrence of cardiovascular disease associated with persistent high blood pressure, reduce mortality, and help high blood pressure patients lead a normal life like healthy people [44]. Prescribing antihypertensive drugs to achieve the recommended target blood pressure remains the most important step in the management of patients with high blood pressure. Medicines targeting blood pressure must be well-tolerated, economically available, and easy to take in order to maintain long-term resistance [45,46].

A number of reports indicate the involvement of U-II in the conservation of water, sodium and chloride [47,48] in fish species. Studies have shown that inhibition of UTR activity by the antagonist urantide leads to increased GFR, dieresis and natriuresis, suggesting that endogenous U-II has a tonic effect on basal renal function. Altered expression of U-II in disease states has prompted the development of a number of UTR antagonists [49].

The strongest UTR antagonist is palosuran (a 4-ureido-quinoline derivative, ACT-058362) [15] [16]. Palosuran is selective for human UTR. The use of these and other compounds in various models of disease has shown that UT antagonism has potential therapeutic benefits. Palosuran improves kidney function in rodents and diabetics [50]. However, the potential therapeutic potential of palosuran in the treatment of high blood pressure and its complications has not been investigated [51].

High blood pressure is a serious medical condition that greatly increases the risk of heart, brain, kidney and other diseases. Today, hypertension is considered the leading cause of cardiovascular disease worldwide. An estimated 1.13 billion people worldwide have high blood pressure, most of whom (two-thirds) live in low- and middle-income countries.

Despite the effectiveness of currently available antihypertensive drugs, there is still a need for new, more effective treatment strategies, especially in hypertensive patient populations [52,53]. The urotensin system is believed to play an important role in the pathophysiology of hypertension. Urotensin II, as the most powerful known vasoconstrictor in mammals [54], is activated in hypertension. Plasma urotensin II was elevated in hypertensive patients compared with normal blood pressure controls and was directly related to systolic blood pressure. These results suggest the possibility that urotensin II (U - II) may play an etiological role in hypertension and its complications [55,56].

Palosuran is a promising non-peptide UTR antagonist designed to inhibit U-II calcium accumulation and mitogen-activated protein kinase phosphorylation. There are few published data on the use of palosuran in patients with hypertension and they are mutually exclusive [57,58]. In rat models of acute kidney failure and diabetes, pallosuran significantly improved renal function, reduced tubular and tubulointerstitial lesions, and improved survival [59,60].

Based on the above, it is interesting to study the effect of the urotensin receptor antagonist - pallosurane - on blood pressure in laboratory rats with experimental hypertension.

In recent years, the interest of researchers and scientists in the cyclic vasoactive neuropeptide urotensin-2 has increased significantly. The role of the UII system in human pathophysiology is not yet fully understood. Urotensin-II (U-II) occurs as a regulator of vascular tone in the cardiovascular

and central nervous system, in the kidneys, in the lungs, in the liver, in the ovaries, in the endocrine glands and is involved in many physiological and pathological processes [61,62]. Circulating blood levels of human UR-II, the strongest vasoconstrictor peptide identified to date, are elevated in hypertensive patients. U-II binds to the U receptor, activates the Gq protein, and induces the activation of the inositol triphosphate cycle by activating phospholipase C. U-II is a more powerful vasoconstrictor than endothelin-1, vasopressin, and prostaglandins, which constrict blood vessels. U-II acts as an endothelium-independent vasoconstrictor and endothelium-dependent vasodilator [63,64].

Vasoconstriction is mediated by smooth muscle cell receptors (SMC) and appears to be variable and strongly dependent on the vascular bed, while vasodilation is mediated by endothelium [65]. However, in a painful state of chronic heart failure or hypertension, U-II loses its ability to expand [66]. It goes without saying that such a loss and such dysfunction of endothelial cells will promote a contractile response rather than a relaxing one [67,68].

Elevated U-II levels and overexpression of urotensin receptors (UTRs), which have been demonstrated in high blood pressure, heart failure, diabetes, portal hypertension, and renal failure, suggest that the U-II / UTR system may play a critical role in the development of these diseases. [20], [21]. In this regard, the study of UTR antagonists appears to be interesting and promising for the treatment of high blood pressure and other comorbidities of high blood pressure [69,70].

This study was designed to assess the effect of the urotensin-2 receptor antagonist - Palosuran on blood pressure and serum electrolytes in laboratory rats with renovascular hypertension (2 kidneys + 1 clip) and determine possible changes in sodium, potassium, calcium levels [71,72].

Studies have shown that Palosuran decreases mean arterial pressure in rats with renovascular hypertension. The vasodilating effect of palosuran exceeds the inhibitory effect of L-NAME on NO and the urotensin-induced endothelium-independent vasoconstrictive effect, especially in the early stages of hypertension. The antihypertensive effect of Palosuran was less manifested in the case of relatively late onset of treatment. Supposedly, the damaging effects of hypertension on blood vessels increase the production of U-II and enhance the endothelium-independent vasoconstrictive effect of urotensin [73,74,75].

There are currently four main classes of antihypertensive drugs available: diuretics, calcium channel blockers, renin-angiotensin system (RAS) blockers, and beta-blockers. Despite their ability to lower blood pressure, significantly improve patient long-term prognosis, and reduce cardiovascular outcomes, it is important to consider the tolerability profile of antihypertensive drugs, as tolerability is a key factor in long-term adherence and side effects. For example, diuretics/thiazides can cause hyponatremia, hypokalemia, hyperuricemia, high cholesterol and LDL cholesterol, serum creatinine/urea and risk of diabetes. Patients may experience weakness, muscle cramps, impotence, and gout attacks. Anti-aldosterone diuretics can cause dizziness, drowsiness, allergic reactions, sexual dysfunction, nausea, vomiting, and hyperkalemia. ACE inhibitors cause persistent dry cough, angioedema, dry mouth, nausea, rash, hyperkalemia, increased serum creatinine levels. Hyperkalemia, elevated serum creatinine, nausea, dry mouth, abdominal pain are common manifestations of angiotensin receptor blockers. Calcium antagonists/dihydropyridines cause peripheral edema, headache, redness, palpitations, constipation, nausea and gingival hyperplasia. Beta-blockers increase the risk of diabetes, increase triglycerides, lower HDL cholesterol, worsen asthma, cause fatigue, insomnia, nightmares, decreased exercise, rash, and weight gain [76,77,78]. Thus we can say that the problem of the effective treatment of arterial hypertension has not lost its relevance and its solution in a given clinical situation often remains very difficult [79,80,81].

The results obtained showed a significant difference between hypertensive and nonhypertensive healthy rats for blood electrolytes. At the early stage of disease modeling, Palosuran significantly decreased serum Na + and increased K+ concentrations in hypertensive rats. Na+ and K+ concentrations were maintained within the normal range even after administration of L-NAME, except during the late-onset of treatment. Palosuran might represent a new therapeutic option in individuals with hypertension disease at early Palosuran is a non-peptide UTR antagonist with promise in drug development has been developed to inhibit the accumulation of calcium by U-II and the phosphorylation of mitogen-activated protein kinase. Data in the literature on the use of palosuran in hypertensive individuals are scarce and mutually exclusive [22,23,24,25]. In rat models of acute renal failure and diabetes, palosuran significantly improved renal function, decreased the number of tubular and tubulointerstitial lesions and improved survival [26]. Based on all of the above, it is interesting to study the effect of the urotensin receptor antagonist - Palosuran on blood pressure in laboratory rats with experimental arterial hypertension.

Materials and methods

The study was carried out on male Wistar rats weighing 200-250 g after an adaptation period of at least 1 week. All rats were housed in a laboratory with eight people per cage under controlled climatic conditions with a 12-hour light-dark cycle and free access to regularly pelleted rat food and drinking water. The protocol used in this study for the use of rats as an animal model for the study was monitored and approved by the Ethics Committee on Animal Welfare and Use of the Tbilisi State Medical University (N39 - 08/17/2019).

For experimental modeling of hypertension, we used the Reno-vascular (the two-kidney, one-clip - 2K1C) H. Goldblatt model [27,28,29]. Under general anesthesia (Nembutal - 50 mg/kg), after separation of the renal artery from the vein and nerve, the silver clip (0.2 mm internal diameter) was placed on the left renal artery close to the aorta.

The experimental animals were divided into 3 groups: Group I - healthy, intact rats; Group II - hypertensive rats; Group III - hypertensive rats, subjected to treatment with palosuran, started after 4 weeks of disease modeling; Group IV - hypertensive rats, subjected to treatment with palosuran, started after 8 weeks of disease modeling. Palosuran was injected intraperitoneally with the dose of 10 mg/kg, daily, for 4 weeks.

In the group's II and III rats, NO-synthase inhibitor - L-NAME (10 mg/kg, single dose) was administered intraperitoneally also after the completion of the treatment with palosuran.

Systemic arterial pressure (systolic pressure, diastolic pressure) was measured once a week for 12 weeks using arterial pressure measurement system "Систола" (non-invasive tail-cuff method for BP measurement). The mean arterial pressure was calculated. Plasma renin concentration was determined using ELISA (HumaStar HS).

All statistical tests were conducted using IBM SPSS Statistics. Differences between control and treated animals were determined by using the Independent-Samples T-test. The criterion for significance was set to $P < 0.05$.

Results and discussion

Changes in mean arterial pressure (MAP) compared with MAP in animals of the 1st group (healthy rats) were found in experimental rats at various stages of renovascular hypertension.

The results of the experiment (Table N1, N2) showed that after 1 week of modeling of the disease, SBP did not increase significantly, after 2 weeks SBP increased by 24% ($p < 0.05$), after 4 weeks

SBP increased by 42%. ($p < 0.02$), after 8 weeks there was a significant increase in MAP by 44% ($p < 0.02$), and after 12 weeks of modeling the MAP disease was 53% ($p < 0.001$) compared to the MAP of the group of 1 animal;

In healthy rats, after the administration of palosuran, SBP decreased by 33% ($p < 0.02$). Against the background of palosuran, after L-NAME injection, there was an increase in MAP by 23% compared to rats receiving palosuran, and a statistically insignificant decrease in MAP by 17% compared to the data for healthy rats.

In hypertensive rats after starting treatment with palosuran at week 4 of illness, MAP was modeled at week 8 of hypertension, decreasing by 32% ($p < 0.001$) compared to untreated hypertensive control rats.

Against the background of palosuran, L-NAME showed a trend towards MAP 18% higher compared with rats receiving palosuran, and a statistically significant decrease in MAP by 20% ($p < 0.02$) compared with MAP of animals of group I.

In rats with high blood pressure, after starting treatment with palosuran at 8 weeks of illness, following the example of 12 weeks of high blood pressure, palosuran showed relatively less effect on SBP than with earlier treatment. However, SBP was still significantly reduced by 23% ($p < 0.02$) compared to the control group (untreated hypertensive rats).

After the administration of L-NAME against the background of palosuran, an increase in MAP of 16% was observed compared with rats receiving palosuran, and, compared with untreated rats, a decrease in MAP of 10% was also not statistically significant.

As the results of the study have shown, there is a progressive rise in serum Na+ and a decrease in K+ concentrations compared to the data of healthy rats due to a significant relationship between electrolyte levels and blood pressure [22,23]. Notably, serum total sodium was consistently and significantly higher in hypertensive groups than in the non-hypertensive, healthy animal group, while, serum potassium was lower.

The increase in serum Na+ at renovascular hypertension develops as a result of renal artery ischemia and activation of RAAS leading to increased sodium reabsorption. By the 8th week of hypertension, the slight decrease in serum Na+ level could be explained as a compensatory reaction of kidneys. In the first, one-clip two-kidney Goldblatt hypertension, the ischemic kidney secretes renin, which leads to increased angiotensin II formation and hence elevation of blood pressure. As blood pressure rises, sodium excretion by the intact contralateral kidney increases (pressure natriuresis), therefore, there is no sodium retention.

Decreased level of serum potassium level revealed in our experimental studies at the late stage of the hypertensive disease could be explained by the sodium and potassium reciprocal relationship in the kidneys. Potassium levels often change with sodium levels. When sodium levels go up, potassium levels go down, and when sodium levels go down, potassium levels go up. Potassium levels are also affected by a hormone called aldosterone. In the case of kidney hypoxia and activated RAAS system the hormone aldosterone acting on the distal tubules triggers potassium excretion and resorption of sodium.

In carried out investigations we could not establish any significant differences in the serum mean levels of calcium between the healthy, control and treated group animals. It is possible that intracellular calcium levels may be more important in systemic hypertension than serum calcium levels, which was not measured in our study. Anumber of experimental studies suggest that intracellular Ca^{2+} concentration is abnormally increased in vascular myocytes from hypertensive animals [24] and calcium intakemay affect blood pressure by increasing intracellular calcium in

vascular smooth muscle cells leading to vasoconstriction, and by increasing vascular volume through the renin-angiotensin-aldosterone system (RAAS).

Treatment with Palosuran decreased serum Na+ and increased K+ levels in rats with renovascular hypertension at an early stage of hypertension. Na+ concentration in hypertensive rats' correlates with the results of mean arterial pressure at different stages of hypertension. Although Palosuran reveals a hypotensive effect and maintains serum Na+ concentration within the normal range, at late stages of hypertension and relatively letter onset of the treatment effect of Palosuran on electrolytes was not statistically significant.

As the results of the study have shown, 1 week after hypertension modeling, only a tendency for an increase in MAP was observed, while a statistically significant increase in blood pressure was created after 2 weeks of disease modeling. After 4 weeks, a progressive increase in blood pressure was reliable and statistically significant.

The increase in blood pressure at renovascular hypertension, first of all, develops due to the renal artery ischemia in the clipped kidney leading to hypoxia, activation of the renin-angiotensin-aldosterone system (RAAS), total peripheral vasoconstriction and water retention.

3 weeks after modeling of hypertension, reduction in MAP could be explained by the compensatory reaction of the second, intact kidney, decreasing renin production and inhibiting the RAAS system to restore homeostasis. However, on the 4 weeks of renovascular hypertension, the compensatory reaction of the intact kidney fades away, the pressure regulatory system is unable to maintain the blood pressure within the normal range and it increases significantly. At this stage of hypertension, increased blood pressure and MAP manifested in experimental animals supposedly are caused due to the complex action of RAAS and activated sympathetic nervous system. The latter results in a further increase in renin production and peripheral vasoconstriction.

After treatment with palosuran, the blood pressure significantly was decreased in all study groups. The antihypertensive effect of palosuran was demonstrated in both cases, at early treatment (started after 4 weeks of renovascular hypertension modeling) and at relatively late treatment (started after 8 weeks of hypertension modeling) of hypertensive rats.

Palosuran is known to have an antagonistic effect on U-II receptors, thereby reducing the vasoconstrictive effect of U-II. According to the literature, U-II in small doses induces the active production of NO (by activating NO-synthase) and consequently, the dilation of blood vessels as an endothelium-dependent vasodilator. This phenomenon can explain the decline in MAP in all study groups of experimental animals [30].

After administration of L-NAME, there was not a statistically significant increase in MAP compared to animals treated with palosuran, while MAP was decreased compared to control, untreated hypertensive rats, but this decrease was statistically significant only in the group of rats, where treatment was started earlier.

Table N1. Mean arterial pressure (MAP) in healthy and hypertensive rats after treatment with Palosuran and L-NAME injections at different stages of renovascular hypertension.

N	Groups	Mean Arterial Pressure – MAP (mm/Hg)		
		Before treatment	Palosuran	Palosuran + L-NAME
1	Healthy rats	95 ±3,1	64±3,0**	79± 2,5
2	1 week after modeling hypertension	97±3,5	-	-

3	2 weeks after modeling hypertension	118±4,1*	-	-
4	3 weeks after modeling hypertension	101 ±9,2	-	-
5	4 weeks after modeling of hypertension	135 ± 10,0**	-	-
6	8 weeks after modeling of hypertension	137± 8,3**	93 ± 5,5***	110± 8,2**
7	12weeks after modeling of hypertension	145 ± 10,0***	112± 7,2**	130±9,5

*- p<0.05; **- p<0.01; ***- p<0.001

Tab. N2 Effects of Palosuran and L-NAME on serum electrolytes (mmol/L) in healthy and hypertensive rats at different stages of hypertension.

	Groups	Without treatment			+ Palosuran			Palosuran + L-NAME		
		Na^+	K^+	Ca^{++}	Na^+	K^+	Ca^{++}	Na^+	K^+	Ca^{++}
1	Healthy rats	145,2	4,5	9,2	137,0	4,9	9,24	139,1	5,0	9,25
2	4th week of hypertension	169,1**	4,1	9,0	-	-	-	-	-	-
3	8th week of hypertension	165,0**	4,3	9,1	144,1**	4,88*	9,25	149,0*	4,6	9,22
4	12th week of hypertension	188,1***	3,0**	9,22	175,3	3,2	9,22	179,1	3,1	9,24

*-p<0.05; **- p<0.01; ***-p<0.001

Table 3. Systolic and diastolic blood pressure in healthy and hypertensive rats after treatment with Palosuran and L-NAME injections at different stages of renovascular hypertension.

N	Groups		Systemic Blood Pressure (mm/Hg)		
			Without treatment	Palosuran	Palosuran + L-NAME
1	Healthy rats	Systole	110 ± 3,4	81 ± 4,1**	98± 3,2
		Diastole	87± 4,8	55 ± 3,1**	69± 4,2*
2	1 week after hypertension modeling	Systole	114± 4,1	-	-
		Diastole	91± 4,5	-	-
3	2 weeks after hypertension modeling	Systole	159 ± 2,7**	-	-
		Diastole	98 ± 4,2*	-	-
4	3 weeks after hypertension modeling	Systole	117± 5,7	-	-
		Diastole	93 ± 4,5	-	-
5	4 weeks after hypertension modeling	Systole	185 ± 9,3**	-	-
		Diastole	110 ± 5,4**	-	-
6	Treatment started after 4 weeks of hypertension modeling - 8th week	Systole	192 ± 9,3**	134 ± 5,7***	143 ±11,3**
		Diastole	110 ± 5,4**	72 ± 3,1**	94± 4,3**

7	Treatment started after 8 weeks of hypertension modeling - 12th week	Systole	205 ±10,1***	149± 8,1**	181± 10,7
		Diastole	115 ±7,1***	94± 5,2**	104± 6,1

*- p<0.02; **- p<0.01; ***- p<0.001

Table N4 Plasma Renin concentration (PR) in healthy and hypertensive rats at different stages of hypertension after treatment with palosuran and injections of L-NAME.

N	Groups	Renin – PR (ng / ml)		
		Before treatment	+ Palosuran	Palosuran + L-NAME
1	Healthy rats	1,72 ± 0,5	1,52 ±0,3	1,65 ±0,4
2	1 week after hypertension modeling	1,79 ± 0,3	-	-
3	2 weeks after hypertension modeling	2,49± 0,4**	-	-
4	3 weeks after hypertension modeling	2,45 ± 1,3**	-	-
5	4 weeks after hypertension modeling	1,94 ± 0,1	-	-
6	8 weeks after hypertension modeling	4,5 ± 1,4***	3,02 ± 0,9**	3,32 ± 0,5*
7	12 weeks after hypertension modeling	5,75 ± 1,5***	4,39 ±1,5**	5,71 ±1,2

* – p < 0,05 , ** – p < 0,01, *** – p < 0,001

In healthy rats after administration of Palosurandecrease in serum Na^+ by 6,5% was not statistically significant. The same, unreliable alterations in Na^+ concentrations were detected in rats treated with Palosuran after administration of L-NAME. Serum Na^+ was increased by 1,5% and compared with the results of untreated rats' serum Na^+ was decreased by 4,1% (p>0,05).

After 4th, 8th and 12th weeks of disease modeling in hypertensive rats there was progressive and reliable rise in serum Na^+ by 17%, 14% (p<0.01) and 30% (p<0,001) compared to the data of healthy rats. Although, after 8 weeks of disease modelling serum Na^+ was increased by 14% (p <0.001), it was lesser by 3% compared to the data obtained by 4th weeks of disease modelling.

After administration of L-NAME, as a NO-synthase inhibitor, a significant increase in blood pressure was expected compared to the data of the control group animals. But, experiments revealed just the opposite reaction in palosuran-treated rats, especially in the case of the early-onset of treatment. This may be explained by the fact that palosuran inhibiting the effect of urotensin is likely increased NO production thereby inhibiting the vasoconstrictive effect of L-NAME.

In the case of treatment started relatively later, the antihypertensive effect of palosuran was less manifested. We suppose that the damaging effects of hypertension on blood vessels increase the production of U-II and enhance the endothelium-independent vasoconstrictive effect of urotensin [31].

In experimental rats, the plasma rennin concentration (PR) at different stages of modeling of renovascular hypertension was changed compared to the norm (tab N3). In particular, after 1 week of disease modeling, there was a tendency of increase in PR by 4%; On 2nd week, PR was increased significantly by 45% (p <0.01); In the 3rd week of hypertension increase in PR was relatively less - 42% (p <0.01). By the 4th week, PR decreased and it was not statistically different compared to the norm; After 8 weeks, the PR increased by 162% (p <0.001) and after 12 weeks the PR was increased extremely by 234% (p < 0,001).

In healthy rats after administration of palosuran decrease in PR by 12% was not statistically significant. Administration of L-NAME in rats treated with palosuran showed only a tendency of increase in PR by 9% also and compared to untreated hypertensive rats, decrease in PR by 4% PR was not statistically significant as well.

In hypertensive rats treated with palosuran started 4 weeks after disease modeling, by the 8th week of hypertension, palosuran induced a statistically significant decrease in PR by 33% ($p < 0.01$) compared to data from hypertensive, untreated rats. Administration of L-NAME in rats treated with palosuran showed a tendency of increase in PR by 9%. PR was reduced by 26% ($p < 0,05$) compared to data of untreated hypertensive rats.

In hypertensive rats subjected to treatment with palosuran, started after 8 weeks of disease modeling, on the 12th week of hypertension PR was decreased by 24% ($p < 0.01$) compared to control, untreated rats. In treated rats' injection of L-NAME increased PR by 30%. Compared to the control, untreated rats, the effect of L-NAME on PR was not statistically significant.

Thus, the experiment revealed that changes in PR were observed at different stages of modeling of renovascular arterial hypertension, compared to PR in hypertensive rats. In particular, by the 2nd and 3rd weeks after disease modeling, PR was increased almost uniformly compared to the norm, 1.45-fold and 1.42-fold, most likely due to renal ischemia.

4 weeks after modeling of hypertension PR decreased and it was not different from the PR of healthy rats. Although PR was within the normal range that could be explained by a second, intact kidney-compensatory mechanism decreasing renin production [32,33], the BP has remained at high levels.

High arterial pressure which was revealed by experiment in the presence of relatively low PR could be explained by an increase in blood osmotic pressure, increase in circulating blood volume and increase in vascular basal tone due to hyperproduction of aldosterone, leading to the increased sodium reabsorption with further increase in blood osmolality and increased production of antidiuretic hormone, stimulating the secretion of adrenocorticotropic hormone and potentiating peripheral vasoconstriction [34,35].

The increase in basal tone supposedly is caused by an increase in the amount of sodium in the blood vessel walls, leading to water retention causing their swelling and thickening. In addition, sodium increases the sensitivity of α-adrenoceptors in blood vessel walls in response to catecholamine. Aldosterone also facilitates the release of norepinephrine from the sympathetic nerve endings and as a result, increases vascular neurogenic tone also [36,37].

By the 8th week of disease modeling, PR was increased 2,6-fold compared to the norm, and 3.34-fold by the 12th week of hypertension correlating with the data of systemic blood pressure and MAP.

Palosuran produced a significant decrease in PR in all study group animals compared to control (especially in case of early onset of treatment), except in healthy rats, where only a tendency of decrease in PR was observed.

In healthy rats after administration of palosuran arterial pressure and PR were not changed significantly that could be explained by the fact that urotensin production is relatively low in healthy rats, hence the effects of the palosuran is less respectively. It should also be noted that in healthy rats, both palosuran and L-NAME were administered at a single dose and samples were taken 2 hours after injection of preparations. The hypotensive effect of palosuran supposedly develops due to its vasodilatatory effect, which later is reflected in renin production. Probably, this short period of time (2 hours) at single administration of the drugs is not sufficient for the reliable changes in PR. The same could be said for the tendency of increase in PR after injection of L-NAME in treated rats.

Decreasing effects of palosuran on PR were seen both early and late in treatment at weeks 8 and 12 of hypertension, but PR was significantly lower at the start of treatment than at the late start of treatment.

From the results of the experiments, it can be concluded that palosuran shows an antihypertensive effect in the early stages of hypertension under laboratory conditions. Rats with renovascular hypertension lead to significant changes in serum Na^+ and K^+ levels, with the exception of serum Ca^{++} concentration.

Palosuran reduced the serum Na^+ concentration and increased the K + concentration in hypertensive rats. The Na^+ and K^+ concentrations were also kept within normal limits after administration of L-NAME, with the exception of a late start on treatment. The effect of palosuran on serum electrolyte levels in the late stages of arterial hypertension has not been observed.

Conclusion

Based on the study results Palosuran significantly reduced PR compared to untreated hypertensive rats that persisted with L-NAME except for late initiation of treatment. Palosuran may represent a new treatment option for people with essential hypertension. Palosuran reduced serum Na^+ concentration and increased K^+ concentration in hypertensive rats. Concentrations of Na^+ and K^+ were maintained within normal limits even after administration of L-NAME, except for late initiation of treatment. From the results of the experiments, it can be concluded that Palosuran exhibits an antihypertensive effect in healthy and hypertensive rats. The vasodilatory effect of palosuran is superior to the inhibitory effect of L-NAME on NO and the endothelial-independent vasoconstrictor effect induced by urotensin, particularly in the early stages of hypertension. With stable arterial hypertension, PR gradually increases from the norm.

REFERENCES

1. Desai N, Sajjad J, Frishman WH. Urotensin II: a new pharmacologic target in the treatment of cardiovascular disease. Cardiol Rev. 2008 May-Jun; 16(3):142-153;
2. Suguro T, Watanabe T, Ban Y, et al. Increased human urotensin II levels are correlated with carotid atherosclerosis in essential hypertension. Am J Hypertens. 2007 Feb; 20(2):211-217;
3. Douglas SA, Ohlstein EH. Human urotensin-II, the most potent mammalian vasoconstrictor identified to date, as a therapeutic target for the management of cardiovascular disease., Trends Cardiovasc Med. 2000 Aug; 10(6):229-237;
4. Gardiner SM, March JE, Kemp PA, et al. Regional heterogeneity in the haemodynamic responses to urotensin II infusion in relation to UT receptor localisation.JPharmacol. 2006 Mar; 147(6):612-621;
5. Lapp H, Boerrigter G, Costello-Boerrigter LC, et al. Elevated plasma human urotensin-II-like immunoreactivity in ischemic cardiomyopathy.Int J Cardiol. 2004 Mar; 94(1):93-97;
6. Bottrill FE, Douglas SA, Hiley CR, White R, Br. Human urotensin-II is an endothelium-dependent vasodilator in rat small arteries. J Pharmacol. 2000 Aug; 130(8):1865-1870;
7. Matsushita M, Shichiri M, Imai T, et al. Co-expression of urotensin II and its receptor (GPR14) in human cardiovascular and renal tissues. J Hypertens. 2001 Dec; 19(12):2185-2190;
8. Maguire JJ, Davenport AP. Is urotensin-II the new endothelin? Br J Pharmacol 137: 579–588, 2002;

9. Douglas S. A., Dhanak D., Johns D. G. From “gills to pills”: urotensin-II as a regulator of mammalian cardiorenal function. Trends Pharmacol. Sci. 2004; 25:76–8510.1016/j.tips.2003.12.005.
10. Sondermeijer B., Komp A., Komesaroff P., Krum H. Effects of exogenous urotensin-II on vascular tone in skin microcirculation of patients with essential hypertension. Am.J. Hypertens. 2005; 22:1341–1344
11. Douglas SA, Ohlstein EH. Human urotensin-II, the most potent mammalian vasoconstrictor identified to date, as a therapeutic target for the management of cardiovascular disease. Trends Cardiovasc Med. 2000; 10: 229–237;
12. Cheung, Bernard MY; Leung, Raymond; Man, Yu Bun; Wong, Louisa YF. Plasma concentration of urotensin II is raised in hypertension. Journal of Hypertension: July 2004,v. 22 - Issue 7 pp. 1341-1344;
13. Douglas SA, Ashton DJ, Sauermelch CF, Coatney RW, Ohlstein DH, Ruffolo MR, et al. Human urotensin-II is a potent vasoactive peptide: pharmacological characterization in the rat, mouse, dog and primate. J CardiovascPharmacol. 2000; 36: S163–S166;
14. Douglas SA, Sulpizio AC, Piercy V, Sarau HM, Ames RS, Aiyar NV, et al. Differential vasoconstrictor activity of human urotensin-II in vascular tissue isolated from the rat, mouse, dog, pig, marmoset and cynomolgus monkey. Br J Pharmacol. 2000; 131: 1262–1274;
15. Gardiner SM, March JE, Kemp PA, Davenport AP, Bennett T. Depressor and regionally-selective vasodilator effects of human and rat urotensin II in conscious rats. Br J Pharmacol. 2001; 132: 1625–1629;
16. Gardiner SM, March JE, Kemp PA et al. Regional heterogeneity in the haemodynamic responses to urotensin II in relation to UT receptor localization. Br J Pharmacol 2006; 147:612-621
17. Watanabe T, Kanome T, Miyazaki A, Katagiri T. Human urotensin II as a link between hypertension and coronary artery disease. Hypertens Res, 2006; 29: 375–387;
18. Zhu YC, Zhu YZ, Moore PK. The role of urotensin II in cardiovascular and renal physiology and diseases. Br J Pharmacol 2006; 148: 884–901;
19. Song W, Abdel-Razik AE, Lu W, Ao Z, Johns DG, et al. Urotensin II and renal function in the rat. Kidney Int 2006; 69: 1360– 1368;
20. Balment RJ, Song W, Ashton N. Urotensin II: ancient hormone with new functions in vertebrate body fluid regulation. Ann N Y AcadSci 2005; 1040: 66–73;
21. Bond H., Winter M.J., Warne J.M. , et al. Plasma concentrations of arginine vasotocin and urotensin II are reduced following transfer of the euryhaline flounder (Platichthysflesus) from seawater to fresh water. Gen Comp Endocrinol, 125 (2002), pp. 113-120;
22. ouglas S.A., Dhanak D., Johns D.G. From ‘gills to pills’: urotensin-II as a regulator of mammalian cardiorenal function. Trends PharmacolSci, 25 (2004), pp. 76-85;
23. Carotenuto A., Grieco P., Rovero P., et al. Urotensin-II receptor antagonists. Curr Med Chem, 13 (2006), pp. 267-275;
24. ClozelM. , C. Binkert, M. Birker-Robaczewska, et al. Pharmacology of the urotensin-II receptor antagonist palosuran (ACT- 058362; 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulfate salt): first demonstration of a pathophysiological role of the urotensin system. J PharmacolExpTher, 311 (2004), pp. 204-212;

25. Lim et al., 2004 Lim M., Honisett S., Sparkes C. D., Komesaroff P., Kompa A., Krum H. Differential effect of urotensin II on vascular tone in normal subjects and patients with chronic heart failure. Circulation. 2004; 109, 1212–1214;
26. American Journal of Hypertension. Am J Hypertens 2007;20: 211–217;
27. Lim M, Honisett S, Sparkes CD, et al. Differential effect of urotensin II on vascular tone in normal subjects and patients with chronic heart failure. Circulation. 2004 Mar 16; 109(10):1212-1216;
28. Clozel M, Hess P, Qiu C, Ding SS, Rey M J.The urotensin-II receptor antagonist palosuran improves pancreatic and renal function in diabetic rats. PharmacolExpTher. 2006 Mar; 316(3):1115-1121;
29. Pehlivan Y, Turkbeyler IH, et al. Urotensin inhibition with palosuran could be a promising alternative in pulmonary arterial hypertension. Onat AM1, Hypertension. 2010; 55 (5):1206-1209;
30. Sidharta PN, Wagner FD, Bohnemeier H, et al. Pharmacodynamics and pharmacokinetics of the urotensin II receptor antagonist palosuran in macroalbuminuric, diabetic patients. ClinPharmacolTher. 2006 Sep; 80(3):246-256;
31. Vogt L1, Chiurchiu C, Chadha-Boreham H. et al. Effect of the urotensin receptor antagonist palosuran in hypertensive patients.TrendsPharmacol Sci. 2004 Feb; 25(2):76-85;
32. Sidharta PN, Wagner FD, Bohnemeier H, Jungnik A, Halabi A, Krahenbuhl S, et al. Pharmacodynamics and pharmacokinetics of the urotensin II receptor antagonist palosuran in macroalbuminuric, diabetic patients. ClinPharmacolTher. 2006; 80: 246–256;
33. Clozel M, Hess P, Qiu C, Ding SS, Rey M. The urotensin-II receptor antagonist palosuran improves pancreatic and renal function in diabetic rats. J PharmacolExpTher. 2006; 316: 1115–1121;
34. Kajaia A, Gabunia L, Ghambashidze K., et al. Urotensin-2Receptor Antagonist - Palosuran Decreases Blood Pressure And Plasma Renin Concentration In Laboratory Rats With Renovascular Hypertension. International Journal of Progressive Sciences and Technologies (IJPSAT) ISSN: 2509-0119. 2021, vol. 26, No. 1, pp. 16-24;
35. Goldblatt P. The Goldblatt experiment: a conceptual paradigm. In: Hypertension: Pathophysiology, Diagnosis and Management, edited by J. H. Laragh and B. M. Brenner. New York: Raven, 1995; pp. 23–35;
36. Mitchell K., NavarL..Intrarenal actions of angiotensin II in the pathogenesis of experimental hypertension. In: Hypertension: Pathophysiology, Diagnosis, and Management, edited by J. H. Laragh and B. M. Brenner. New York: Raven, 1995, pp.1437– 1450;
37. Ploth D. Angiotensin-dependent renal mechanisms in two-kidney one-clip renal vascular hypertension. Am. J. Physiol. 1983. 245 (Renal Fluid Electrolyte Physiol. 14): F131–F141;
38. Kim, M-H & Choi, M-K Seven dietary minerals (Ca, P, Mg, Fe, Zn, Cu, and Mn) and their relationship with blood pressure and blood lipids in healthy adults with self-selected diet. Biol Trace Elem Res. 2013, 153, 69–75;
39. Gijsbers, L, Dower, JI, Mensink, M et al. Effects of sodium and potassium supplementation on blood pressure and arterial stiffness: a fully controlled dietary intervention study. J Hum Hypertens. 2015, 29, 592–598;
40. Tostes R.C.A., Wilde D.W., Bendhack L.M., Webb R.C. Calcium handling by vascular myocytes in hypertension. Braz J Med Biol Res, March, 1997, v. 30(3) 315-323.

41. Clozel M, Binkert C, Birker-Robaczewska M, et al. Pharmacology of the urotensin-II receptor antagonist palosuran (ACT- 058362; 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulfate salt): first demonstration of a pathophysiological role of the urotensin system. J PharmacolExpTher. 2004; 311: 204–212;
42. Clozel M, Hess P, Qiu C, Ding SS, Rey M. The urotensin-II receptor antagonist palosuran improves pancreatic and renal function in diabetic rats. J PharmacolExpTher. 2006; 316: 1115–1121;
43. Ames RS, Sarau HM, Chambers JK, Willette RN, Aiyar NV, Romanic AM, et al. Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14. Nature. 1999; 40: 282–286;
44. Goldblatt P. The Goldblatt experiment: a conceptual paradigm. In: Hypertension: Pathophysiology, Diagnosis and Management, edited by J. H. Laragh and B. M. Brenner. New York: Raven, 1995; pp. 23–35;
45. Mitchell K., NavarL..Intrarenal actions of angiotensin II in the pathogenesis of experimental hypertension. In: Hypertension: Pathophysiology, Diagnosis, and Management, edited by J. H. Laragh and B. M. Brenner. New York: Raven, 1995, pp.1437–1450;
46. Ploth D. Angiotensin-dependent renal mechanisms in two-kidney one-clip renal vascular hypertension. Am. J. Physiol. 245 (Renal Fluid Electrolyte Physiol. 14): F131–F141, 1983).
47. Ishihata A, Ogaki T, Aita T, Katano Y. Role of prostaglandins in urotensin II-induced vasodilatation in the coronary arteries of aged rats. Eur J Pharmacol 523: 119–126, 2005;
48. Lin L., Ding WH., Jiang W., Zhang YG., Qi YF., Yuan WJ., Tang CS. Urotensin-II activates L-arginine/nitric oxide pathway in isolated rat aortic adventitia. Peptides 25: 1977–1984, 2004;
49. Katano Y, Ishihata A, Aita T, Ogaki T, Horie T. Vasodilator effect of urotensin II, one of the most potent vasoconstricting factors, on rat coronary arteries. Eur J Pharmacol 402: 209–211, 2000;
50. Gibson A. Complex effects of Gillichthys urotensin II on rat aortic strips. Br J Pharmacol 91: 205–212, 1987;
51. Kimiko Ishiguro, Hiroyuki Sasamura, Yusuke Sakamaki, Hiroshi Itoh, Takao Saruta. Developmental Activity of the Renin- Angiotensin System during the “Critical Period” Modulates Later L-NAME–Induced Hypertension and Renal Injury. Hypertension Research. 2007, p.30–75;
52. Liffert Vogt, Carlos Chiurchiu, Harbajan Chadha-Boreham, et al. Effect of the Urotensin Receptor Antagonist Palosuran in Hypertensive Patients With Type 2 Diabetic Nephropathy. Hypertension. 2010;55:1206-1209;
53. Wendy J. Bottinor, Megan M. Shuey, Ali Manouchehri, et al. Renin-Angiotensin-Aldosterone System Modulates Blood Pressure Response During Vascular Endothelial Growth Factor Receptor Inhibition. JACC: CARDIOONCOLOGY, 2019;1(1); http://creativecommons.org/licenses/by-nc-nd/4.0/;
54. Marisa K. Ames, Clarke E. Atkins, Bertram Pitt. The renin-angiotensin-aldosterone system and its suppression. J Vet Intern Med. 2019;33(2):
55. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet. 2008;371:1513–1518;

56. Burnier M., Kjeldsen S., Heagerty A., Williams B. Drug treatment of hypertension Oxford MedicineOnlinehttps://oxfordmedicine.com/view/10.1093/med/9780198784906.001.0001/med-9780198784906-chapter-569;
57. Podzolkov V., Tarzimanova A., Georgadze Z. Modern Principles of Treatment of Uncontrolled Hypertension. Rational Pharmacotherapy in Cardiology Home. 2019; 15(5): 736-741;
58. Suguro T, Watanabe T, Ban Y, et al. Increased human urotensin II levels are correlated with carotid atherosclerosis in essential hypertension. Am J Hypertens. 2007 Feb; 20(2):211-217;
59. Totsune K, Takahashi K, Arihara Z, et al. Elevated plasma levels of immunoreactive urotensin II and its increased urinary excretion in patients with Type 2 diabetes mellitus: association with progress of diabetic nephropathy. Peptides. 2004 Oct; 25(10):1809-1814;
60. Bousette N., Hu F., Ohlstein E. H., Dhanak D., Douglas S. A., Giaid A. Urotensin-II blockade with SB-611812 attenuates cardiac dysfunction in a rat model of coronary artery ligation. J. Mol. Cell. (2006). Cardiol. 41, 285– 29510.1016/j.yjmcc.2006.05.008;
61. Каджаия А.А, Габуния Л.И, Гамбашидзе К.Г, Пачкория К.З, Сулашвили Н.В, Гогиберидзе А.П; Effect of U-II-receptor antagonist – Palosuran on Arterial Pressure and Myocardium in Hypertensive Lab. Rats; ISBN 978-88-32012-34-7; DOI10.51582/interconf.19-20.07.2021; UDC 001.1; Index Copernicus International; SCIENTIFIC EDITION; InterConf-Scientific Publication Center; Scientific Collection InterConf, №67; Proceedings of the 4 th International Scientific and Practical Conference «Theory and Practice of Science: Key Aspects» (19- 20 of July, 2021); Rome, Italy-2021; Pp: 307-316.
62. L. Gabunia, D. Vadachkoria, Sh. Khetsuriani, N. Gamkrelidze, L. Rukhadze, N. Sulashvili; Mechanisms of Pharmacological Action of Ecstasy Substances, Consequences of Episodic and Chronic Use and Expected Complications; Caucasus Journal of Health Sciences and Public Health; E ISSN 2449-2450 ISSN 2449-2647 The University of Georgia Publishing House; www.caucasushealth.ge Official Journal of the University of Georgia and Iv.Javakhishvili Tbilisi State University with Support of the Arctic University of Tromsø/Norway; Volume 4, Supplement 6; July 20-24, 2020; Pp 66-69.
63. Groszmann RJ, Abraldes JG. Portal hypertension: from bedside to bench. J ClinGastroenterol 2005; 6(4 Suppl 2): S125–S130
64. McConnell M, Iwakiri Y. Biology of portal hypertension. HepatolInt 2018; 12(Suppl 1):11–23
65. Vilaseca M, García-Calderó H, Lafoz E, García-Irigoyen O, Avila MA, Reverter JC, Bosch J, Hernández-Gea V, Gracia-Sancho J, García-Pagán JC. The anticoagulant rivaroxaban lowers portal hypertension in cirrhotic rats mainly by deactivating hepatic stellate cells. Hepatology 2017; 65(6): 2031–2044
66. Vilaseca M, García-Calderó H, Lafoz E, Ruart M, López-Sanjurjo CI, Murphy MP, Deulofeu R, Bosch J, Hernández-Gea V, Gracia-Sancho J, García-Pagán JC. Mitochondria-targeted antioxidant mitoquinone deactivates human and rat hepatic stellate cells and reduces portal hypertension in cirrhotic rats. Liver Int 2017; 37(7): 1002–1012
67. Rockey DC, Fouassier L, Chung JJ, Carayon A, Vallee P, Rey C, Housset C. Cellular localization of endothelin-1 and increased production in liver injury in the rat: potential for autocrine and paracrine effects on stellate cells. Hepatology 1998; 27(2): 472–480
68. Iwakiri Y. Pathophysiology of portal hypertension. Clin Liver Dis 2014; 18(2): 281–291

69. Nishimura Y, Ito T, Hoe K, Saavedra JM. Chronic peripheral administration of the angiotensin II AT(1) receptor antagonist candesartan blocks brain AT(1) receptors. Brain Res 2000; 871(1): 29–38
70. Ames RS, Sarau HM, Chambers JK, Willette RN, Aiyar NV, Romanic AM, Louden CS, Foley JJ, Sauermelch CF, Coatney RW, Ao Z, Disa J, Holmes SD, Stadel JM, Martin JD, Liu WS, Glover GI, Wilson S, McNulty DE, Ellis CE, Elshourbagy NA, Shabon U, Trill JJ, Hay DW, Ohlstein EH, Bergsma DJ, Douglas SA. Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14. Nature 1999; 401(6750): 282–286
71. Ross B, McKendy K, Giaid A. Role of urotensin II in health and disease. Am J PhysiolRegulIntegr Comp Physiol 2010; 298(5): R1156–R1172
72. Thanassoulis G, Huyhn T, Giaid A. Urotensin II and cardiovascular diseases. Peptides 2004; 25(10): 1789–1794
73. Kemp W, Roberts S, Krum H. Increased circulating urotensin II in cirrhosis: potential implications in liver disease. Peptides 2008; 29 (5): 868–872
74. Liu D, Chen J, Wang J, Zhang Z, Ma X, Jia J, Wang Y. Increased expression of urotensin II and GPR14 in patients with cirrhosis and portal hypertension. Int J Mol Med 2010; 25(6): 845–851
75. Liu DG, Wang J, Zhang ZT, Wang Y. The urotension II antagonist SB-710411 arrests fibrosis in CCl4 cirrhotic rats. Mol Med Rep 2009; 2(6): 953–961
76. Clozel M, Binkert C, Birker-Robaczewska M, Boukhadra C, Ding SS, Fischli W, Hess P, Mathys B, Morrison K, Müller C, Müller C, Nayler O, Qiu C, Rey M, Scherz MW, Velker J, Weller T, Xi JF, Ziltener P. Pharmacology of the urotensin-II receptor antagonist palosuran (ACT-058362; 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)- ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulfate salt): first demonstration of a pathophysiological role of the urotensin system. J PharmacolExpTher 2004; 311(1): 204–212
77. Mejias M, Coch L, Berzigotti A, Garcia-Pras E, Gallego J, Bosch J, Fernandez M. Antiangiogenic and antifibrogenic activity of pigment epithelium-derived factor (PEDF) in bile duct-ligated portal hypertensive rats. Gut. 2015; 64(4): 657–666
78. Clozel M, Hess P, Qiu C, Ding SS, Rey M. The urotensin-II receptor antagonist palosuran improves pancreatic and renal function in diabetic rats. J PharmacolExpTher 2006; 316(3): 1115–1121
79. Hsu SJ, Lee FY, Wang SS, Hsin IF, Lin TY, Huang HC, Chang CC, Chuang CL, Ho HL, Lin HC, Lee SD. Caffeine ameliorates hemodynamic derangements and portosystemic collaterals in cirrhotic rats. Hepatology 2015; 61(5): 1672–1684
80. Delgado MG, Gracia-Sancho J, Marrone G, Rodríguez-Vilarrupla A, Deulofeu R, Abraldes JG, Bosch J, García-Pagán JC. Leptin receptor blockade reduces intrahepatic vascular resistance and portal pressure in an experimental model of rat liver cirrhosis. Am J PhysiolGastrointest Liver Physiol 2013; 305(7): G496–G502
81. Darlington AS, Dippel DW, Ribbers GM, van Balen R, Passchier J, Busschbach JJ. A prospective study on coping strategies and quality of life in patients after stroke, assessing prognostic relationships and estimates of cost-effectiveness. J Rehabil Med 2009; 41(4): 237–241.

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

SCIENTIFIC TALKS ON PRESCRIPTIVE ISSUANCES OF PHARMACISTS PROFESSIONAL REGULAR WELL-BEING, SAFETY, HYGIENIC, SANITARY, AND HEALTH INQUIRIES IN PHARMACEUTICS ACCORDING TO NEW COVID-19 PANDEMIC REGULATION IN 2021

Nana Gorgaslidze[1], Nodar Sulashvili [2]

[1]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Tbilisi State Medical University, Head of The Department of Social and Clinical Pharmacy, Tbilisi, Georgia.

[2]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Invited Professor/Lecturer of Tbilisi State Medical University, Tbilisi, Georgia;
Email: n.sulashvili@ug.edu.ge

ABSTRACT

Personnel are required to follow the rules of personal hygiene and industrial sanitation, to carry out the relevant personnel to perform food, smoking, as well as storage of food, tobacco and personal medicines in pharmacies, training and scientific research laboratories and departures. Pharmaceutical establishments do not comply with the hygienic norms of the internal and external environment, physical, chemical and biological factors of the labor process. The facility also does not take into account psychosocial factors related to safety (stress, communication, post-traumatic stress, etc.); Most pharmaceutical establishments (50-60%) do not have a fire board with appropriate equipment, evacuation exit and scheme. Also has no person responsible for the matter; Disobsibility and specialist protection/separation facility prior to pandemic were minimal (increased by 99%) during pandemic; The state should create an appropriate legislative and institutional framework; We think this will help transform the existing department into an effective labor inspectorate. The possibility will be created of the institutional capacity of its independence and efficiency, and the law will also provide guarantees for the individual independence of inspectors; Also, the bill should directly refer to the Labor Inspectorate as the body responsible for law enforcement. Protecting safe working conditions involves the use of ineffective and reliable means of preventing industrial injuries and occupational diseases, technologies, equipment and others. It is natural that the fields, technological processes, etc., are characterized by their specifics and the safety rules should be different for them.In pharmacies, laboratories, training and scientific research laboratories, warehouses, production equipment are subject to daily cleaning. Cabinets in storage rooms should be cleaned as needed, but at least once a week. Wet cleaning of the pharmacy, laboratory/ factory (floor and equipment) before starting work. Only dry cleaning of laboratory / production using disinfectants is not allowed. Waste and rubbish should be collected in special containers with a moving lid and should be removed at least once a day. Hand-washed sinks, toilets and garbage containers should be cleaned, rinsed and disinfected daily. We believe that the right, legal approach, strict control and state policy in the field of drug trafficking are a prerequisite for creating a safe environment. Most importantly, despite the interests of the owners of the Georgian pharmaceutical industry and modern marketing approaches, the safety of the population and employees remains a priority.

Keywords: Pharmacists, professional, regular, well-being, hygienic, sanitary, health pharmaceutical, institution, covid-19 pandemic.

Introduction

The employer is obliged to provide the employee with the safest working environment for health. The need for individual measures to protect and maintain the health of employees is particularly high in some areas of employment [1]. In order to protect the health of employees in the workplace, as well as the importance of the work performed, national legislation provides for cases and rules for mandatory periodic medical examination of an employee at the expense of the employer. Periodic and regular medical examinations are required depending on the content of the activity. With the exception of cases provided for by a regulatory enactment, the employer has the right to determine additional conditions for a medical examination [2-3].

Working conditions

An important prerequisite for the rational use of employees' working time and, in general, for increasing the efficiency of their work are normal working conditions and the establishment of rational internal rules for work and rest at the enterprise. Work should be carried out in normal, favorable conditions, and when planning a workplace and its technological equipment, it is necessary to take into account the latest advances in technology and technology [4]. This significantly helps to reduce staff fatigue, save time, improve staff efficiency and ultimately improve work efficiency and success. Quite common in the West is the so-called. "The theory of human capital". According to this theory, the knowledge and skills of employees are considered to belong to their organization, which generates income. And the costs of acquiring this knowledge (personnel recruitment, selection, salary, adaptation, training, certification, improvement of working conditions) are considered an investment. Although the efficiency of such investments is the highest and, in addition, people are the most important resource for them, there are still records in the educational and scientific literature of these countries that seem to be the least developed, for example, finance, manufacturing. , marketing, materials Management of technical supply [5-6]. In the Georgian realities, only the first steps are being taken in this direction against a very poor background of economic development, wages, employment and living standards. Thus, when it comes to the successful management of an organization, it should in principle be said that limiting investments in human resources, ignoring the factor of trust and respect, inadequate staff motivation, reducing concern and social insecurity by boomerangs return to the development of the company [7-8].

The purpose of the labor legislation in Georgia is to regulate the relationship between the employer and the employee through clearly defined legal regulation that excludes the exploitation of the employee and creates the possibility of work based on human dignity, freedom and self-development. Accordingly, the purpose of labor legislation is to regulate private legal relations at the normative level to the extent that it is necessary for the proper social protection of workers. The employer is obliged to provide the candidate with information about the work to be performed, working conditions, contract form, remuneration and legal status of the employee during the employment relationship.The performance of the assigned work is usually subject to organizational regulation and the daily and/or weekly hourly work schedule set by the employer. Under such organizational arrangements, it is important to classify time into work, break, and leisure time [9-11].

Working time includes the time that an employee must use to fulfill a contractual obligation. Break time is the period of time between working hours, while break time is defined by labor law as leave periods and days off .Overtime work is voluntary, although the Labor Code provides for exceptional cases where overtime work becomes mandatory for an employee. These cases are:- To prevent

natural disasters and/or to eliminate their consequences;-Unpaid; To prevent an industrial accident and/or to liquidate its consequences with appropriate compensation. The Labor Code establishes the right of the employer to take paid leave of 24 working days and unpaid leave of 15 calendar days. Depending on the specifics of the work, the Labor Code provides for additional leave for those working in heavy, harmful or hazardous work in the amount of 10 calendar days a year. The list of such works is approved by the order of the Minister for Internally Displaced Persons from the Occupied Territories of Georgia, Labor, Health and Social Protection [12-14].

The International Labor Organization has developed international labor standards, which are set out in the Declaration of Fundamental Principles and Rights, which are widely recognized and of particular importance. They are widely used regardless of a country's level of development or ratification of cultural property and related conventions [15-16].

These standards are composed of qualitative rather than quantitative standards and do not define specific levels of working conditions, wages, or occupational safety and health standards. They are not intended to measure comparative advantage. The main labor standards are human rights, they are recognized in internationally ratified international human rights instruments, including the Convention on the Rights of the Child [17-18].

Employees' rights in the UK include the right to work, a paid disciplinary process during which they are eligible for escort, daily breaks, paid leave and more. Safety and social resilience include: protecting employees' rights and safe working conditions, preventing human trafficking and eliminating child labor. In pharmaceutical institutions, hygiene standards are required and adhered to. Pharmacy institutions are all institutions in which pharmaceutical activities are carried out. When carrying out pharmaceutical activities under the influence of high-risk factors, possible cases of occupational diseases of an employee may develop [19-20].

An occupational disease (acute or chronic) develops under the influence of factors that threaten the working environment and the production process, causes a deterioration in his health and/or restriction of his professional ability to work in the short or long term, and is determined by the legislation of Georgia. Therefore, the specifics of pharmaceutical activities should be taken into account, in particular: the development of a new pharmaceutical product (molecule), the use of various chemicals and technologies, which, in turn, require special precautions. Also, one cannot ignore the necessary characteristics during storage, transportation, delivery, consumption of finished products, and, as a result, the need to comply with sanitary and hygienic working conditions [21-22].

The International Labor Organization (ILO) was formed in 1919 as part of the League of Nations to protect workers' rights. Later, the ILO joined the United Nations. The UN itself protects the rights of workers.

1. Everyone has the right to work, free choice of work, fair and favorable working conditions and protection from unemployment;
2. Everyone has the right to equal pay for equal work without any discrimination;
3. Everyone who works has a just and favorable standard of living that ensures the dignity of himself and his family and, if necessary, provides other means of social protection;
4. Everyone has the right to form trade unions and join trade unions to protect their interests.
5. Everyone has the right to rest, including reasonable limitations of working hours and paid vacation.

Related to the pharmaceutical industry: measures related to waste collection, processing, waste disposal, pollution control and other waste management processes. Therefore it is necessary to consider:

1. Sanitary-hygienic characterization of working conditions - physical, chemical, biological factors of the production and/or working environment and the labor process;
2. The permissible norms of chemical substances in the air of the working zone of the pharmaceutical institution shall be used for the hygienic assessment of the working conditions for the following purpose: A) To determine the conformity with the hygienic norms to check the working conditions of the employees and to make a hygienic conclusion; B) To determine the priority direction during the implementation of remedial measures and to determine its effectiveness; C) To create a database at the level of enterprise, field, region, republic; D) To determine the level of occupational risk, to take preventive measures and to justify social protection measures; E) To investigate cases of occupational diseases and poisoning.

ISO – The normative act of the International Organization for Standardization provides:

1. The purpose of labeling and marking hazardous chemicals is to inform the contact persons and the user about the harmful effects of these substances on health and the environment, in order to ensure their safe use;
2. In order to safely treat a hazardous chemical and maintain its consumer properties, the creator/manufacturer shall classify the substance / preparation according to the hazard before submitting it to the state examination and registration application, as well as develop a draft of the mark and label;
3. Each category of hazard classification shall be abbreviated, accompanied by the relevant risk phrase or phrases;
4. If the substance is classified as flammable, sensitizing or hazardous to the environment, only the phrase risk shall be used;
5. If a substance is classified as carcinogenic, mutagenic or toxic, the appropriate abbreviation is used to indicate the category (eg 1,2,3) [21-22].
6. Hazard classification categories are expressed by the following abbreviations: a) Explosive: E b) Oxidizing: O c) Particularly flammable: F + d) Highly flammable: F flammable: R10 f) Highly toxic: T + g) Toxic: T h) Harmful: Xn i) Corrosive: C j) Irritant: Xi l) Sensitizing: R42 and / or R43 m) Carcinogenic: Carc. Cat. (1) n) Mutagenic: Muta. Cat. (1) n) For toxic reproduction: Repr. Cat. (1) o) for hazardous environment: N and / or R52, R53, R59.
7. Hazard classification categories are represented by symbols with risk R-phrases and safety S-phrases.
8. The user who carries out the use of hazardous chemicals is obliged to ensure the maintenance of the label and mark on the container.

In order to investigate and study the possible danger, the data are important, in particular the information on the label, which is emphasized in the mentioned normative act. Required:

A) For the substance - trade name, chemical name, synonyms common according to IUPAC and CAS number; B) For the drug - trade name, chemical names of the constituents according to IUPAC, CAS numbers and concentrations; C) State registration number; D) Scope of application; E) Complete information about the manufacturer, importer or distributor of the substance / preparation: name, surname, address, telephone; F) Date of manufacture, expiration date, batch or series number, storage conditions, net, mass; G) Symbols and signs of the relevant classification of danger; H) R-phrases indicating a specific hazard; I) S-phrases denoting security measures; J) Information on first aid.

The same document defines

1. How to provide the required information on the label: A)For hazardous chemicals used within the country - in Georgian; B)For export chemicals in several foreign languages (English, Russian, German, French, Spanish, etc.); C)The inscription should be easy to understand for the carrier and the professional user.
2. The label shall indicate the prohibition of re-use of packaging or material, as well as recommendations for its disposal and decontamination;
3. The label must be firmly affixed to the packaging container or material as soon as the chemical is packaged;
4. The dimensions of the label are determined according to the volume of the container. The size of the label should not exceed: a) in case of volume up to 3 liters - 52X74 mm; B) in case of volume more than 3 liters and not more than 50 liters - 105X148 mm; C) in case of volume more than 50 liters and not more than 500 liters - 148X210 mm;
5. Each symbol on the label should occupy 1/10 of the surface of the container and at the same time should not be less than 1 cm;
6. Danger symbols shall be displayed in accordance with Annex 3. If the danger is indicated by more than one symbol, then on the label: A) When displaying the necessary E symbol, it is not necessary to display the F, F + and O symbols; B) It is not necessary to display the symbols Xn, Xi, C when the necessary T + or T symbol is displayed; C) it is not necessary to display the symbols Xn, Xi when displaying the necessary C symbol; D) Necessary Xn, display of the symbol Xi is not required when displaying the symbol;
7. Symbols should be drawn in a square on a black, orange-yellow background;
8. Risk phrases for the label are selected according to the hazard criteria. A maximum of six phrases are used to describe the risk. Mixed risk phrases are used when necessary. If a substance is characterized by several categories of hazard the standard phrases should cover all of them;
9. Safety S-phrases for the label are selected according to the risk phrases. A maximum of six S-phrases are usually sufficient to form security measures [23-27].
From a safety point of view, special importance is attached to the transportation of a pharmaceutical product, which is set out in the same Act as follows:
1. In case of transportation of a chemical substance, the label of the transport container shall include additional information on the number of packed container places placed in the transport container, the net and gross mass of each place, an indication on the normative-technical documentation;
2. If it is practically impossible to label and mark the container of a hazardous chemical due to the size of the container or the nature of the packaging, the relevant information must be reflected in the attached documentation;
3. Requirements for marks include: A) The markings on the label must reflect accurate information about the hazardous chemical; B) The label must be firmly attached to the container. Its size must comply with the requirements set by the norms. The inscription should be clear and easy to understand; (C) Labels with signs and symbols depicted on them must be uniform, including the R-phrases of risk and the S-phrases of safety used in the colors used [28-29].
This document addresses the safety issues of the pharmaceutical product in pharmaceutical establishments, as well as the cases when the patient uses the pharmaceutical product. The Ministry of Labor, Social Affairs, and the Ministry of Internally Displaced Persons from the Occupied Territories of Georgia (hereinafter referred to as the Ministry) is the Labor Safety Supervision Authority in Georgia. Protecting the health of the employed population, preventing occupational and occupational diseases, promoting a safe environment in the workplace. The beneficiaries of the

program are citizens of Georgia. The program provides state-sponsored occupational health research for various services, including state-owned enterprises [30-31].

By the decree of the Government of Georgia, the state program for monitoring the working conditions was approved, the implementation of which was entrusted to the central office of the Ministry. The target group of the program includes employers who give their prior consent to the monitoring. In addition, under this program, employers receive a notification about the inspection 5 working days before the monitoring procedure. Within the program, the target group is selected and the monitoring sequence is determined. The program does not establish the rules for conducting monitoring and its regulation is linked to the issuance of an individual act of the Minister. Violation of labor safety norms is controlled by a labor safety specialist - a person with appropriate qualifications appointed/ invited by the employer, who ensures the introduction and management of labor safety measures to prevent violations of labor safety norms [32-33].

According to the Georgia-EU Association Agenda for 2014-2016, Georgia has committed itself to establishing a labor inspection mechanism and institution that would have adequate potential to test working conditions and meet International Labor Organization standards.This issue is also defined in Chapters 13 and 14 of the Georgia-EU Association Agreement, the implementation of which is a future perspective.

Among the main tasks and functions of the mentioned department, the implementation of state supervision is defined:

- Implementation of technical regulations and labor safety mechanism for compliance with working conditions in the field of labor safety requirements, observance of safety rules during the production process and other work environment safety control, in case of violation of which the department is authorized to use the sanctioning mechanism;
- Supervise the observance of labor legislation and the investigation and registration of accidents at the place of employment;
- Take preventive measures against human trafficking in order to prevent forced labor;
- Analysis of labor law, violations of labor and health safety and the causes of industrial injuries, development of proposals and recommendations for their elimination and prevention;
- Review of applications, complaints and proposals within the scope of authority granted by the legislation of Georgia.
- Other rights provided by the statute [34-35].

Aim and objectives of the research

The aim of the research was to study the legal-normative basis of labor safety, equipment and sanitary-hygienic requirements of activities in pharmaceutical institutions, to identify their strengths and weaknesses, pros and cons, to reflect a specific problem and to find ways to solve, eliminate and resolve it. In order to achieve the above-mentioned goal, we considered it necessary to determine the quality and compliance of the work space safety of the research facilities with the Organic Law of Georgia on Labor Safety. Assessing the risk of harm to personnel and consumers was considered an existing epidemic. Regarding safety - according to the data of the study period.

Materials and methods

The information source of the paper is the materials of the survey of pharmacists, international economic journals, reports of the Ministry of Internally Displaced Persons from the Occupied

Territories, Labor, Health and Social Affairs, statistical collections of the State Department of Statistics, Georgian laws, bylaws and other legal acts.

In general, the subject of research was the Georgian pharmaceutical market, which creates a danger not only for consumers but also for employees. The objects of research are pharmacies operating in the market, pharmaceutical companies, pharmaceutical companies, regulatory bodies and employees working there.

Based on the existing theoretical foundations of occupational safety, we considered it necessary to identify the methodological and practical issues, the set of materials from which we selected the objects of research.

The 2 types of questionnaires for pharmacists were selected. The questionnaire, on the one hand, considers whether there is a regulatory legal framework on labor safety in Georgia and, on the other hand, whether all the requirements provided by the legal framework are met, to what extent they comply with the requirements and standards.

Through this questionnaire, we focused on the following key issues:

- What information do pharmacists have about occupational safety, including sanitation?
- Is labor safety in pharmaceutical institutions regulated in Georgia;
- Is there a legal normative basis for sanitary requirements;
- If regulated, then how much is actually done in pharmaceutical establishments;
- Whether employees are provided with information on safety rules when hired and whether there is an appropriate entry in the employment contract.

As a research method, we used specific quantitative and qualitative studies, based on the results of which we drew some conclusions and developed recommendations.

Results and discussion

The target segment of the research was 5 objects,

- 2 of them were pharmaceutical factories:
- GMP Ltd;
- Neopharm Ltd.
- 2 Drugstores
- Pharmacy PSP Ltd
- Aversi-Pharma Ltd
- And the regulatory body

Ministry of Internally Displaced Persons from the Occupied Territories, Labor, Health and Social Affairs of Georgia, LEPL Agency for Regulation of Medical and Pharmaceutical Activities.

The answers to each question from each of the five objects are presented in summary form (we did not consider it necessary to present the results separately at this stage). With this we tried to present an overall picture of the data actually available. The survey was conducted with a pre-compiled questionnaire, the anonymity of the respondents was protected.

Table №1. Q 1. Is there occupational safety at your workplace?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	48.9	30.8	Yes	79.7
No	51.1	30.8	No	20.3
I do not know	-	-	I do not know	-

It is noteworthy that 48.9% of respondents in the workplace believe that occupational safety is protected and 51% state that it is not protected, which changed significantly during the pandemic and increased by 30%. We think more attention is needed in this direction. See Table №1.

Table №2. Q2. Is the essence of your job a labor safety specialist?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	39.4	12.3	Yes	51.7
No	28.2	4.9	No	33.1
I do not know	32.4	17.1	I do not know	15.3

The urgency of this question has increased during the pandemic, but the respondents' answers are not in full compliance and a shortcoming has been identified. It is estimated that 51.7% of the institutions are security specialists. And the difference between pandemic and pandemic time is only 12.3%. See Table №2.

Table №3. Q 3. Are you aware of the health risk factors in your workspace?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	49.6	37.6	Yes	87.2
No	50.4	37.6	No	12.8
I do not know	-	-	I do not know	-

It is unfortunate that 50% were unaware of the existence of health hazards in the workplace and the degree of interest in information during the pandemic changed by 37.6% to 87.2%. It should definitely be noted that pharmaceutical activity is associated with life-threatening substances. And especially if the touch is long. See Table №3.

Table №4. Q 4. Is the compliance of the production environment and the physical, chemical and biological factors of the labor process with the hygienic norms of your facility?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	44.7	11.2	Yes	55.9
No	22.7	6.1	No	28.8
I do not know	32.6	17.3	I do not know	15.3

According to the answers to this question, there is no favorable situation in the pharmaceutical facility in this regard, the need for permanent identification of health hazards in the workplace has been identified. See Table №4.

Table №5. Q 5. Is there an evacuation board/drawing in your workspace?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	62.4	32.5	Yes	94.9
No	37.6	32.5	No	5.1
I do not know	-	-	I do not know	-

Before the pandemic, 62.1% said that during the pandemic - 94.9%, according to the survey results, during the pandemic, the number of medical institutions where the evacuation board was posted increased by 32.5%. It is known that the evacuation board is a plan of the floors of a building (pharmacy), which shows the evacuation exits, rescue facilities and their locations, etc. The spread of the evacuation board in the pharmacy was due to the sharply increased number of patients in pandemic conditions and the stressful environment created by the situation caused the pharmacists to lose attention, thus increasing the risk of harmful events (flammable substance ignition, fire hazard, etc.). See Table №5.

Table №6. Q 6. Do you think that all workplaces should have the appropriate safety requirements? (Fire extinguisher, hood, alarm, etc.)?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	73.2	20.8	Yes	94
No	26.8	20.8	No	6
I do not know	-	-	I do not know	-

Prior to the pandemic, 26.8% of respondents thought that appropriate safety precautions were not necessary in the facility, however, the current situation changed the majority view on this issue and 94% of respondents after the pandemic noted the need for appropriate security equipment, which was completely logical. The quarantine and isolation declared during the pandemic led to a change in the usual rhythm of life before adapting to the existing situation, people had to deal with a situation that was foreign and unusual to them, and mistakes were often made at high risk of adverse events. There has been an increase in rescue services, fire and emergency medical services and, consequently, continuous work in a busy schedule. All this made it necessary to place appropriate safety equipment in the workplace to be able to respond in a timely manner to the situations created. See Table №6.

Table №7. Q 7. Do you think the institution should take into account psycho-social factors (stress, communication, post-traumatic stress)?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	66.2	16	Yes	82.2
No	19	2.1	No	16.9
I do not know	14.8	13.9	I do not know	0.9

Almost all respondents to this question state that psycho-social factors should be taken into account in the institution. And positive responses, i.e. necessity before pandemic and pandemic time difference was 16%. Difference (66.2% before pandemic and 82.2% during pandemic). But it should also be noted that 33.8 (19 + 14.8) does not know the psycho-social factors should be taken into account in the institution. See Table №7.

Table №8. Q 8. Do you think if it is necessary to teach labor safety rules as a discipline?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	84.5	13	Yes	97.5
No	15.5	13	No	2.5
I do not know	-	-	I do not know	-

Quite interesting answers to the question of whether safety rules need to be learned. In both cases, the difference between the responses of the respondents is small and 13%. Nearly 90% believe that occupational safety needs to be taught. And as far as I know to date this issue is included in the Pharm Case and Organization and Economics curriculum. See Table №8.

Table №9. Q 9. Is there a dezo-barrier in the pharmaceutical facility / pharmacy?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	63.4	36.5	Yes	99.9
No	36.6	36.5	No	0.1
I do not know	-	-	I do not know	-

It is noteworthy that before the pandemic, 36.6% of respondents reported that there were no dezo barriers in pharmacies. The results of the survey differ significantly from the data obtained during COVID-19 infection. 99.9% of respondents confirm that there are dezo barriers in pharmacies. See Table №9.

Table №10. Q 10. Are there safety / separation glasses at pharmacy counters?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	75.2	23.5	Yes	98.7
No	24.8	23.5	No	1.3
I do not know	-	-	I do not know	-

In this case, the protective glasses at the pharmacy counters, or the specialist and patient separating glasses mentioned above, were significantly increased during the pandemic. But more than 23% of respondents think they do not know. See Table №10.
The start date of the study was October 2019, which lasted until May 2020. Thus, the data were collected, which we conditionally divided before the Covid-19-related contraction (February) and and during the Covid-19 activation period. In both cases, due to the current situation, we used the same topical questions. Accordingly, an average of 142 respondents (from all five facilities) were interviewed. The answers are presented with two data. All the first diagrams presented are data up to Covid-19. Second, even the data obtained during Covid19.

Table №11. Q 11. Is labor safety regulated in Georgia?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	30.7	43.9	Yes	74.6
No	25	5.5	No	19.5

I do not know	44.3	38.4	I do not know	5.9

The data show that 44.3% of respondents were not informed about labor safety regulations in Georgia. And, 25% thought that security was not regulated at all. However, it should be noted that during the pandemic, the survey was conducted again and 74.6% of respondents believe that occupational safety is regulated by law. We also note that the need for labor safety regulation is growing, accounting for 43.9%. See Table №11.

Table №12. Q 12. Do you know the law on labor safety?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	34.8	33.8	Yes	68.6
No	65.8	43.4	No	31.4
I do not know	-	-	I do not know	-

The answers to this question show that if 34.8% knew about the Labor Law of Georgia before the pandemic, the developed situation necessitated knowledge with a difference of 33.8%. See Table №12.

Table №13. Q 13. Is labor safety regulated in pharmaceutical institutions?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	30.3	40.0	Yes	70.3
No	33.1	11.9	No	21.2
I do not know	36.6	28.1	I do not know	8.5

The data show that 30.3% of the respondents did not know about the regulation of occupational safety in a pharmaceutical facility before the pandemic. In the conditions of the pandemic, the interest in this direction increased by 40.0% and also the number of respondents who were unaware decreased from 36% to 28.1% from 8.5%, which somehow indicates a necessary tendency for self-development. See Table №13.

Table №14. Q 14. Do you know the legal normative based on sanitary requirements?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	41.8	319	Yes	73.7
No	58.2	31.9	No	26.3
I do not know	-	-	I do not know	-

The answers to the question about the degree of informativeness about the sanitary requirements of the legal normative base in pharmaceutical institutions do not look very good. The data show that it seems that all respondents are familiar with this issue, but it seems that the current situation also played a role here and the degree of improvement of knowledge amounted to - 31.9%. See Table №14.

Table №15. Q 15. Are sanitary requirements regulated in pharmaceutical facilities?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	32.4	45.6	Yes	78
No	34.5	17.6%	No	16.9
I do not know	33.1	28	I do not know	5.1

Unfortunately, 31.1% of respondents did not have information about the regulation of sanitary requirements. In this regard and 34.5% believed that it was not regulated. But in a re-survey, informatics increased by 45.6%, with 78% believing it to be regulated. The number of those who did not know decreased by 28% to 5.1%. See Table №15.

Table №16. Q 16. On the territory of Georgia, is there any registration of occupational disease at work with the existing high-risk, severe, harmful hazardous conditions?

Before Covid-19 (%)		Differences (%)	During Covid-19 (%)	
Yes	41.8	9.0	Yes	50.8
No	25.5	0.8	No	26.3
I do not know	32.6	9.7	I do not know	22.9

On this question, we think that the level of informatics is low and it should also be noted that before the pandemic and during the pandemic, interest in this area changed by only 9.0%. There are small gaps between the responses of respondents who do not know whether accounting is taking place. See Table №16.

Interest in hiring employers to learn about occupational safety rules increased from 49.3% to 72% to 22.7%. Respondents who did not know and were not informed when hiring accounted for 50.0% which decreased by 22.7% and amounted to 28%. It should be noted that a high rate would be high on all of the above questions to maintain a high degree of information on all occupational safety regulations when hiring. We think that this information is important and should be taken into account.

Discussion

Healthcare is the area of activity that is most strictly regulated by the state. Today, the health care system, which includes all departmental and sectoral levels of the state economy, is not only a combination of medical-prophylactic, rehabilitation and recovery institutions, but also it is closely connected with ecology, labor protection, social programs, etc. One of the most important functions of health is to promote and restore the balance and harmony of individual and public health. We think we need: Expand the scope of the draft law on labor safety and extend it to all places of employment, without exception;

Equip the Labor Inspectorate with an unconditional and free access to the places of employment, which implies the authority of the mechanism, by its own decision, to carry out inspections of the places of employment without the prior permission of the court; The Law of Georgia on Labor Safety envisages an appropriate system of sanctions, including the proper rules for the application of sanctions and adequate amounts of fines, which will have both preventive and responsive effects;

The state should create an appropriate legislative and institutional framework; We think this will help transform the existing department into an effective labor inspectorate. The possibility will be

created of the institutional capacity of its independence and efficiency, and the law will also provide guarantees for the individual independence of inspectors; Also, the bill should directly refer to the Labor Inspectorate as the body responsible for law enforcement.At present, the legal-normative base of labor safety, equipment and sanitary-hygienic requirements in Georgia creates a safe environment for activities in pharmaceutical establishments, the permanent control of compliance with the norms of which guarantees full protection for those in contact with the pharmaceutical product;

We believe that the right, legal approach, strict control and state policy in the field of drug trafficking are a prerequisite for creating a safe environment. Most importantly, despite the interests of the owners of the Georgian pharmaceutical industry and modern marketing approaches, the safety of the population and employees remains a priority;

Evaluation and analysis of the data obtained from our research suggest that there is a need to tighten and control safety regulations in the pharmaceutical facility; 44.3% of respondents are not informed about labor safety regulations in Georgia; More than 33% of respondents are unaware of the regulation of occupational safety in a pharmaceutical facility; Low legal-normative base and level of awareness on sanitary requirements in pharmaceutical institutions;50% of respondents were unaware of the presence of potential or existing health hazards in the workplace.

Conclusions

Based on the study of the problems of this issue and the results of the research, we can draw the following conclusions:

- Pharmaceutical establishments do not comply with the hygienic norms of the internal and external environment, physical, chemical and biological factors of the labor process. The facility also does not take into account psychosocial factors related to safety (stress, communication, post-traumatic stress, etc.);
- Most pharmaceutical establishments (50-60%) do not have a fire board with appropriate equipment, evacuation exit and scheme. Also has no person responsible for the matter;
- Disobsibility and specialist protection / separation facility prior to pandemic were minimal (increased by 99%) during pandemic;
- 97% of respondents believe that labor safety should be taught in all its characteristics.

REFERENCES

1. Order N215 / N of the Minister of Labor, Health and Social Affairs of Georgia of July 11, 2007 "On the List and Approval of the Rules for Compulsory Periodic Medical Examination of the Employee at the Employer's Expense". 195 Ibid., Annex N1, first paragraph.
2. http://www.matsne.gov.ge 30016007010003017653, 2008, Article 5-6;
3. http://www.matsne.gov.ge 30016007010003017653, 2008, Article 5
4. PHSS-Pharmaceutical Regulation And Pharmaceutical Science. 2019.
5. TOM PETERS RE-IMAGINE! October 6, 2003 Edition.
6. Victor H. Vroom Expectancy Theory, Encyclopedic Dictionary.
7. William L. (“Bill”) White “Cleanroom Technology” 2008 Edition.
8. Ejibadze O. The Future of Management, Electronic Journal "Social Sciences", 2011, №2, p.
9. Ramishvili B., Strategic Management, Chapter I. The Essence and Importance of Strategic Management, Tbilisi, 2013.
10. Civil Code, Minister of Labor, Health and Social Affairs of Georgia 2017; Article 12

11. N. Sulashvili., M. Beglaryan., N. Gorgaslidze., S. Kocharyan; PECULIARITIES OF PRIORITIES AND CHALLENGE OF PHARMACEUTICAL SCIENCES TO BE CONSIDERE IN IMPROVEMENT OF REGULATION ISSUES OF PHARMACISTS PROFESSION; ISSN 1987 − 8826 Nano-Studies; Nano Studies 2020, № 20; Nano Studies is an annual International Scientific Journal; Nano Studies' topics include Nanoscience and Nanotechnology, and related problems of Physics, Chemistry, and Materials Science; http://www.nanostudies.org/ Nano Studies, 2020, №20, Tbilisi-Georgia, Pp 149-162.
12. Civil Code, Minister of Labor, Health and Social Affairs of Georgia 2017; Article 5.6
13. Law of Georgia on Fire Safety 12.05.1998;
14. Law of Georgia on Drugs and Pharmaceutical Activities, 1997.
15. Resolution N650 of the Government of Georgia of December 2, 2014 "On Approval of State Health Care Programs for 2014".
16. http://www.matsne.gov.ge 30016007010003017688, 2009, Appendix 1, 2, 3
17. N.Sulashvili, M.Beglaryan N.Gorgaslidze; The Higher Educational Challenges, Recent Pharmaceutical Professional Issues and Occupational Specification of Pharmacists In Georgia;Удк 615.1:339.188ISSN 2415-8593 Materials of IX International Scientific-Practical Conference- "Management and Marketing In The Modern Economy, Science, Education And Practice". Ministry of Health Of Ukraine; Ministry of Education And Science of Ukraine; Ukrainian Marketing Association, National Pharmaceutical University Of Ukraine, Department of Pharmaceutical Management And Marketing. March 18, 2021, Kharkiv-2021. Pp 53-68.
18. Van Mil J. F., Schulz M., Tromp TFD. Pharmaceutical care, European developments in concepts, implementation, teaching, and research: a review // Pharm World Sci. 2014;26(6); pp. 303–321.
19. N.Sulashvili, M.Beglaryan, N.Gorgaslidze; Pharmacist Vocational Features, Regulations Framework and Profession Enhancement Challenges of Pharmaceutics.Caucasus Journal of Health Sciences and Public Health; E ISSN 2449-2450; ISSN 2449-2647; The University of Georgia Publishing House.www.caucasushealth.ge; Official Journal of the University of Georgia and Iv. Javakhishvili Tbilisi State University with Support of the Arctic University of Tromsø/Norway. Volume 4, Supplement 8, July 20-24, 2020; Pp 31-36.
20. Michael Ira Smith, Albert I. Wertheimer, Jack E. Fincham; Pharmacy and the US Health Care System; Pharmaceutical Press // 4th Revised edition edition (April 15, 2013);pp. 402-426.
21. International Pharmaceutical Federation (FIP). Continuing Professional Development/Continuing Education in Pharmacy // Global Report 2014. The Hague: International Pharmaceutical Federation; 2014.
22. Resolution N38 of the Government of Georgia of 5 February 2015 "On the Approval of the State Program for Monitoring Labor Conditions" 189 Ibid., Article 3; 191 Ibid., Article 3.3.
23. Order N147 / N of the Minister of Labor, Health and Social Affairs of Georgia of May 3, 2007 "On Approval of the List of Hard, Harmful and Dangerous Jobs"
24. Order N01-10 / N of the Minister of Labor, Health and Social Affairs of Georgia of April 21, 2015, Article 2.1.
25. N. Sulashvili, M. Beglaryan, N. Gorgaslidze, S. Kocharyan, N. Chichoyan; THE SCIENTIFIC DISCUSSION OF THE FEATURES OF PHARMACEUTICAL OCCUPATIONAL PRINCIPLES ADJUSTMENT, CHALLENGES, PERSPECTIVES AND

INNOVATIONS; Tbilisi State Medical University, Faculty of Public Health; CONFERENCE BOOK; OF THE FIRST INTERANATIONAL CONFERENCE “FUTURE OF HEALTH CARE IN THE 21 CENTURY”, Tbilisi-2021; Pp:108-135.

26. Technical Regulation on Fire Safety Terms and Conditions, 2011, Annex №1
27. Labor Code, Minister of Labor, Health and Social Affairs of Georgia; Article 17.1.
28. N. Sulashvili, M. Beglaryan, S. Kocharyan, N. Gorgaslidze; Scientifically Study Of Prospects of Modern Scientific Achievements And Research Challenges of Pharmacists Occupational Features In Pharmaceutics And Medicine; Удк 615.1:339.188 ISSN 2415-8593 Materials of IX International Scientific-Practical Conference- “Management And Marketing In The Modern Economy, Science, Education and Practice”.Ministry of Health of Ukraine; Ministry of Education and Science of Ukraine; Ukrainian Marketing Association, National Pharmaceutical University of Ukraine,Department Of Pharmaceutical Management and Marketing. March 18, 2021, Kharkiv. Pp:26-41.
29. Julakidze E. Fundamentals of Management, Kutaisi, Khandzta Publishing House, 2013.Ashbourne Eide, Katharina Krause, Alan Rosa, Economic, Social and Handbook of Cultural Rights , Second Revised Edition, p. 263. 2 Ibid., P. 268.
30. European Commission - EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines;2017
31. FDA - Food and Drug Administration.2018
32. ICCCS-International Confederation of Contamination Control Societes, 2014.
33. Institute of Environmental Sciences and Technology - IEST-RP-CC023- “microorganisms in cleanrooms”,2016.
34. Institute of Environmental Sciences and Technology - IEST-RP-CC027 – “Personnel practices and procedures in cleanroom and controlled anviroments”; 2018.
35. ISO - International Organization for Standardization.2020.

THE FEATURES AND PROSPECTS OF CLINICAL PHARMACY SERVICES OPPORTUNITIES WITH STATEMENT ON PHARMACEUTICAL CARE IN WESTERN GEORGIA

Nato Alavidze[1], Nodar Sulashvili[2]

[1]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia.

[2]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Invited Professor/Lecturer of Tbilisi State Medical University, Tbilisi, Georgia.

Email: n.sulashvili@tsmu.edu

ABSTRACT

The purpose of this study was to evaluate the opportunities and challenges of clinical pharmacy services from the perspective of practitioners in various clinics and hospitals in western Georgia. This improves the quality of life for patients. Thus, pharmaceutical care can be considered as a form of clinical pharmacy. It can be considered the establishment of clinical pharmacy in Georgia, when the record of clinical pharmacy appeared in the National Register of Qualifications, however, there is still no legal framework. a document that would define the role of clinical pharmacy and career opportunities, although many clinics participate in international clinical trials, in which, according to the international protocol, a clinical pharmacist should participate, although at this stage such a profession and personnel are not fixed in clinics, it turns out that general pharmacists practitioners formally perform the functions of a clinical pharmacist, which is confirmed by our survey. The role of the pharmacist in Georgia needs to be expanded, which is still a problem: Some clinical guidelines have been prepared in Georgia. Unfortunately, we have not yet noticed a pharmacist in the writing group of any of the guidelines. We believe that the participation of the clinical pharmacist in the process of preparing recommendations is already necessary. Our study was conducted on the basis of the Medical Center of Western Georgia - "Evex Hospitals". Western Georgia Referral Hospital is the largest hospital in the Evexi Hospitals network, serving more than 1,200 inpatients and 10,000 outpatients every month and performing up to 600 surgical interventions.

The hospital has an emergency room for both adults and children. In the entire region, only the referral hospital of Western Georgia has a department of neonatology and pediatric resuscitation. The hospital has a full-fledged cardiology and cardiac surgery service, which contributes to reducing mortality from cardiovascular insufficiency throughout the region. We have established that clinical pharmacy services are actually implemented in the EVEX network hospitals in Western Georgia, although there is still no specific legal framework. Clinic Networked health workers are receptive to clinical pharmacy services, but we have identified some potential challenges to strengthening and promoting clinical pharmacy services. In addition, existing opportunities to improve services should be used wisely. The participation of a clinical pharmacist is important at all stages of creating a treatment algorithm. A clinical pharmacist is obliged to participate in the formation of a policy for the use of medicines, to cooperate with specialists in the development of methodological recommendations and guidelines for the treatment of certain diseases, to participate in the sale and purchase of medicines, the creation of medicinal formulations, etc. The pharmacist profession has

not yet evolved into a clinical profession but is now more than ever focused on its transformation from a product-centric profession (including drug procurement, preparation, and evaluation) to a patient-centric profession. The clinical pharmacist has an important role to play in ensuring the health of the patient.
Keywords: Pharmaceutical services; professional practice; pharmacy service; hospital; pharmacists; medical staff; quality, Georgia.

Introduction

Adult medicine touches all walks of life. It is a combination of ambulatory care, internal medicine and family practice rolled into one, with a "smattering" of every other discipline. The field of adult medicine demands a well-rounded. It enables you to see things from a broad perspective, yet allows you to delve into issues as deeply as you desire. Adult medicine touches all areas of life. It is a combination of outpatient care, internal medicine and family practice, with all other disciplines "turned on". The field of adult medicine requires a well-integrated omnidirectional mentality. allows to look at things from a broad perspective, but it also allows you to delve deeper into problems [1-3].

Currently, clinical pharmacists have in-depth therapeutic knowledge and scientific skills to act as experts in drug therapy in medical settings. In Georgia, there has been talk for a long time about the establishment of an institute of clinical pharmacists, but it seems that due to the inertia of the administrative infrastructure, it has not yet been officially created. At the same time, the medical, including pharmaceutical, infrastructure in Georgia is developing rapidly, and we can safely say that practice forced some pharmacists to take on this function - in fact (functionally), the institute of clinical pharmacists was formed by life. For example: pharmacists of the "reception desk" of large pharmaceutical companies often have to consult patients, "pharmacists-consultants" of insurance companies actually perform the function of clinical pharmacists [4-7].

Clinical pharmacy, as we have already mentioned, is a complex science. One of its characteristics and a distinguishing feature from related fields of medicine is the integration of information technology with (mathematical, engineering) sciences. In 2007, about 5,400 medicines were registered in Georgia, and their number is growing rapidly. The number of drugs is much higher in economically developed countries. Naturally, the manipulation of this volume of information, conducting a comparative analysis, is impossible without specialized information systems, which requires not only the use of these sciences, but also integration with them. Therefore, for several years in Georgia, within the framework of Lali Dateshidze's project “Georgian Electronic Medical Encyclopedia”, work has been underway to create an “automated workplace” for a clinical pharmacist [8-11].

The main difference between clinical pharmacists and conventional registered pharmacists in the ability of clinical pharmacists to interact with patients and that they can recommend specific medications and drug doses for a particular patient in order to make a drug more effective. the patient is well. The term "pharmaceutical care" originated from clinical pharmacy. The two concepts are compatible and seem to have similar goals. One way to distinguish between the two would be to describe clinical pharmacy as a pharmaceutical practice within a larger pharmaceutical care system in which the pharmacist would contribute. The goal is to achieve pharmacotherapeutic outcomes and improve the quality of life of patients. Pharmaceutical care can be defined as "the direct, prompt delivery of medical care to achieve specific outcomes that improve the patient's quality of life." Thus, pharmaceutical care can be considered part of clinical pharmacy [12-15].

The purpose of this statement is to help pharmacists understand pharmaceutical care. Such an understanding should precede efforts to introduce pharmaceutical care, which is the highest priority in all practices.

Many pharmacists have embraced the concept of pharmaceutical care with enthusiasm, but there has also been significant inconsistency in the way it has been described. Some characterize it as a new name for clinical pharmacy; Others describe it as any action by pharmacists that can lead to favorable outcomes for patients [16-18].

Directly in clinical settings, there are many goals and tasks that clinical pharmacists can perform. For example, in the United States, clinical pharmacists work in almost 80% of medical institutions, which contributes to the rational use of drugs and saves on drugs by about 10-20%. The participation of a clinical pharmacist is important at all stages of creating a treatment algorithm. A clinical pharmacist is obliged to participate in the formation of a policy for the use of medicines, to cooperate with specialists in the development of methodological recommendations and guidelines for the treatment of certain diseases, to participate in the sale and purchase of medicines, the creation of medicinal formulations, etc. in processes [20-22].

The profession of pharmacist has not yet developed as a clinical profession in Georgia and is now more than ever focused on transforming from a product-oriented profession (including drug procurement, preparation and evaluation) to a patient-centered profession. The clinical pharmacist has an important role to play in ensuring the health of the patient. The American College of Clinical Pharmacy (ACCP) in 2006 identified the main differences between clinical pharmacists and regular registered pharmacists as clinical pharmacists [23-25]

This improves the quality of life for patients. Thus, pharmaceutical care can be considered as a form of clinical pharmacy. It can be considered the establishment of clinical pharmacy in Georgia, when the record of clinical pharmacy appeared in the National Register of Qualifications, however, there is still no legal framework. a document that would define the role of clinical pharmacy and career opportunities, although many clinics participate in international clinical trials, in which, according to the international protocol, a clinical pharmacist should participate, although at this stage such a profession and personnel are not fixed in clinics, it turns out that general pharmacists practitioners formally perform the functions of a clinical pharmacist, which is confirmed by our survey. The role of the pharmacist in Georgia needs to be expanded, which is still a problem: Some clinical guidelines have been prepared in Georgia. Unfortunately, we have not yet noticed a pharmacist in the writing group of any of the guidelines. We believe that the participation of the clinical pharmacist in the process of preparing recommendations is already necessary [26-28].

The participation of a clinical pharmacist is important at all stages of creating a treatment algorithm. A clinical pharmacist is obliged to participate in the formation of a policy for the use of medicines, to cooperate with specialists in the development of methodological recommendations and guidelines for the treatment of certain diseases, to participate in the sale and purchase of medicines, the creation of medicinal formulations, etc. The pharmacist profession has not yet evolved into a clinical profession, but is now more than ever focused on its transformation from a product-centric profession (including drug procurement, preparation, and evaluation) to a patient-centric profession. The clinical pharmacist has an important role to play in ensuring the health of the patient [29-32].

In 2006, the American College of Clinical Pharmacy identified a key difference between clinical pharmacists and regular registered pharmacists. Clinical pharmacists improve the quality of life of patients. Thus, pharmaceutical care can be considered a form of clinical pharmacy. The establishment of clinical pharmacy in Georgia in 2019 can be considered the moment when an entry

for clinical pharmacy appeared in the national qualification system, however, there is still no regulatory document defining the role of clinical pharmacy. clinical pharmacy and career opportunities, although many clinics across the country are participating in international clinical trials, in which, according to the international protocol, a clinical pharmacist should be involved, although at this stage such a profession and staff are not fixed in clinics, it turns out that general practitioners formally perform the functions of a clinical pharmacist, which is confirmed by our survey that the pharmacist is needed to expand the role in Georgia.

Clinical pharmacy as the field of pharmacy concerned with the science and practice of rational drug use. By this definition, the possibilities of clinical pharmacists are endless. There are many career options available to pharmacists seeking clinical opportunities in their practice. As a clinical pharmacist, may provide general clinical services. However, there are various highly specialized areas that cover different patient groups [33-35].

Pharmaceutical care to be an important new concept, which represents the growth of the profession beyond clinical pharmacy, as it is often practiced, and beyond the other activities of pharmacists, including drug preparation and dispensing. However, in Europe all of these professional activities are important and strongly supports the need for pharmacists to participate. In practice, these activities should be integrated and culminate in pharmaceutical care provided by individual pharmacists to individual patients [36-39].

The philosophy of pharmaceutical care (PC) is the sum of responsibilities of the pharmacist to meet all of the patient's drug-related needs through direct patient care and cooperation with other facets of the health care system. Clinical pharmacists possess in-depth therapeutic knowledge and scientific skills that allow them to act as drug therapy experts in healthcare setting.[1] The American College of Clinical Pharmacy (ACCP) defined clinical pharmacy as a discipline with specialized pharmacists concerned with the science and practice of rational drug therapy. Clinical pharmacists apply scientific evidence to ensure and advice on best use of medications for optimal drug therapy. Further, they also engage in various research activities to generate new knowledge and practical skills that furthermore can improve patients' health and quality of life. Over the years pharmacists' roles have evolved to include participation in bedside rounds as part of a multidisciplinary health care team, and in patient profile review aimed at the identification and resolution of any drug-related problems. Pharmacist interventions, such as counseling the patient to improve their adherence and compliance, have contributed to a consistent development of clinical pharmacy services all over the world. Despite the importance of these receptive services to the improvement of patient outcomes, clinical pharmacists face many challenges such as poor awareness among general public, lack of specific legislation and recognition from other health care providers. Possible reasons may be unacceptance of pharmacists' professional standing by other health practitioners, lack of leadership qualities, patients' perceptions, and existence of communication gaps between pharmacists and doctors. In particular, these challenges are highly noted in developing countries. Physicians' expectations and perceptions towards the pharmacists' roles and responsibilities are the main factor influencing the advancement of clinical pharmacy service in hospitals [40-44].

Recent reforms in hospital implementation guidelines state that pharmacists should be assigned to hospitals for the benefit of the patients. Prioritizing the national guidelines, the undergraduate pharmacy curriculum shifted towards patient-focused practice by including a mandatory 1-year clerkship program as part of the academic training. Hospital, clinical pharmacists began to work as integral parts of the health care teams. Clinical pharmacists sporadically provided various patient care services. This includes medication therapy management, dosage adjustments, interventions to

optimize drug therapy, and provided drug information to health professionals and patients. Recently, the has launched the postgraduate program of clinical pharmacy (MSc) to improve and advance the work force in hospital. A better understanding of health professionals' perspectives regarding clinical pharmacy services can provide a greater opportunity to identify the challenges and future opportunities of clinical pharmacists in hospital. Thus, the present qualitative study aimed to explore challenges and opportunities of clinical pharmacy services offered in hospital through health practitioners' perspectives [45-48].

A clinical pharmacist is not a competitor of a doctor in any case, on the contrary, must refer patients who need qualified medical care to a doctor. It is difficult to imagine a pharmacist who does not know the alphabet of medicine and does not have relevant knowledge of the main clinical syndromes. He should be especially well versed in the nomenclature of medicinal drugs (primarily, even non-prescription drugs). Essentially, a clinical pharmacist must provide defined pharmaceutical care (in English-speaking countries, the term pharmaceutical care is used) and must make a decision on dispensing this or that medication [49-51].

While curricula have been adapted to prepare pharmacists for this new role, changes in practice have focused on other issues, such as the emerging covid epidemic, which has led to significant changes in healthcare. Care sector in relation to practice and legislation.

Clinical pharmacy should be seen as a distinct professional approach to hospital pharmacy. it Is important for pharmacists to have a complete picture of a patient's condition so that they can evaluate drug therapy and communicate effectively with other members of the healthcare team. Pharmacists should establish a good relationship and liaise with the multidisciplinary medical team by asking them to move from the dispensary to the wards where they administer drugs and visit doctors. Human resource issues and a shortage of trained clinical pharmacists have meant that pharmacists cannot work in clinical settings. Specifically, the following pharmaceutical assistance functions were missing [52-54].

The concept of pharmaceutical care has evolved into integrated drug management as part of clinical pharmacy. Drug treatment has expanded as treatment regimens have become more complex and specialized, especially in more complex patients who may have five comorbidities and take an average of eight drugs at the same time. To achieve the best results of drug therapy in such patients, systematic and complex drug therapy is necessary [55-57].

Objective

The purpose of this study was to evaluate the opportunities and challenges of clinical pharmacy services from the perspective of practitioners in various clinics and hospitals in western Georgia.

Methods research design

Qualitative in-depth interviews were conducted from April 11 to August 1, 2022 at the West Georgia Medical Center. Western Georgia Referral Hospital is the largest hospital in the Evexi Hospitals network, serving more than 1,200 inpatients and 10,000 outpatients every month and performing up to 600 surgical interventions.

The hospital has an emergency room for both adults and children. In the entire region, only the referral hospital of Western Georgia has a department of neonatology and pediatric resuscitation. The hospital has a full-fledged cardiology and cardiac surgery service, which contributes to reducing mortality from cardiovascular insufficiency throughout the region.

Participants were recruited through personal contacts and convenience sampling methods. Selected participants were contacted in person or by phone to set up interview appointments. A total of 75 healthcare professionals (an equal number of participating physicians, pharmacists, and nurses) working at a West Georgia Specialty Hospital were selected for interviews, and efforts were made to ensure representation from each department where clinical pharmacy services are provided.

Results and discussion

A total of 115 medical professionals from various specialties were interviewed to express their opinion about the competence of clinical pharmacists and to identify challenges and opportunities related to their clinical services. Opportunities for clinical pharmacists include recognition of their clinical services in medical specialties, new government policies, and more hospital referrals, according to interviewees' report. However, inadequacy of service delivery, discontinuation of clinical pharmacy services across departments, poor drug information services, lack of adherence, lack of trust in clinical pharmacists, conflicts of interest due to unclear scope of practice, and lack of collaboration with other healthcare professionals.

Our study was conducted on the basis of the Medical Center of Western Georgia - "Evex Hospitals". Western Georgia Referral Hospital is the largest hospital in the Evexi Hospitals network, serving more than 1,200 inpatients and 10,000 outpatients every month and performing up to 600 surgical interventions.

The hospital has an emergency room for both adults and children. In the entire region, only the referral hospital of Western Georgia has a department of neonatology and pediatric resuscitation.

The hospital has a full-fledged cardiology and cardiac surgery service, which contributes to reducing mortality from cardiovascular insufficiency throughout the region.

We have established that clinical pharmacy services are actually implemented in the EVEX network hospitals in Western Georgia, although there is still no specific legal framework. Clinic Networked health workers are receptive to clinical pharmacy services, but we have identified some potential challenges to strengthening and promoting clinical pharmacy services. In addition, existing opportunities to improve services should be used wisely.

The creation and development of clinical pharmacy was due to the increase in the number of medicines. It is becoming more and more difficult for a doctor to make a rational decision in a particular clinical situation - to choose drugs that will give us the maximum effect in a multi-criteria sense, at the lowest cost.

The experience of economically developed countries confirms that in the modern conditions of the development of pharmaceutical production, a highly qualified specialist is needed, who, first of all, would have full knowledge of medicines and, at the same time, focused academic knowledge in the field of disease treatment. This specialist is a clinical pharmacist.

The well-coordinated work of the clinical pharmacist and the clinician makes it possible to rationally use the growing arsenal of medicines. Obviously, this is only possible by creating an atmosphere of cooperation between the clinical pharmacist and the doctor. To create a collaborative atmosphere, it is not enough to educate clinical pharmacists, it is also necessary to educate physicians.

In Western European countries, the specialty "Clinical Pharmacy" appeared and took shape in the 70s of the last century. The field of activity of specialists in this area is not limited to work only in pharmacies. They help physicians in the rational selection of drugs, taking into account their pharmacokinetics, pharmacodynamics, interactions with other drugs, as well as the cost of treatment.

In fact, the full demand for clinical pharmacy is created only if the model of insurance medicine works correctly. Georgia is gradually entering this phase of development of the insurance business.
The work of insurance companies should be focused on interaction with clinics and pharmacies that have highly qualified specialists. These specialists must have systemic knowledge in the field of medicine, pharmacology, clinical pharmacology, clinical pharmacy, physician and clinical pharmacist.
The clinical pharmacist is by no means a competitor to the doctor, on the contrary, he must refer patients in need of qualified medical care to the doctor. It is difficult to imagine a pharmacist who does not know the ABC of medicine and does not have the appropriate knowledge about the main clinical syndromes. He should be especially well versed in the nomenclature of medicines (primarily, even over-the-counter ones). In essence, the clinical pharmacist must provide certain pharmaceutical care (in English-speaking countries, the term "pharmaceutical care" is used) and make a decision on the dispensing of a particular drug.
While curricula have been adapted to prepare pharmacists for this new role, practical developments have focused on other issues, such as the emerging Covid-19 epidemic, which has led to significant changes in healthcare. Care sector in relation to practice and legislation.
ASHP - The American Society of Hospital/Clinical Pharmacy considers pharmaceutical care to be an important new concept that represents the growth of the profession beyond clinical pharmacy, as it is often practiced, and beyond other activities of pharmacists, including drug preparation and dispensing. However, all of these professional activities are important, and ASHP continues to actively support the need for pharmacists to participate in them. In practice, these activities should be integrated and culminate in pharmaceutical care provided by individual pharmacists to individual patients [58-60].
The Philosophy of Pharmaceutical Care (PC) is a combination of the pharmacist's responsibility to meet all of the patient's drug-related needs, in collaboration with direct patient care and other aspects of the healthcare system. Clinical pharmacists have deep therapeutic knowledge and scientific skills that enable them to act as drug therapy experts in healthcare settings. On rational drug therapy. Clinical pharmacists use scientific evidence to provide and make recommendations on the best use of medicines for optimal drug therapy. In addition, they also participate in various research activities to gain new knowledge and practical skills that can further improve the health and quality of life of patients. Team and patient profile analysis to identify and resolve any drug-related issues. Pharmacist interventions, such as patient counseling to improve adherence and adherence to treatment, have contributed to the consistent development of clinical pharmacy services worldwide. Despite the importance of these medication services in improving patient outcomes, clinical pharmacists face many challenges. such as low public awareness, lack of specific legislation, and acceptance by other health care providers. Possible reasons may be rejection of the professional position of pharmacists by other practitioners, lack of leadership, patient perceptions, and gaps in communication between pharmacists and physicians. In particular, these problems are particularly noticeable in developing countries. For example, Europe and countries with limited resources such as Georgia. Physicians' expectations and perceptions of the role and responsibilities of the pharmacist are major factors influencing clinical pharmacy services. Clinical service implementation guidelines should be reformed [61-63].
A study of the experience of other countries shows that pharmacists should be included in the clinical team of patients in hospitals in favor of the Bachelor / Master of Pharmacy training programs should move to patient-centered practice, including a mandatory one-year internship program. Part

of academic preparation. Clinical pharmacists in the hospital should start working as an integral part of the medical teams. Currently, pharmacists in clinical pharmacies, like real clinical pharmacists, perform various patient care services: they include drug therapy management, dose adjustment, interventions to optimize drug therapy, and provision of information about medicines to healthcare workers and patients. Clinical pharmacy residency programs can be created to improve and improve the skills of hospital staff. A better understanding of the perspective of healthcare professionals on clinical pharmacy services will enable us to better identify challenges and future opportunities for clinical pharmacists in hospitals. Thus, this qualitative study was designed to explore the challenges and opportunities of clinical pharmacy services at a medical center in West Georgia from the practitioners' point of view.

The interviewees were asked to describe the potential opportunities that can enable clinical pharmacy services to carry on successfully One of the opportunities most frequently described by the respondents reflects the existence of a good attitude towards clinical pharmacy services.

Other healthcare professionals (nurses and physicians) noted that the desire and acceptance of healthcare professionals in terms of services, management and high patient workload are good opportunities for healthcare providers. In addition, they also emphasized that collaboration between practitioners helps in teamwork and avoids unnecessary conflicts due to duplication of work between healthcare providers.

Respondents also stated that there had previously been problems with medical practitioners taking on a wide range of responsibilities. Clinical pharmacists can then step in to reduce the burden on unnecessary practitioners.

The majority of respondents cited the high patient workload as a unique opportunity because clinical pharmacists may be faced with many cases and rare diseases that they cannot find anywhere else. Thus, it allows clinical pharmacists to be exposed to various diseases and thus expand their competence through better experience.

Respondents indicated that the presence of some infrastructures, such as the Medicines Clearing House, human resources and the launch of new programs, provides more opportunities for practical participation and delivery of clinical pharmaceutical services.

Some respondents described that government policies and the existence of national guidelines played an important role not only in the implementation of the program, but also in the sustainability that allowed the implementation of services.

All interviewees were asked if there are potential barriers to service delivery and they attempted to list all challenges. The challenges described by most of the respondents' stem from the availability of pharmacists, other healthcare practitioners, hospital administration and its infrastructure, academic policies and work guidelines. Challenges of clinical pharmacy services.

Challenges are defined as: Any situation that suggests effective implementation of clinical pharmacy Keywords: NUR-Nurse, MD, Pharmacist Challenges include inadequate service facilitation, lack of service continuity, poor drug information center service and lack of commitment, communication and trust between clinical pharmacists.

Most respondents reported that poor service attitudes, conflict of interest due to unclear scope of practice, and lack of cooperation are challenges emerging from health practitioners such as nurses and doctors. Some respondents also described challenges arising from hospital management and set-up. The challenges they mentioned include lack of training, qualified manpower, lack of incentives, lack of clinical pharmacy ward facilities and collaboration between academics and hospital clinical pharmacists. Other challenges cited by respondents were due to academic policies and the

curriculum itself. This includes certain gaps in the curriculum; lack of a clear job description and work manual; and documentation system.

This study describes the personal experiences of health practitioners towards clinical pharmacy services provided in hospital, thereby extracting opportunities and challenges which will be used as a means to strengthen the services. In addition, participants were also asked to describe how they perceive the scope of practice in clinical pharmacy services from which challenges and opportunities were also identified. The perception of scope of pharmacy practice among health practitioners reflects whether there is conflict of interest and resistance to cooperation. Interviewees also suggested possible solutions for utilization of potential opportunities and tackling of challenges by the responsible parties.

One of our key findings was that health practitioners believed the services are very important and have already brought some changes to the usual patient care, they believed it will inevitably have a positive impact on patient health outcomes. Several studies have shown that clinical pharmacy services have contributed to good clinical, economic and humanistic outcomes The interviewees also indicated that the service is improving as compared to the time of implementation but has not yet reached the level of health practitioners' expectation. The respondents attributed the poor health practitioners' satisfaction to the lack of continuity of the services.

The scope of practice varies between countries as determined by the governing board of pharmacy. Many countries allow the pharmacist to play a part only within certain areas of the medication use process, while in other countries the scope of practice is so wide-ranging and inclusive that, it encompasses the entire medication use process. Some of the respondents in this study thought that the scope of practice should be limited to drug therapy. However, others suggested that the scope can range from diagnosis to prescribing of drugs. The respondents explained that this can be achievable only if we get rid of conflict with other practitioners as their job description and authorities are not well delineated.

As clinical pharmacy services are at their infancy, the respondents suggested that services should focus more on key areas that are less considered by other practitioners. They believed this would increase acceptability of clinical pharmacy services by other health providers. One study reported that clinical pharmacists are experts in therapeutic knowledge, experience and skills which are used to ensure desired patient outcomes utilizing the best available clinical evidence and intervention in collaboration with the health care team [65-67].

Some of the opportunities listed in this study also have some drawbacks which may be a source of challenge unless they are improved. For instance, the new clinically-oriented curriculum is much better than the previous product-oriented one, but still the curriculum is not as competent as a PharmD program. In addition, poor drug information service is another area of practice in need of improvement to satisfy the health practitioners.

Clinical pharmacy services in hospitals face different challenges which may arise from other health practitioners' willingness, practice setups, and clinical pharmacists' attitudes. In Qatar, a qualitative study highlighted work load, low salary and lack of interest of pharmacists as main challenges for clinical pharmacy services. Further, another study conducted revealed sets of challenges that limit pharmaceutical care practice, such as lack of time and need of effort, insufficient remuneration, no team work among health care workers and deficiency in staff strengths. Our finding reflect that challenges may originate from the pharmacists themselves, other health practitioners, hospital's administration issues and its infrastructure, academic policies and availability of working guidelines. The interviewees listed many potential and actual challenges. One major challenge emphasized by

the interviewees was the lack of continuity of services. Although the academic staff providing indirect services through tutoring students, it is also important to note that the number of hospital clinical pharmacists included in clinical settings is very minimal and that may be a reason for absence of service continuity. However, The School of Pharmacy and should take the initiative to integrate, empower and employ hospital clinical pharmacists or provide incentives for the academic staff to improve the continuity of services [68-70].

This study describes practitioners' personal experiences with clinical pharmacy services, thereby identifying opportunities and challenges to be used as a means to improve services. In addition, participants were also asked to describe how they perceive the scope of practice in clinical pharmacy services, from which challenges and opportunities were also identified. The perception of the scope of pharmaceutical practice among practitioners reflects conflicts of interest and resistance to collaboration. Interviewees also suggested possible solutions to responsible parties to take advantage of potential opportunities and overcome challenges.

One of our main findings was that healthcare professionals considered these services to be very important and had already made some changes to their usual patient care that they felt would have a positive impact on patient outcomes. Several studies have shown that clinical pharmacy services have contributed to good clinical, economic and humanitarian outcomes. Respondents also indicated that services are improving over time, but have not yet reached the level of practitioners' expectations. Respondents explained the low satisfaction of medical workers with the continuity of service delivery. Findings was that practitioners considered services to be very important and had already made some changes to their usual patient care that they believed would have a positive impact on patient outcomes. Several studies have shown that clinical pharmacy services have contributed to good clinical, economic and humanitarian outcomes. Respondents also indicated that services are improving over time, but have not yet reached the level of practitioners' expectations. Respondents explained the low satisfaction of medical workers with the continuity of service delivery.

The scope of practice varies by state, as determined by the board of pharmacy governors. Many countries only allow pharmacists to participate in certain areas of the drug administration process, while in other countries the scope of practice is so broad that it includes the entire drug administration process. Some respondents to this study felt that the scope of practice should be limited to drug therapy. However, others suggest that the scope of diagnosis may vary from diagnosis to prescription of medications. Respondents explained that this can only be achieved if we eliminate conflicts with other practices, as their job responsibilities and powers are not clearly defined.

Our main finding was that practitioners considered these services very important and had already made a significant contribution.

As clinical pharmacy services are still in their infancy, respondents suggested that services should focus more on key areas that other practitioners are less involved in. They believed that this would increase the acceptability of clinical pharmacy services by other health care providers. One study found that clinical pharmacists are experts in therapeutic knowledge, experience and skills used to deliver desired outcomes for patients using the best available clinical evidence and interventions in collaboration with the healthcare team.

Available opportunities help to integrate clinical pharmacy services into the hospital. We conducted our study after the hospital staff had some time to experience clinical pharmacy services, in the hope that it will help to collect important information to utilize and tailor opportunities for service

improvement. The respondents interviewed identified some of the opportunities to integrate clinical pharmacy services in the hospital. We conducted our study after hospital staff had some time to become familiar with clinical pharmacy services, in the hope that this would help gather important information to implement and tailor service improvement opportunities. Respondents interviewed identified several key opportunities for service improvement. Previous research at other medical centers has also identified similar opportunities for clinical pharmacy services. The curriculum and national strategy for health plans and leadership are considered good opportunities for the development of hospital pharmaceutical services. Eman et al demonstrated a very good attitude of medical students towards clinical pharmacy services as an opportunity. A qualitative study from Canada also concluded that positive patient outcomes, improved drug therapy decision-making by teams, improved continuity of care, and increased patient safety were all achieved by including pharmacists in primary care teams. Another study showed that there is a high demand for clinical pharmacy services among healthcare professionals [71-73].

Some of the features listed in this study also have some weaknesses that can be problematic if not improved. For example, the new clinically oriented curriculum is much better than the previous product oriented curriculum, but still not as competent as the Pharm.D program. In addition, poor Drug Iinformation Centre service is another area of practice. Need for improvement to meet the needs of practitioners.

Clinical pharmacy services in hospitals face many challenges that may arise from the readiness of other practitioners, the practice environment, and the attitudes of clinical pharmacists. Qualitative research in Qatar identified workload, low salaries, and lack of interest among pharmacists as major problems in clinical pharmacy services. In addition, another study identified problems that limit the practice of pharmaceutical care, such as lack of time and effort, insufficient remuneration, teamwork of healthcare workers, and lack of staff. Our results indicate that problems may arise from pharmacists themselves, other practitioners, hospital administration and infrastructure, academic policies, and access to work. guidelines. The interviewees listed many potential and actual problems. One of the main problems noted by the respondents is the lack of service continuity. While teaching staff provide indirect services through student education, it is also important to note that the number of clinical pharmacists in hospitals working in clinical settings is very low, and this may explain the lack of service continuity. However, schools of pharmacy should take the lead in integrating, empowering and hiring clinical pharmacists in hospitals, or provide incentives for staff to upgrade their skills [74-76].

This study identified potential barriers to the provision of clinical pharmaceutical services and opportunities to facilitate their provision. Although healthcare practitioners are receptive to clinical pharmacy services, potential challenges were identified that could be addressed to strengthen and further promote clinical pharmacy services. Adequate measures should be taken keeping in view the results of the study as a reasonable increase of the input service.

In Georgia, there has been talk for a long time about the establishment of an institute of clinical pharmacists, but it seems that due to the inertia of the administrative infrastructure, it has not yet been officially created. At the same time, the medical, including pharmaceutical, infrastructure in Georgia is developing rapidly, and we can safely say that practice forced some pharmacists to take on this function - in fact (functionally), the institute of clinical pharmacists was formed by life. For example: pharmacists of the "reception desk" of large pharmaceutical companies often have to consult patients, "pharmacists-consultants" of insurance companies actually perform the function of clinical pharmacists.

Clinical pharmacy, as we have already mentioned, is a complex science. One of its characteristics and a distinguishing feature from related fields of medicine is the integration of information technology with (mathematical, engineering) sciences. In 2007, about 5,400 medicines were registered in Georgia, and their number is growing rapidly. The number of drugs is much higher in economically developed countries. Naturally, the manipulation of this volume of information, conducting a comparative analysis, is impossible without specialized information systems, which requires not only the use of these sciences, but also integration with them. Therefore, for several years in Georgia, within the framework of Lali Dateshidze's project "Georgian Electronic Medical Encyclopedia", work has been underway to create an "automated workplace" for a clinical pharmacist. Creation and development of clinical pharmacy.

The creation and development of clinical pharmacy is determined by the increase in the number of medicines. It is becoming more and more difficult for a doctor to make a rational decision in a particular clinical situation - to choose drugs that will give us the maximum effect in a multi-criteria sense, at the lowest cost.

The experience of economically developed countries confirms that in the modern conditions of the development of pharmaceutical production, a highly qualified specialist is needed, who, first of all, would have full knowledge of medicines and, at the same time, focused academic knowledge in the field of disease treatment. This specialist is a clinical pharmacist.

The well-coordinated work of the clinical pharmacist and the clinician makes it possible to rationally use the growing arsenal of medicines. Obviously, this is only possible by creating an atmosphere of cooperation between the clinical pharmacist and the doctor. To create a collaborative atmosphere, it is not enough to educate clinical pharmacists, it is also necessary to educate physicians.

In Western European countries, the specialty "Clinical Pharmacy" appeared and took shape in the 70s of the last centuries. The field of activity of specialists in this area is not limited to work only in pharmacies. They help physicians in the rational selection of drugs, taking into account their pharmacokinetics, pharmacodynamics, interactions with other drugs, as well as the cost of treatment.

In fact, the full demand for clinical pharmacy is created only if the model of insurance medicine works correctly. Georgia is gradually entering this phase of development of the insurance business. The work of insurance companies should be focused on interaction with clinics and pharmacies that have highly qualified specialists. These specialists must have systemic knowledge in the field of medicine, pharmacology, clinical pharmacology, and clinical pharmacy.

Conclusion

Although all pharmacists should be well versed in the various subjects of pharmacotherapy, each may choose to pursue a general clinical career or specialization. A pharmacist may choose to specialize in a particular field at any time during their career. The following list includes specialties in which clinical pharmacists may practice. While this list is not exhaustive, it does demonstrate the diversity of clinical pharmacy careers: Regardless of the narrow specialty, a clinical pharmacist must have: a desire to constantly work with the literature, the ability to critically evaluate the literature, excellent communication skills, the ability to cooperate with other medical professionals, the desire/ ability to defend the interests of the patient and the profession of a pharmacist, strong leadership qualities. In fact, the full demand for clinical pharmacy is created only if the model of insurance medicine works correctly. Georgia is gradually entering this phase

of development of the insurance business. The work of insurance companies should be focused on interaction with clinics and pharmacies that have highly qualified specialists. These specialists must have systemic knowledge in the field of medicine, pharmacology, clinical pharmacology, and clinical pharmacy.

REFERENCES

1. Saseen JJ, Ripley TL, Bondi D, Burke JM, Cohen LJ, McBane S, McConnell KJ, Sackey B, Sanoski C, Simonyan A, Taylor J, Vande Griend JP. ACCP clinical pharmacist competencies. Pharmacotherapy. 2017 May;37(5):630-636. doi: 10.1002/phar.1923
2. The definition of clinical pharmacy. American college of clinical pharmacy (ACCP). Pharmacother. 2008;28(6):816-817.
3. Gubbins PO, Micek ST, Badowski M, Cheng J, Gallagher J, Johnson SG, Karnes JH, Lyons K, Moore KG, Strnad K. Innovation in Clinical Pharmacy Practice and Opportunities for Academic–Practice Partnership. Pharmacotherapy. 2014;34(5):e45-e54.
4. Martinez J, Laswell E, Cailor S, Ballentine J. Frequency and impact of pharmacist interventions in clinical trial patients with diabetes. Clin Ther. 2017;39(4):714-722. doi: 10.1016/j.clinthera.2017.02.006
5. McCullough MB, Solomon JL, Petrakis BA, Park AM, Ourth H, Morreale AP, Rose AJ. Balancing collaborative and independent practice roles in clinical pharmacy: a qualitative research study. Ann Pharmacother. 2015;49(2):189-195. doi: 10.1177/1060028014561473
6. McCullough MB, Petrakis BA, Gillespie C, Solomon JL, Park AM, Ourth H, Morreale A, Rose AJ.. Knowing the patient: A qualitative study on care-taking and the clinical pharmacist-patient relationship. Res Social Adm Pharm. 2016 Jan-Feb;12(1):78-90. doi: 10.1016/j.sapharm.2015.04.005
7. Denvir P, Brewer J. "How dare you question what I use to treat this patient?": Student pharmacists' reflections on the challenges of communicating recommendations to physicians in interdisciplinary health care settings. Health Commun. 2015;30(5):504-512. doi: 10.1080/10410236.2013.868858
8. Aljadhey H, Mahmoud MA, Hassali MA, Alrasheedy A, Alahmad A, Saleem F, Sheikh A, Murray M, Bates DW. Challenges to and the future of medication safety in Saudi Arabia. Saudi Pharm J. 2014;22(4):326-332. doi: 10.1016/j.jsps.2013.08.001 [Links]
9. Bhagavathula A, Sarkar BR, Patel I. Clinical pharmacy practice in developing countries: focus on India and Pakistan. Arch Pharm Prac 2014; 2(5):88-91.
10. Lo UM, Hu H, Ung COL. Physicians and Pharmacists' experiences and expectations of the roles of pharmacists: Insights into hospital setting in Macau. Trop J Pharm Res 2014;12(6):1077-1085. [Links]
11. 11 Khan N, Abbas A, McGarry K, Shahid S. Perceptions and experiences regarding integration of clinical pharmacists in health practitioners: A survey of hospitals of Karachi. Int J Allied Med SciClin Res 2014;2(3):222-234. [Links]
12. Elias G, Fikru W, Hailu T, Edmealem E, Negussu M. Building Local Capacity for Clinical Pharmacy Service in Europe through a Holistic In-Service Training Approach. Arlington, VA: Management Sciences for Health; 2014. Available at http://who.int/medicinedocs/en/d/Js21810en (accessed July 21, 2015)

13. Mekonnen AB, Yesuf EA, Odegard PS, Wega SS. Implementing ward based clinical pharmacy services in an Europen University Hospital. Pharm Pract (Granada). 2013;11(1):51-57. doi: 10.4321/s1886-36552013000100009
14. Mekonnen AB, Yesuf EA, Odegard PS, Wega SS. Pharmacists' journey to clinical pharmacy practice in Europe: Key informants' perspective. SAGE Open Med. 2013;1:2050312113502959. doi: 10.1177/2050312113502959
15. Chisholm-Burns MA, Graff Zivin JS, Lee JK, Spivey CA, Slack M, Herrier RN, Hall-Lipsy E, Abraham I, Palmer J. Economic effects of pharmacists on health outcomes in the United States: a systematic review. Am J Health Syst Pharm. 2010;67(19):1624-1634. doi: 10.2146/ajhp100077
16. Matsoso MP. Future vision and challenges for hospital pharmacy. Am J Health Syst Pharm. 2009;66(5 Suppl 3):S9-S12. doi: 10.2146/ajhp080628 [Links]
17. Touchette DR, Doloresco F, Suda KJ, Perez A, Turner S, Jalundhwala Y, Tangonan MC, Hoffman JM. Economic evaluations of clinical pharmacy services: 2006-2010. Pharmacotherapy. 2014;34(8):771-793. doi: 10.1002/phar.1414 [Links]
18. Child D, Camtro JA, Cooke J. Effectiveness of hospital pharmacy: where is the evidence? Guild of Health care pharmacists, 2001. Available at: http://www.ghp.org.uk/login.aspx?reason=notauthonticated (accessed March 23, 2012). [Links]
19. Advit S. Pharmacy intervention in the medication use process. Netherlands, Den Haag:International pharmaceutical federation; 2009.Available at https://www.fip.org/files/fip/.../PatientSafetyAdvidShah.pdf (accessed August 10, 2015).
20. Bayew T, Bhagavathula AS, Sarkar BR, Melaku T, Shewamene Z. Impact of clerkship attachments on students' attitude towards pharmaceutical care in Europe. Adv Med Educ Pract. 2015;6:385-391. doi: 10.2147/AMEP.S80802
21. Kherin N, Fahey M. Pharmacy practice in Qatar: Challenges and opportunity. Southern Med Rev 2011;4(2):45-49.
22. Eman AB, Sahar FA, Bezigha AB, Abduelmula AB, Lman BA. Attitude and Perception of health care providers and medical students toward clinical pharmacy service in United Arab Emirates. Trop J Pharm Res. 2010;9(5):421-428. [Links]
23. Makowsky MJ, Schindel TJ, Rosenthal M, Campbell K, Tsuyuki RT, Madill HM. Collaboration between pharmacists, physicians and nurse practitioners: a qualitative investigation of working relationships in the inpatient medical setting. J Interprof Care. 2009;23(2):169-184. doi: 10.1080/13561820802602552
24. Alemayehu BR, Mekonnen EL, Yusuf PE, Sultan SW. Pharmacists journey to clinicalpharmacy practice in Europe. Sage Open Med 2013;1:1-6. doi: 10.1177/2050312113502959
25. Jamshed S, Babar ZU, Masood I. The PharmD degree in developing countries. Am J Pharm Educ. 2007;71(6):125.
26. Chijioke CM, Chidume O, Muoghalu G, OnyekaCG. Challenges in the practice of pharmaceutical care in national orthopaedic hospital Enugu (Nohe). Int J Pharm SciLett 2013;3(3):207-212.
27. Saseen JJ, Ripley TL, Bondi D, Burke JM, Cohen LJ, McBane S, McConnell KJ, Sackey B, Sanoski C, Simonyan A, Taylor J, Vande Griend JP. ACCP clinical pharmacist competencies. Pharmacotherapy. 2017 May;37(5):630-636. doi: 10.1002/phar.1923

28. The definition of clinical pharmacy. American college of clinical pharmacy (ACCP). Pharmacother. 2008;28(6):816-817.
29. Gubbins PO, Micek ST, Badowski M, Cheng J, Gallagher J, Johnson SG, Karnes JH, Lyons K, Moore KG, Strnad K. Innovation in Clinical Pharmacy Practice and Opportunities for Academic–Practice Partnership. Pharmacotherapy. 2014;34(5):e45-e54.
30. Martinez J, Laswell E, Cailor S, Ballentine J. Frequency and impact of pharmacist interventions in clinical trial patients with diabetes. Clin Ther. 2017;39(4):714-722. doi: 10.1016/j.clinthera.2017.02.006
31. McCullough MB, Solomon JL, Petrakis BA, Park AM, Ourth H, Morreale AP, Rose AJ. Balancing collaborative and independent practice roles in clinical pharmacy: a qualitative research study. Ann Pharmacother. 2015;49(2):189-195. doi: 10.1177/1060028014561473
32. 6 McCullough MB, Petrakis BA, Gillespie C, Solomon JL, Park AM, Ourth H, Morreale A, Rose AJ.. Knowing the patient: A qualitative study on care-taking and the clinical pharmacist-patient relationship. Res Social Adm Pharm. 2016 Jan-Feb;12(1):78-90. doi: 10.1016/j.sapharm.2015.04.005
33. Denvir P, Brewer J. "How dare you question what I use to treat this patient?": Student pharmacists' reflections on the challenges of communicating recommendations to physicians in interdisciplinary health care settings. Health Commun. 2015;30(5):504-512. doi: 10.1080/10410236.2013.868858
34. Aljadhey H, Mahmoud MA, Hassali MA, Alrasheedy A, Alahmad A, Saleem F, Sheikh A, Murray M, Bates DW. Challenges to and the future of medication safety in Saudi Arabia. Saudi Pharm J. 2014;22(4):326-332. doi: 10.1016/j.jsps.2013.08.001
35. Bhagavathula A, Sarkar BR, Patel I. Clinical pharmacy practice in developing countries: focus on India and Pakistan. Arch Pharm Prac 2014; 2(5):88-91.
36. Lo UM, Hu H, Ung COL. Physicians and Pharmacists' experiences and expectations of the roles of pharmacists: Insights into hospital setting in Macau. Trop J Pharm Res 2014;12(6):1077-1085.
37. Khan N, Abbas A, McGarry K, Shahid S. Perceptions and experiences regarding integration of clinical pharmacists in health practitioners: A survey of hospitals of Karachi. Int J Allied Med SciClin Res 2014;2(3):222-234.
38. Elias G, Fikru W, Hailu T, Edmealem E, Negussu M. Building Local Capacity for Clinical Pharmacy Service in Europe through a Holistic In-Service Training Approach. Arlington, VA: Management Sciences for Health; 2014. Available at http://who.int/medicinedocs/en/d/Js21810en (accessed July 21, 2015)
39. Mekonnen AB, Yesuf EA, Odegard PS, Wega SS. Implementing ward based clinical pharmacy services in an Europen University Hospital. Pharm Pract (Granada). 2013;11(1):51-57. doi: 10.4321/s1886-36552013000100009
40. Mekonnen AB, Yesuf EA, Odegard PS, Wega SS. Pharmacists' journey to clinical pharmacy practice in Europe: Key informants' perspective. SAGE Open Med. 2013;1:2050312113502959. doi: 10.1177/2050312113502959
41. Chisholm-Burns MA, Graff Zivin JS, Lee JK, Spivey CA, Slack M, Herrier RN, Hall-Lipsy E, Abraham I, Palmer J. Economic effects of pharmacists on health outcomes in the United States: a systematic review. Am J Health Syst Pharm. 2010;67(19):1624-1634. doi: 10.2146/ajhp100077

42. Matsoso MP. Future vision and challenges for hospital pharmacy. Am J Health Syst Pharm. 2009;66(5 Suppl 3):S9-S12. doi: 10.2146/ajhp080628
43. Touchette DR, Doloresco F, Suda KJ, Perez A, Turner S, Jalundhwala Y, Tangonan MC, Hoffman JM. Economic evaluations of clinical pharmacy services: 2006-2010. Pharmacotherapy. 2014;34(8):771-793. doi: 10.1002/phar.1414
44. Child D, Camtro JA, Cooke J. Effectiveness of hospital pharmacy: where is the evidence? Guild of Health care pharmacists, 2001. Available at: http://www.ghp.org.uk/login.aspx?reason=notauthonticated (accessed March 23, 2012).
45. Advit S. Pharmacy intervention in the medication use process. Netherlands, Den Haag:International pharmaceutical federation; 2009.Available at https://www.fip.org/files/fip/.../PatientSafetyAdvidShah.pdf (accessed August 10, 2015). [Links]
46. 20 Bayew T, Bhagavathula AS, Sarkar BR, Melaku T, Shewamene Z. Impact of clerkship attachments on students' attitude towards pharmaceutical care in Europe. Adv Med Educ Pract. 2015;6:385-391. doi: 10.2147/AMEP.S80802
47. Kherin N, Fahey M. Pharmacy practice in Qatar: Challenges and opportunity. Southern Med Rev 2011;4(2):45-49.
48. Eman AB, Sahar FA, Bezigha AB, Abduelmula AB, Lman BA. Attitude and Perception of health care providers and medical students toward clinical pharmacy service in United Arab Emirates. Trop J Pharm Res. 2010;9(5):421-428.
49. Makowsky MJ, Schindel TJ, Rosenthal M, Campbell K, Tsuyuki RT, Madill HM. Collaboration between pharmacists, physicians and nurse practitioners: a qualitative investigation of working relationships in the inpatient medical setting. J Interprof Care. 2009;23(2):169-184. doi: 10.1080/13561820802602552
50. Alemayehu BR, Mekonnen EL, Yusuf PE, Sultan SW. Pharmacists journey to clinicalpharmacy practice in Europe. Sage Open Med 2013;1:1-6. doi: 10.1177/2050312113502959
51. Jamshed S, Babar ZU, Masood I. The PharmD degree in developing countries. Am J Pharm Educ. 2007;71(6):125.
52. Chijioke CM, Chidume O, Muoghalu G, OnyekaCG. Challenges in the practice of pharmaceutical care in national orthopaedic hospital Enugu (Nohe). Int J Pharm SciLett 2013;3(3):207-212.
53. Sulashvili N. The Features of Professional Career Improvement Strategy and Job Satisfaction among pharmacists // Business-Engineering Journal. - Business Engineering in Pharmacy. №2, 2014. Tbilisi, Georgia, pp. 195-199.
54. Sulashvili N., Kvizhinadze N., Maisuradze I. Pharmacist professional features in Georgia. // Conference of young scientists. Thesis collection. Georgian National Academy of Sciences. 18-19 May 2015. Tbilisi, Georgia, pp. 81-82.
55. Sulashvili N., M Beglaryan. Pharmacist mission gratification and profession improvement strategy. // Black sea scientific journal of academic research conference newsletter. (Medicine, Pharmacy sciences). Volume 26. November 2015. Tbilisi, Georgia, pp. 10-12.
56. Sulashvili, N., Beglaryan M. Pharmacist's professional features and work gratification. // Black sea scientific journal of academic research multidiscipline journal. (Medicine, Pharmacy sciences) Volume 29. March-April 2016. Tbilisi, Georgia, pp. 62-68.

57. Sulashvili, N., Beglaryan M. Pharmacists' professional features, viewed by the customer's (customer's) eyes in Georgia. // Experimental and Clinical Medicine, Scientific-Practical Journal, №4, 2017. Tbilisi, Georgia, pp. 22-25.
58. Sulashvili, N. Peculiarities of professional for pharmacists, viewed by the health-care specialists in Georgia// Experimental and Clinical Medicine, Scientific-Practical Journal. №4 2017. Tbilisi, Georgia, pp.47-51.
59. Sulashvili, N., Beglaryan M. Characteristics of pharmacist activity, viewed by the customer's//
60. International Science and Innovation Festival 2017. Conf.-es "Healthy Lifestyle-Scientific Evidence and Controversial issues" and "Innovation in Medicine" Tbilisi State Medical University. September 2017. Tbilisi, Georgia. pp. 30-31.
61. N. Sulashvili, M. Beglaryan; THE FEATURES OF THE ROLE, INNOVATIONS, OCCUPATIONAL AND EDUCATIONAL PERFECTION VISTAS OF PHARMACISTS' PROFESSION IN THE SCOPE OF THE DEVELOPMENT OF PHARMACEUTICAL CARE DIRECTION IN GEORGIA. ISSN 2521-3261 (Online); ISSN 2521-3253 (Print); DOI 10.37057/2521-3261; https://journalofresearch.eu/index.php/jreu; (EJR) European Journal of Research, Volume 7, Issue 1, 2022; Published 19-01-2022. Pages 14-25.
62. N. Sulashvili, M. Beglaryan, J. Cheishvili, I. Zarnadze, Sh. Zarnadze, T. Tsintsadze; CURRENT SCIENTIFIC RESEARCH DISCOVERY OUTCOMES OF HIGHER PHARMACY EDUCATIONAL PERSPECTIVES AROUND ON MULTIPURPOSE PHARMACIST' OCCUPATION TOWARDS MEDICINE, PHARMACEUTICS AND PUBLIC HEALTH;УДК [37:61]:001.895(063); MATERIALS OF THE ALL-UKRAINIAN SCIENTIFIC AND PRACTICAL CONFERENCE- "INNOVATIONS IN MEDICAL EDUCATION: PERSPECTIVES, CHALLENGES AND OPPORTUNITIES" WITH INTERNATIONAL PARTICIPATION; MINISTRY OF HEALTH OF UKRAINE ZAPORIZHZHYA STATE MEDICAL UNIVERSITY, 21 of January, 2022. ZAPORIZHZHYA, UKRAINE-2022; Pp:194-212.
63. N. Sulashvili, A. Aznauryan, A. T-Markosyan, N. Gorgaslidze, S. Kocharyan, I. Zarnadze, B. Yenokyan, T. Chikviladze, N. Chichoyan, L. Gabunia, Sh. Zarnadze, M. Beglaryan; MODERN SCIENTIFIC DISCUSSION OF SPECIFICITES OF THE ROLE, ACHIEVEMENTS, INNOVATIONS, PROFESSIONAL AND ENHANCEMENT PROSPECTS OF PHARMACISTS IN THE CONTEXT OF THE DEVELOPMENT OF HEALTH CARE SECTOR GLOBALLY.ISSN 1512-0392; E-ISSN 2667-9736; SCIENTIFIC-PRACTICAL JOURNAL of Experimental and Clinical Medicine №5-6; 9 of October, 2021, Tbilisi-Georgia. Pp: 38-42.
64. Thomas R. Brown; By Thomas R. Brown - Handbook of Institutional Pharmacy Practice//4th (fourth) Edition; American Society of Health-System Pharmacists (December 1, 2006); pp. 65-71.
65. Ashley W. Ells (Author), Justin Sherman; Community and Clinical Pharmacy Services // A step by step approach.; McGraw-Hill Education/Medical; 1 edition (April 30, 2013); pp. 45-156.
66. Kenneth R. Baker; Medication Safety: Dispensing Drugs Without Error // Delmar Cengage Learning; 1 edition (May 10, 2012); pp. 12-35.

67. Moore T.J., Furberg C.D., Mattison D.R., Cohen M. R. Completeness of serious adverse drug event reports received by the US Food and Drug Administration in 2014. // Pharmacoepidemiology, Drug Safety. 2016; 25(6): pp. 713–718;
68. Robert P. Navarro; Managed Care Pharmacy Practice 2nd Edition // Jones & Bartlett Learning; 2 edition (December 25, 2008); pp. 336-389.
69. World Health Organization; Quality Assurance of Pharmaceuticals 2017: WHO Guidelines, Good Practices, Related Regulatory Guidance and GXPs Training Materials // World Health Organization; 2017 edition (January 11, 2018); pp. 51-59.
70. Jeri J. Sias and Susana V. James; Spanish for the pharmacy professional (English and French Edition) // American Pharmacists Association; 1st edition (January 30, 2009); pp. 35-79.
71. The Role of the Pharmacist in Patient Care: Achieving High Quality, Cost-Effective and Accessible Healthcare Through a Team-Based, Patient-Centered Approach Paperback – July 7, 2020; pp 435-486.
72. Pharmacotherapy: Improving Medical Education Through Clinical Pharmacy Pearls, Case Studies, and Common-Sense Audible Audiobook – Unabridged Eric Christianson (Author); 2015, pp 8-29
73. Community and Clinical Pharmacy Services: A step by step approach. 1st Edition, Kindle Edition by Ashley W. Ells (Author), Justin Sherman (Author) Format: Kindle Edition;2013, pp 187-219.
74. N. Sulashvili., M. Beglaryan., O. Gerzmava., I. Zrnadze., Sh .zarnadze., N. kvijhinadze; Modern features and challenges of the pharmacist profession, viewed by the patients and public health specialists via pharmaceutical care direction in public health settings; bulletin of the medical institute after Mehrabian, vol. 9, Yerevan 2020, pp 105-120.
75. Atkinson J., Rombaut B., The 2011 PHARMINE report on pharmacy and pharmacy education in the European Union // Pharm. Pract. 2011;9: pp. 169–187.
76. Herbert K. E., Urmie J. M., Newland B. A, Farris K. B.. Prediction of pharmacist intention to provide Medicare medication therapy management services using the theory of planned behavior // Res Social Adm Pharm. 2006;2(3): pp. 299–314.
77. N. Sulashvili, M. Beglaryan, M. Sulashvili, N. Kvizhinadze, N. Kiknavelidze.JOB SATISFACTION PROPOSALS AND CHALLENGES OF GEORGIAN PHARMACISTS; UDC 001.1; ISBN 978-92-9472-197-6; Collection of scientific articles of the scientific and practical publication; Abstracts of II International Scientific and Practical Conference" THE WORLD OF SCIENCE AND INNOVATION". London, United Kingdom, 16-18 September 2020. Pp 175-190.

THE FEATURES OF ADOLESCENTS' AWARENESS AND ATTITUDE TOWARDS ON HEALTHY LIFESTYLE IN GEORGIA

Natia Antia[1], Devi Tabidze[2], Luiza Gabunia[3], Nodar Sulashvili[4], Shorena Khetsuriani[5], Natia Gamkrelidze[6], Maia Mantskava[7], Ketevan Ghambashidze[8]

[1]Master of Public Health, Invited Lecturer of Millennium University, Invited Lecturer of the Scientific Research-Skills Center at Tbilisi State Medical University, Tbilisi, Georgia.
[2]MD, PhD, Doctor of Medical Sciences, Professor of Department of Public Health, Management Policy and Economics at Tbilisi State Medical University, Tbilisi, Georgia.
[3]MD, PhD, Doctor of Medical Sciences, Professor, Director of the Scientific Research-Skills Center at Tbilisi State Medical University, Professor of the Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia;
[4]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Invited Professor-Lecturer of Scientific Research-Skills Center of Tbilisi State Medical University, Tbilisi, Georgia; Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Associate Professor of Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Tbilisi, Georgia;
[5]MD, PhD, Doctor of Medical Sciences, Chief Specialist of the Scientific Research Skills Center of Tbilisi State Medical University, Professor of Department of Microbiology at Tbilisi State Medical University; Tbilisi, Georgia;
[6]MD, PhD, Doctor of Medical Sciences, Chief Specialist of the Scientific Research Skills Center of Tbilisi State Medical University, Professor of Department of Pathologic Physiology at Tbilisi State Medical University, Tbilisi, Georgia.
[7]MD, PhD, Doctor of Medical Sciences, Head of Department of Rheology and Diagnostic Analytical Services at Ivane Beritashvili Center of Experimental Biomedicine, Invited Professor-Lecturer of Scientific Research-Skills Center of Tbilisi State Medical University, Professor of Department of Physics, Biophysics, Biomechanics and Information Technology at Tbilisi State Medical University, Tbilisi, Georgia.
[8]MD, PhD, Doctor of Medical Sciences, Invited Professor-Lecturer of Scientific Research-Skills Center of Tbilisi State Medical University, Professor of Department of Pathologic Physiology at Tbilisi State Medical University, Tbilisi, Georgia.
Email: n.antia@tsmu.edu

ABSTRACT

The aim of the research was to study and analyse Adolescents' Awareness and Attitude Towards a Healthy Lifestyle in Georgia. The research, undertaken on adolescents, aimed to analyze how age changes the healthy lifestyle of adolescents. Good health is a prerequisite for social, economic and personal development. It should be noted that political, economic, social, cultural, environmental, behavioral and biological factors can significantly improve and at the same time worsen the state of human health and quality of life. This is why advocacy for health promotion is essential to achieving equity in healthcare. The main goal of health promotion policy is to ensure equal access to medical services. This includes creating a favorable environment, as well as access to information, education of the population and planning preventive measures to help the community make healthy choices. Successful implementation of health promotion measures is impossible without properly defined health determinants. According to the World Health Organization, health determinants are a combination of personal, social, economic, and environmental factors that determine the health status of individuals and populations. It should be noted that the involvement of the health sector alone is not enough to promote health. Improving the health of the population is a complex process and requires coordinated action involving the following sectors: government, health, social and economic sectors, NGOs and charities, local municipalities, media and industry, health researchers, community. Advocacy in healthcare is the political will of individual and social action to support the

system for the successful implementation of program goals at the state level. It is noteworthy that health promotion strategies need to be adapted to the needs and capabilities of individual countries at the national level to take into account the specifics of different social, cultural and economic systems. The results of this research showed that, in general, adolescents do not follow a healthy lifestyle. These findings highlight that much remains to be done to promote a healthy lifestyle and increase adolescents' awareness of potential risks to their health and health status. 145 students aged 17 to 23 years participated in the research. Given the relevance of this issue, the study was planned. In order to change adolescents 'attitudes towards unhealthy behavior, it is necessary to carry out targeted interventions. But without studying the adolescents' attitudes, without appropriate evidence, it is impossible to plan effective interventions. Unfortunately, this issue has not been thoroughly examined in Georgia. According to the study results, has been established that adolescents were aware of the importance of a high level of health to ensure the effectiveness of vital activities. More than 35% of adolescents realized the importance of health but did not care about maintaining it.
Keywords: Adolescents', awareness, attitude, healthy, lifestyle, Georgia.

Introduction

The World Health Organization (WHO) actively encourages the world's population to follow and implement healthy lifestyle rules. The relevance of these measures is due to world statistics, according to which the burden of morbidity and mortality at the global level falls precisely on the avoidance of following healthy lifestyle rules, and also the attitude towards a healthy lifestyle in the country has not been properly studied. This issue must be carefully studied and appropriate evidence-based recommendations should be prepared. In the course of the research, many accents were revealed that were neglected by the contingent of adolescents. For example, health education is a necessary component of measures aimed at implementing a healthy lifestyle, so that individuals realize the need for activities necessary for their own health. The study also confirmed the need for integrated work of public, governmental, and non-governmental organizations to achieve success.

The main burden of morbidity and mortality of the world population falls on non-communicable diseases. Based on global morbidity rates, 22 of the 25 leading causes of Years Lost due to Disability (YLDs) in 2015 were 22 non-communicable diseases. Chronic diseases such as arterial hypertension, stroke, obesity, arthritis, type 2 diabetes are the major public health challenges of the 21st century. According to the US Centers for Disease Control and Prevention, 7 of the top 10 causes of death in 2010 are related to chronic diseases, which account for 48% of all deaths. According to WHO (2016), cardiovascular diseases are the leading cause of death worldwide, causing more than 17.5 million deaths each year. According to WHO experts, ischemic heart disease and cerebrovascular disease will be among the top ten causes of disease burden in the world by 2030.

Unhealthy lifestyle and related risky behaviors such as tobacco use, unhealthy diet, low rate of physical activity, excessive alcohol consumption are the main causes of chronic diseases. It should be noted that the causes of death, chronic diseases and unsatisfactory quality of life at an early age are precisely the unhealthy behaviors that can be changed by man himself. According to the US Centers for Disease Control and Prevention, physical activity in 52% of the world's adult population is below the minimum standard, and 47% of the adolescent population has at least one risk factor for chronic disease, such as uncontrolled high blood pressure, LDL. He increased rate, obesity. Between 2009 and 2010, approximately 78 million adults developed obesity. However, the body index of 20% of adults exceeded the allowable norm (CDC, 2012).

Every day, 3,200 teens in the world start smoking while 2,100 become regular smokers; WHO estimates that the number of smokers in the world will reach 1.7 billion by 2025; However, excessive alcohol consumption causes the death of 88,000 people in one year (CDC, 2012).

According to the "Health Statistics 2015" jointly developed by the Ministry of Labor, Health and Social Affairs of Georgia and the National Center for Disease Control and Public Health, 97% of deaths in the country are due to non-communicable diseases (94%) and injuries (3%).

Health-threatening behaviors and associated chronic diseases are associated with the greatest economic costs globally. However, it should be noted that these diseases can be prevented through targeted interventions and preventive measures. In order to establish a healthy lifestyle, prevent chronic diseases and reduce related health care costs, the World Health Organization has established and successfully implemented health prevention programs and strategies. Strategic areas include promoting healthy eating, promoting regular physical activity, preventing tobacco use, reducing the harm caused by alcohol in the community, and improving mental health.

Health promotion is the combination of individual, group and community strategies to prevent chronic diseases, change human behavior, addiction and improve health education. Health promotion measures significantly improve the quality of life and health status of individuals and the community. Addressing health resources as a preventative measure not only contributes to financial cost-effectiveness, but also improves the economic and social situation of the country.

Based on the above, the purpose of the planned study was to examine the level of knowledge of staff about ways to prevent the spread of hepatitis C in beauty salons to protect their business activities from unpredictable costs.

The following key themes and terms were identified in the literature search: health promotion, strategy, prevention, methods, national policy, perspective, evidence, vision, implementation, indicators, effectiveness, education.

Health promotion and disease prevention is a process aimed at controlling and improving the state of human health. Given that health is a state of complete physical, mental, economic and social well-being, health promotion goes beyond the competence of the health sector alone and involves the overall public provision of human well-being (WHO, 1989).

Good health is a prerequisite for social, economic and personal development. It should be noted that political, economic, social, cultural, environmental, behavioral and biological factors can significantly improve and at the same time worsen the state of human health and quality of life. This is why advocacy for health promotion is essential to achieving equity in healthcare. The main goal of health promotion policy is to ensure equal access to medical services. This includes creating a favorable environment, as well as access to information, education of the population and planning preventive measures to help the community make healthy choices. Successful implementation of health promotion measures is impossible without properly defined health determinants (WHO, 2016). According to the World Health Organization, health determinants are a combination of personal, social, economic, and environmental factors that determine the health status of individuals and populations (WHO - Health Promotion Glossary, 1998).

An international document on health promotion also includes the Rio Political Declaration on Social Determinants of Health (Rio Political Declaration on Social Determinants of Health, 2011), adopted at the World Health Organization's October 21, 2011 World Conference in Rio. The aim of the conference was to share knowledge and experience on social determinants of health among the member states of the World Health Organization in order to achieve "equity of health" and to develop a unified strategy. The declaration states that health inequality between country and country is

unacceptable both politically and socially and economically. It should be noted, however, that the goal of Equality in Healthcare is achievable by promoting health and focusing on sustainable development, taking measures to improve the quality of life, and creating a peaceful, healthy living environment. Rio's political declaration is based on World Health Assembly WHA62.14 Resolution "Reducing health inequalities through action on social determinants of health resolution" (WHA62.14, Reducing health inequities through action on social determinants of health resolution, 2009).

Health promotion is a major concern for European countries. It is from the European region that the recommendations of the World Health Organization on health promotion, such as healthy cities, health promotion in schools, health promotion in hospitals, etc. (Ashton, 1992; WHO, 1991; WHO, 1992; WHO, 1994b; WHO, 1996b; WHO- EC-CE, 1992; WHO-EC-CE, 1997). It is noteworthy, however, that these interventions had highly limited potential and failed to have significant effects on improving health in the European region (De Leeuw, 1989; Tsouros, 1990; Grossman and Scala, 1993; Jensen and Schnack, 1994; Sidell et al., 1997; Pelikan et. al., 1998; Ziglio, 1998). At the same time, it is noteworthy that since the adoption of the Ottawa Charter, the European region has undergone dramatic changes in terms of geopolitical, economic and social development, which in turn has led to new health challenges.

It should be noted that the involvement of the health sector alone is not enough to promote health. Improving the health of the population is a complex process and requires coordinated action involving the following sectors: government, health, social and economic sectors, NGOs and charities, local municipalities, media and industry, health researchers, community. Advocacy in healthcare is the political will of individual and social action to support the system for the successful implementation of program goals at the state level (Strategies for Health and Development: Development Communication in Action. WHO, Geneva, 1992). It is noteworthy that health promotion strategies need to be adapted to the needs and capabilities of individual countries at the national level to take into account the specifics of different social, cultural and economic systems (WHO, 2016).

Based on the above, the aim of the study is to determine the awareness of healthy living in the population of Georgia, to assess the physical health, physical activity and emotional health of the population, to plan health promotion strategies.

The objectives of the research

1. Study of the level of adolescents' awareness and attitude.
2. Retrospective analysis of the results of the conducted sociological research.
3. Based on the results of the research, develop strategies and recommendations for interventions to be implemented.
4. Based on the results of the study, develop the right ways to solve the problem, drawing on evidence.
5. Develop adolescent support and health prevention programs, which are important for the normal growth and development of adolescents in the future.

Work done for the research to be conducted:

1. Careful study and analysis of existing national and international scientific literature on the issue.
2. Development of a research tool.
3. Selection of the research target population.
4. Informing the target population, obtaining informed consent

5. Processing the research results and preparing conclusions and recommendations based on the analysis.

Research Materials and Methods

The research will use the so-called mixed research method, which includes both qualitative and quantitative research methods. For the quantitative method, a self-administered questionnaire will be developed that will assess the level of adolescents' awareness and attitudes towards a healthy lifestyle. In order to study and analyze the adolescents'perceptions and attitudes, qualitative individual interviews with students at universities will be conducted. The results of both the quantitative and qualitative components of the research will be processed statistically. The Stata statistical software package will be used to analyze the quantitative aspects, and the N-Vivo version 12 qualitative data analysis software will be used to analyze the qualitative component of the research, as well as a retrospective analysis of the sociological research results.

Discussion

The research, undertaken on adolescents, aimed to analyze how age changes the healthy lifestyle of adolescents. The results of this research showed that, in general, adolescents do not follow a healthy lifestyle. These findings highlight that much remains to be done to promote a healthy lifestyle and increase adolescents' awareness of potential risks to their health and health status. 145 students aged 17 to 23 years participated in the research. Given the relevance of this issue, the study was planned. In order to change adolescents 'attitudes towards unhealthy behavior, it is necessary to carry out targeted interventions. But without studying the adolescents' attitudes, without appropriate evidence, it is impossible to plan effective interventions. Unfortunately, this issue has not been thoroughly examined in Georgia.

Georgia's healthcare sector has been reformed since 1995. In the first year of the reform, the public health sector, which was a centrally planned, Soviet, Semashko system, was transformed into a private system. In the same year, market mechanisms were introduced in the system, which was reflected in the privatization of pharmacies and dental clinics. The first steps toward the privatization of hospitals were taken in 1996 (Transparency International Georgia, Georgian Hospital Sector Report 2012).

Measures to promote public health were one component of health sector reform. In order to implement the state policy of public health, universal establishment and development of a healthy lifestyle, in 1999 the President of Georgia №107 approved the "List of activities of the state program for the promotion of health and the establishment of a healthy lifestyle for 1999-2005." The document was aimed at improving the health (quality indicators) of the population of the country and the establishment of a healthy lifestyle in the community. The Ministry of Economy of Georgia, together with other interested ministries and agencies, was instructed to develop an indicative socio-economic development plan for the country. The list of health promotion activities for 1999-2005 included anti-tobacco measures, health promotion for children and women, and health promotion for after-school adolescents and youth (Presidential Decree No. 107).

Health promotion and the development of public health are a top priority for Georgia. This is confirmed by the fact that in the document "Millennium Development Goals in Georgia" developed in 2014, four of the eight main goals (reducing child mortality, improving maternal health, fighting HIV / AIDS, malaria, and other diseases, and ensuring environmental sustainability) address health issues. The goals set for overcoming hunger, promoting equality, expanding education, protecting

the environment and improving health are uniting peoples around the world to accomplish this worthy task (Millennium Development Goals in Georgia, 2014).

To meet MDG's health-related goals and broader human development goals, the Government of Georgia launched the Universal Health Care (UHC) Program in 2013, which covers all Georgian citizens with a basic package of outpatient, inpatient, and emergency medical services. The above program is based on the 2012 UN Resolution on Universal Health and its global vision. International partners such as the World Health Organization (WHO), the World Bank, and the United States Agency for International Development (USAID) actively support the country in developing universal health care (Millennium Development Goals in Georgia, 2014).

Measures to establish a healthy lifestyle belong to the category of necessary and beneficial activities for the society, which allow to bring maximum benefit to human health at a relatively low cost and at the same time contribute to the economic progress of the country. An essential component of the effectiveness of a healthy lifestyle is the active participation of adolescents in all stages of its implementation. The planned research will improve the awareness of adolescents towards a healthy lifestyle in the country, with the remarkable scientific value of the research results. Organizations working to establish a healthy lifestyle at the national and international levels will receive scientifically substantiated evidence of adolescents' attitudes towards this issue in Georgia. This in turn will play an important role in the effectiveness of future planning activities.

To study and analyze the level of awareness and attitudes of adolescents about a healthy lifestyle. Will enable us to identify the needs of adolescents, develop and implement effective preventive measures.

"Affordable quality health care" is one of the main directions of the Georgian government's strategic development plan - "Modernization and Employment". For this purpose, the Georgian Health Care Plan 2011-2015 was developed. State strategy. This document sets out the strategic goals of the government in the field of health for 2011-2015 and defines the necessary parameters to achieve these goals. The Health Strategy is a document that ensures the awareness and involvement of the Georgian population and the medical community about the ongoing reforms in this field (State Health Strategy of Georgia 2011-2015).

According to the strategic document, the basic principles of the health strategy are equal access, a patient-centered health care system, affordable and effective public health, cooperation between the public and private sectors, promotion of free competition, transparency and community involvement, adequacy of resources, intersectoral approach - Georgia Health State Strategy for 2015).

The main priority of the state strategy for health care (2011-2015) is to monitor the health status of the population and assess the risks. The following priorities have been identified for this function: development of public health system, development of maternal and child services, prevention and control of tuberculosis and HIV/AIDS, prevention and screening of non-communicable diseases, promotion of mental health, promotion of healthy living and healthy lifestyle.

Health Care 2011-2015. According to the state strategy, health promotion combines measures aimed at creating an educational, preventive, and healthy environment. To promote health, it is essential that every citizen fully understand the importance of the negative effects of bad habits and misbehavior, while the government should help create an environment that allows people to take care of their own health. Behavioral health promotions by the government in cooperation with the private and non-governmental sectors are identified as behavioral risk factors (drug use, malnutrition, dynamics, alcohol, tobacco) and road safety education activities.

In order to improve and protect the health of the population, it is necessary to implement targeted programs and measures aimed at promoting health, in particular, the establishment of the concept of a "healthy school", measures to prevent drug addiction and reduce tobacco use, and others. These measures will be implemented in close cooperation with the non-governmental sector, as well as with international organizations (World Health Organization, EU) and other government agencies (National Council for Reproductive Health, Ministry of Education and Science, Civil Registry, Ministry of Sports and Youth Affairs, etc.). Is the basis for the successful implementation of the promotion strategy (State Strategy for Health Protection 2011-2015).
In order to promote health, it is necessary to pay special attention to the improvement of the legislation related to health care and the development and implementation of effective measures for its implementation. In this regard, it is important to take care of road safety, reduce drug use, and provide safe food and a healthy urban environment. In order to synchronize multifaceted measures to promote health, the country's government is ready to strengthen and deepen cross-sectoral cooperation while at the same time intensifying work with the community and encouraging community initiatives to promote healthy behavior (State Health Strategy 2011-2015).

Conclusions

1. The discipline of the research topic is public health.
2. Measures aimed at the implementationof a healthy lifestyle and the prevention of diseases at an early stage are the main tasks of public health.
3. The objective and essence of the planned research is in full compliance with the basic value of public health as a science.
4. It has been established that adolescents were aware of the importance of a high level of health to ensure the effectiveness of vital activities. More than 35% of adolescents realized the importance of health but did not care about maintaining it.

Assessment of the Research

Based on the foregoing, it is worth noting that the study and analysis of the level of adolescents'awareness and attitude towards a healthy lifestyle is an important novelty that requires careful study of the issue and making evidence-basedconclusions.

REFERENCES

1. National Center for Disease Control and Public Health NCDC (2018). Healthcare, Statistical Handbook, Georgia,2018. Viewed on01.12.19;
2. Ministry of Education and Science of Georgia (2015). Healthy Lifestyle. The Teacher's Guide. Viewed on 01.12.19.
3. Ashton, J. (1992) Healthy Cities. Open University Press, Buckingham. Beck, A., Iturralde, E., Haya-Fisher, J., Kim, S., Keeton, V. and Fernandez, A., 2019. Barriers and facilitators to healthy eating among low-income Latino adolescents. Appetite, 138, pp.215-222. (Beck et al., 2019).
4. Effectiveness of a school-based intervention on knowledge, attitude, and practice on healthy lifestyle and body composition in Malaysian adolescents. BMC Pediatrics, 20(1).(Sharif Ishak et al., 2020).

5. Tajik, E., Latiff, L., Siew, C., Awang, H. and Adznam, S., 2020. Designing and Validating a Questionnaire on Healthy Lifestyle to Reduce Depressive Symptoms among Adolescents. Iranian Journal of Psychiatry,.(Tajik et al., 2020).
6. Marques, A., Loureiro, N., Avelar-Rosa, B., Naia, A. and Matos, M., 2020. Adolescents' healthy lifestyle. Jornal de Pediatria, 96(2), pp.217-224. (Marques et al., 2020).
7. Mak, Y., Kao, A., Tam, L., Tse, V., Tse, D. and Leung, D., 2018. Health-promoting lifestyle and quality of life among Chinese nursing students. Primary Health Care Research & Development, 19(6), pp.629-636.
8. L. Ratiani, L. Gabunia, Sh. Khetsuriani, N. Gamkrelidze, N. Gogokhia, T. Makharadze, E. Varazi, N. Antia, N. Sulashvili; C reactive protein, Procalcitonin, Ferritin Levels in Mild, Severe and Critically Ill Patients with Coronavirus Disease 2019 (COVID-19); ISSN: 2509-0119. International Journal of Progressive Sciences and Technologies (IJPSAT); © 2021 International Journals of Sciences and High Technologies; http://ijpsat.ijsht-journals.org; Vol. 26 No. 2 May 2021, pp.281-286.
9. Griban, G., Lyakhova, N., Harlinska, A., Yavorska, T., Kolesnyk, N., Hryshchuk, S. and Obodzinska, O., 2021. STUDENTS' HEALTH LEVEL AS A RESULT OF THEIR LIFESTYLE. Wiadomości Lekarskie, 74(4), pp.874-879.(Griban et al., 2021).
10. Sharif Ishak, S., Chin, Y., Mohd. Taib, M., Chan, Y. and Mohd. Shariff, Z., 2020. Effectiveness of a school-based intervention on knowledge, attitude and practice on healthy lifestyle and body composition in Malaysian adolescents. BMC Pediatrics, 20(1).(Sharif Ishak et al., 2020)
11. Griban, G., Myroshnychenko, M., Tkachenko, P., Krasnov, V., Karpiuk, R., Mekhed, O. and Shyyan, V., 2021. PSYCHOLOGICAL AND PEDAGOGICAL DETERMINANTS OF THE STUDENTS' HEALTHY LIFESTYLE FORMATION BY MEANS OF HEALTH AND FITNESS ACTIVITIES. Wiadomości Lekarskie, 74(5), pp.1074-1078. (Griban et al., 2021)
12. L. Ratiani , L. Gabunia, Sh. Khetsuriani, N. Gamkrelidze, N. Sulashvili , N. Gorgaslidze, E. Varazi, N. Antia; GLOBAL SCIENTIFIC DISCUSSION OF PECULIARITIES OF THE UNIVERSAL PHARMACOLOGICAL PRINCIPLES OF PHARMACOTHERAPEUTIC TREATMENT OF COVID-19 PANDEMIC BEFORE VACCINATION; Tbilisi State Medical University, Faculty of Public Health; CONFERENCE BOOK; OF THE FIRST INTERANATIONAL CONFERENCE "FUTURE OF HEALTH CARE IN THE 21 CENTURY", Tbilisi-2021; Pp:52-99.
13. L. Ratiani, L. Gabunia, N. Sulashvili, N. Gorgaslidze, E. Varazi, N. Antia; GENERAL ACADEMIC REVIEW OF CHARACTERISTICS OF PROBLEMS, ACHIEVEMENTS AND PROSPECTS OF COMPLEX PHARMACOTHERAPEUTIC CURING FOR COVID-19 DISEASES PRIOR TO VACCINES; УДК 615.1 (06) Proceedings of The Scientific-Practical Conference "WE OPEN THE NEW CENTURY: ACHIEVEMENTS AND PROSPECTS" With International Participation, Dedicated to the 100th Anniversary of the National University of Pharmacy; MINISTRY OF HEALTH OF UKRAINE; NATIONAL PHARMACEUTICAL UNIVERSITY OF UKRAINE; 10 of September, 2021, Kharkiv, Ukraine, Pp: 537-541.
14. L. Gabunia, Sh. Khetsuriani, N. Gamkrelidze, L. Ratiani, N. Filipets, L. Metreveli, N. Sulashvili, N. Antia; Pharmacologic Modulation during Cytokine Storm in COVID-19; ISSN: 2790-3990; Impact Factor: 0.70; International Journal of Applied Sciences: Current and Future Research Trends (IJASCFRT); 2021, Volume 12, No 1, Pp 7-12, (13-18);

15. N. Sulashvili, L. Gabunia, L. Ratiani, N. Gorgaslidze, K. Ghambashidze, E. Varazi, N. Antia; THE SCIENTIFIC DISCUSSION OF WORLDWIDE CHALLENGES OF COVID-19 EPIDEMIC AND GENERAL DRUG THERAPY APPROACHES TO COMBAT THE COVID-19 DISEASES; E-ISBN: 978-9916-9769-0-6; DOI suffix: 10.36962/MHPAS06; Website: https://bsj.fisdd.org/, https://scsj.fisdd.org/ CONFERENCE PROCEEDINGS; THE SIXTH INTERNATIONAL SCIENTIFIC– PRACTICAL CONFERENCE IN MODERN MEDICINE AND HEALTH: PROGNOSIS, ACHIEVEMENT AND CHALLENGES; ESTONIA, TALLINN FEBRUARY 25-26, TALLINN-2022; Pp:10-11.
16. Department of Health, State of Western Australia (2012). *Western Australian Health Promotion Strategic Framework 2012–2016* . Retrieved from: http://www.public.health.wa.gov.au/cproot/4462/2/wa_health_promotion_strategic_framework.pdf
17. Government of Canada & Minister of National Health and Welfare (1974). *A New Perspective on the Health of Canadians.* Retrieved from: http://www.phac-aspc.gc.ca/ph-sp/pdf/perspect-eng.pdf
18. Grossman, R. and Scala, K. (1993) Health Promotion and Organizational Development. European Health Promotion Series, No. 2. World Health Organization, Regional Office for Europe, Copenhagen.
19. L. Ratiani, L. Gabunia, N. Sulashvili, N. Gorgaslidze, K. Ghambashidze, J. Cheishvili, M. Beglaryan, E. Varazi, N. Antia; THE FEATURES OF THE GENERAL PREVENTION ACHIEVEMENTS AND UNIVERSAL PHARMACO THERAPY TREATMENT FOR FIGHTING TO THE COVID-19 DISEASES IN 2020; УДК 615.1; НФАУ, 2021; Scientific publication; MATERIAL OF IX INTERNATIONAL SCIENTIFIC-PRACTICAL CONFERENCE, «MODERN ACHIEVEMENTS OF PHARMACEUTICAL TECHNOLOGY AND BIOTECHNOLOGY», WHICH IS DEDICATED TO THE 45TH ANNIVERSARY OF THE DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY OF DRUGS; MINISTRY OF HEALTH OF UKRAINE; NATIONAL UNIVERSITY OF PHARMACY OF UKRAINE; DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY OF DRUGS; DEPARTMENT OF BIOTECHNOLOGY; 11-12 OF NOVEMBER, 2021, KHARKIV-UKRAINE, Pp:27-34.
20. Hall, J., & Taylor, R. (2003) - Health for all beyond 2000: the demise of the Alma-Ata Declaration and primary health care in developing countries. - *MJA 2003*, 178, 17–20 Retrieved from: https://www.mja.com.au/system/files/issues/178_01_060103/hal10723_fm.pdf
21. HSE National Health Promotion Office (2011) *–Health Service Executive– Health Promotion Strategic Framework.* Retrieved from: http://www.healthpromotion.ie/hp-files/docs/HPSF_HSE.pdf
22. Jackson, F., Perkins, F., Khandor, E., Cordwell, L., Hamann, S., & Busaj, S. (2007) Integrated health promotion strategies: a contribution to tackling current and future health challenges. - *Health Promotion International*, 21(S1), 75-83. doi:10.1093/heapro/dal054
23. Jensen, B. B. and Schnack, K. (eds) (1994) Action and Action Competence. Studies in Educational Theory and Curriculum Volume 12. Royal Danish School of Educational Studies, Copenhagen.
24. Levin, L., McMahon, L. and Ziglio, E. (eds) (1994) Economic Change, Social Welfare and Health in Europe. World Health Organization, Regional Office for Europe, Copenhagen.

25. Who-European Commission-Council of Europe (1992) The European Network of Health Promoting Schools. World Health Organization, Regional Office for Europe, Copenhagen.
26. N. Sulashvili, M. Beglaryan, N. Gorgaslidze, T. Chikviladze, I. Zarnadze, N. Chichoyan, L. Gabunia, N. Kvizhinadze, Sh. Zarnadze; THE SCIENTIFIC DISCUSSION ON CHARACTERISTICS OF PHARMACEUTICAL VOCATIONAL INQUIRES AND CHALLENGES IN THE DIRECTION ON PHARMACISTS' PROFESSION, ROLE, PROBLEMS, INNOVATIONS, AND PERSPECTIVES IN PHARMACEUTICS AND MEDICINE GLOBALLY; ISSN 1829-040X; DOI: 10.53821/1829040X; https://orcid.org/0000-0001-9263-6791; BULLETIN OF THE MEDICAL INSTITUTE AFTER MEHRABYAN, VOL. 10 TOM, 2021; YEREVAN 2021; REPUBLIC OF ARMENIA; Pp:26-55.
27. Ministry of Health of the Czech Republic (2014) – Health 2020 National Strategy for Health Protection and Promotion and Disease Prevention . Retrieved from: file:///C:/Users/user/Downloads/Health_2020_%E2%80%93_National_Strategy_for_Health_Protection_and_Promotion_and_Disease_Prevention%20(2).pdf
28. National Center for Chronic Disease Prevention and Health Promotion (2012). Chronic Disease Prevention and Health Promotion, Chronic Disease Overview. Retrieved from: https://www.cdc.gov/chronicdisease/overview/

THE MANIFESTATION OF FEATURES OF ANDROGEN HORMONE CHARACTER OF THE DEVELOPMENT OF NORMAL PHYSIOLOGICAL AND PATHOHISTOLOGICAL PROCESSES IN MALE HEALTH

Marika Sulashvili[1], Luiza Gabunia[2], Levan Ratiani[3], Nana Gorgaslidze[4], Nato Alavidze[5], Natia Kvizhinadze[6], Maya Gogashvili[7], Nodar Sulashvili[8]

[1]MD, Doctor of Family Medicine, Invited Lecturer of Department of Molecular and Medical Genetics at Tbilisi State Medical University, Tbilisi, Georgia. Invited Lecturer of the University of Georgia, School of Health Sciences, Tbilisi, Georgia.

[2]MD, PhD, Doctor of Medical Sciences, Professor, Director of the Scientific Research-Skills Center at Tbilisi State Medical University, Professor of the Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia.

[3]MD, PhD, Doctor of Medical Sciences, Professor, General Director of the First University Clinic of Tbilisi State Medical University, Head of the Department of Emergency Medicine, Reanimatology and Anesthesiology at Tbilisi State Medical University; Tbilisi, Georgia;

[4]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Tbilisi State Medical University, Head of The Department of Social and Clinical Pharmacy, Tbilisi, Georgia.

[5]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia.

[6]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Tbilisi State Medical University, Department of Social and Clinical Pharmacy. Tbilisi, Georgia.

[7]MD, PhD, Doctor of Medical Sciences, Professor of the University of Georgia, School of Health Sciences, Head of the Nursing Department, Tbilisi, Georgia.

[8]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Invited Professor/Lecturer of Tbilisi State Medical University, Tbilisi, Georgia; Invited Professor of the University of Georgia, School of Health Sciences, Tbilisi, Georgia.

ABSTRACT

Aim of the research was to study and analyze features of androgen hormone character of the development of normal physiological and pathohistological processes in male health. The molecular mechanism mediating cellular responses to androgens is complex and involves both genomic and non-genomic effects that are still far from being clearly understood. The genomic effects of androgens are mediated by a specific receptor, the androgen receptor (AR). Testosterone is the main circulating androgen in men and is also present in women, although in much lower concentrations. This hormone plays a vital role in regulating bone mass, fat distribution and sperm production, as well as mood and cognition. Therefore, exogenous testosterone may be an important therapy, especially for patients with symptoms of hypogonadism or low testosterone levels. However, when using testosterone in supraphysiological doses and without medical supervision, a number of risks arise. For men, exogenous testosterone treatment appears to be largely beneficial, at least in part due to the aromatization of testosterone to estradiol, especially when physiological testosterone levels are deficient. However, acetylsalicylic acid self-administration remains a significant cardiovascular safety issue, especially in light of reports of adverse effects on the lipid profile. While clinicians are considering using testosterone to treat age-related symptoms in men, data on the risk of cardiovascular disease with long-term testosterone use remains conflicting and poorly published. Current evidence suggests that, when treated with testosterone in aging women, androgen excess adversely affects risk factors for cardiovascular disease, especially in women with diabetes. Thus,

knowledge of exogenous androgen treatment in men and women remains limited. Despite this, there is a growing use and abuse of androgens in our society, whether for therapeutic or recreational purposes. Whether androgens adversely affect cardiovascular disease in men or women remains a controversial issue that urgently requires further research. Cardiovascular disease (CVD) remains the leading cause of death in the world today. There is a striking gender difference in cardiovascular disease, with men predisposed to earlier onset and more severe disease. Following a recent reassessment and ongoing debate regarding the estrogen protection hypothesis, and given the increasing use and abuse of androgens in our society, the alternative view that androgens may contribute to cardiovascular disease in men is gaining in importance. Whether androgens adversely affect cardiovascular disease in men or women remains a controversial issue in both the cardiovascular and endocrinology communities. This review draws on basic scientific research, animal studies, and clinical studies to outline our current understanding of the effects of androgens on atherosclerosis, a major cardiovascular disease, and the future directions of research on androgens associated with atherosclerosis direction. Testosterone plays an important role in the treatment of true symptomatic hypogonadism in young and older men. There does not appear to be any major problem with testosterone use in otherwise healthy young men with specific indications for testosterone replacement therapy. Testosterone has a specific effect on the cardiovascular system. The use of testosterone in older men and patients with known coronary artery disease is controversial.
Keywords: Androgen, hormone, character, development, normal physiological, male, health.

Introduction

Androgens and estrogens are fat-soluble steroids and can easily cross the plasma membranes of target cells. Once inside the cell, steroid hormones bind to the receptor protein and form a receptor-hormone complex, which then enters the nucleus and binds to DNA. DNA binding causes change in gene expression and thus changes in cell activity. Some steroid hormones stimulate genes to synthesize specific proteins; others block or inhibit protein synthesis. There are a number of hormone-activated events, including mutations in DNA nucleotides, changes in the chemical structure of hormones or their receptors, competition or blockage of receptor-binding sites by endogenous or environmental chemicals that mimic hormones, and natural declines in hormone levels. as a result of aging, which can trigger cellular changes that lead to cancer and reproductive disorders. Androgens are male sex hormones [1-4].

Androgens have a powerful anabolic effect on skeletal muscle and decline with age in parallel with the loss of muscle mass and strength. This loss of muscle mass and function, known as sarcopenia, is a central event in the development of frailty, a vulnerable health condition that portends poor outcomes and rapid functional decline in the elderly. Thus, the potential role of androgen reduction in the development of frailty and their usefulness as a function-promoting therapy in older men has received considerable attention. This review summarizes current concepts and definitions of muscle aging, sarcopenia, and frailty, and evaluates recent advances in the study of androgens and frailty. Current data from observational and interventional studies strongly support the effect of androgens on muscle mass in aging men, but the effect of androgens on muscle strength and especially physical function is less clear. Androgen treatment is generally well tolerated in studies of older men, but concerns remain about treatment at higher doses and use in populations at high risk of cardiovascular disease. Early trials of selective androgen receptor modulators (SARMs) have shown effects on muscle mass and function similar to conventional androgen therapy in the elderly. Important future

directions include the use of these agents in combination with exercise to improve functional ability in various groups of older adults, as well as greater attention to the relationship between concurrent changes in hormone levels, body composition, and physical function [5-8].

Testosterone and androsterone and promote the development of male sexual characteristics. They also promote general anabolic bone growth functions and increased protein synthesis, particularly in muscle. Like all steroid hormones, androgens are formed from cholesterol. The main testicular androgen is testosterone. The production of testosterone is influenced by the gonadotropic hormone produced by the pituitary (tropical) gland. Hormones stimulate target organs to secrete other hormones) and is regulated by a hormone that stimulates interstitial cells. Negative feedback from certain testosterone concentrations in the blood

Along with the nervous system, the endocrine system, which consists of glands that secrete chemical messengers, is one of two communication systems that regulate all reactions and functions of the body. Unlike the nervous system, which sends fast signals via electrochemical transmission along neural pathways to the brain, where they are decoded and sent to the appropriate parts of the body to trigger immediate responses. The endocrine system transmits subtler, slower signals to cellular instructions via chemical messengers. hormones that are produced in the endocrine glands, a body part travels through the bloodstream until it encounters specialized receptors with which it interacts, causing the necessary biological responses in specific target tissues. Hormones act slowly and their effects tend to persist in the body for a long time. Hormones are also specific. Each hormone has a unique chemical conformation that corresponds to a specific receptor protein on the target cell. When a certain hormone comes into contact with its specific receptor, they fit together like a lock and key. But so is flexibility feature of hormones. A particular receptor protein can be present on different cell types in different organs, meaning that the same hormone can be used by the body to have different effects in different tissues. A striking feature of hormones is that drastic changes in cellular activity are caused by very small amounts of chemicals [9-11].

The hair growth cycle and the structure of the hair follicles are highly dependent on various hormones. In particular, the influence of androgens has been extensively studied and described in previous work. To research Androgens affect the hair follicles based on the location of the hair on the body. The primary effect of androgens on hair follicles is related to binding to androgen receptors in dermal papilla cells. Scientific studies also provide information about the sites of androgen production associated with enzymes in the hair structure. In addition to androgens, the pathogenic role of other hormones is currently being investigated. The results of numerous analyzes flow into our evaluation. This review provides a comprehensive, up-to-date understanding of hormonal effects on hair follicles [12-14].

Androgens promote hair follicle contraction and shorten the growth phase of the hair follicle cycle. Drugs with androgenic activity can cause hair loss, such as exogenously administered testosterone, which can be used in hypogonadal men and sometimes postmenopausal women in addition to hormone replacement therapy. Estrogen is known to prolong the anagen stage and counteract androgenetic alopecia. Estrogenic stimuli can cause the hair follicle to enter the anagen phase and vice versa. Use of the estrogen receptor antagonist tamoxifen in women with breast cancer may worsen female hair loss. Tamoxifen competes for the estrogen receptor and creates an environment of relative hyperandrogenism that can potentiate the effects of androgens on follicles [15-16].

Testosterone is the main circulating androgen in men and is also present in women, although in much lower concentrations. This hormone plays a vital role in regulating bone mass, fat distribution and sperm production, as well as mood and cognition. Therefore, exogenous testosterone may be an

important therapy, especially for patients with symptoms of hypogonadism or low testosterone levels. However, when using testosterone in supraphysiological doses and without medical supervision, a number of risks arise.

Androgenic or anabolic androgenic steroids include testosterone and synthetic derivatives, which are primarily used to increase muscle mass and improve appearance and athletic performance. The current global prevalence is estimated. Chronic use of supraphysiological doses of testosterone has been associated with a wide range of physical and mental outcomes, including cardiovascular complications, anxiety, and aggressive behavior. However, relatively little research has been devoted to the brain, although this has increased in recent years [17-19].

Hypogonadism is generally defined as an impairment of the gonads resulting in impaired steroid hormone production and impaired gamete production. Although steroids and gametes were considered products of the gonads for over a century, it became clear during the last decades of the 20th century that the somatic component of the ovaries and testes also secrete protein hormones such as inhibins and anti-Mullerian hormone (AMH), which play an important role as biomarkers of reproductive physiology from fetal life to adulthood. Therefore, given the changes that occur in the physiology of the hypothalamic-pituitary-gonadal system from the prenatal period through puberty, the definition of hypogonadism should be expanded to include ovarian or testicular dysfunction beyond that at what one would expect in old age. it is a reduction in the function of the germinal and/or somatic populations of the gonads, which can lead to an alteration in the secretion of hormones (estrogens, progestogens, androgens, inhibits and/or AMH) and/or the production of gametes [20-22].

The differentiation of gonads into ovaries or testicles at the 7th week of embryonic life depends on a complex network of genes: the presence of the SRY gene on the Y chromosome disturbs the balance between prosthetic and pro-ovarian genes and triggers the differentiation of testicles towards the exterior. Subsequently, the action of two distinct testicular hormones, AMH and androgens, causes the differentiation of the internal ducts, the urogenital sinus and the vulva. AMH secreted by Sertoli cells induces Müller duct involution at 8 and 9 weeks of fetal life. Androgens produced by Leydig cells cause stabilization and differentiation of Wolff's ducts and virilization of the urogenital sinus and vulva between 8 and 13 weeks of the fetus. These processes occurring in the first trimester of fetal life are independent of fetal pituitary gonadotropins: basal AMH expression is controlled by various transcription factors, and androgen production is regulated by placental hCG. Insulin-like factor 3 (INSL3), produced by Lading cells, is involved in testicular descent. Ovarian hormones do not affect fetal sex differentiation [23-25].

Male hypogonadism i.e., reduced testicular function compared to what would be expected for a given age may include decreased secretion of hormones (AMH, inhibits and/or androgens) and/ or impaired sperm production. This may be due to a primary disorder or a secondary defect in the hypothalamic-pituitary system, resulting in primary (testicular or hypergonadotropic) or secondary (central or hypogonadotropic) hypogonadism, respectively. The terms hypergonadotropic and hypogonadotropic, commonly used in adult medicine, should be used with caution in children. Although elevated levels of gonadotropins, particularly FSH, are a hallmark of primary neonatal and infantile hypogonadism, normal levels of gonadotropins may occur later in childhood in 30-70% of boys with anorchid. This highlights that during childhood, the normal development of an intrinsic central inhibitory tone acting on the GnRH pulse generator can overcome the increase in FSH levels due to low serum inhibin levels [26-28].

Male hypogonadism is a condition in which the body does not produce enough testosterone hormone; a hormone that plays a key role in male growth and development during puberty. There is a clear need to educate the entire medical community about hypogonadism, especially primary care physicians who are often the patient's first point of contact. Hypogonadism can significantly reduce the quality of life and lead to loss of livelihood and couples breaking up, leading to divorce. It's also important for doctors to understand that testosterone isn't just a sex hormone. Extensive research is underway showing that testosterone may play key roles in metabolism, vascularity, and brain function in addition to its known effects on bone and body composition. This article served as an introduction to the need to develop sensitive and reliable tests for sex hormones and for the symptoms and treatment of hypogonadism [29-31].

Hypogonadism is a medical term for a decrease in the functional activity of the gonads. The gonads (ovaries or testes) produce hormones (testosterone, estradiol, anti-Müllerian hormone, progesterone, inhibin B, activin) and gametes (eggs or sperm). Male hypogonadism is characterized by a lack of testosterone, a hormone essential for sexual, cognitive, and physical function and development. Clinically, low testosterone levels can lead to a lack of secondary sex characteristics, infertility, muscle wasting, and other abnormalities. Low testosterone levels can be associated with testicular, hypothalamic, or pituitary abnormalities. For people who also have clinical signs and symptoms, clinical guidelines recommend treatment with testosterone replacement therapy [32-33].

With locally advanced disease affecting areas outside the capsule, there is an increased risk of lymph node recurrence and metastasis after prostatectomy. Testosterone (an androgen) is believed to cause prostate cancer; Therefore, treatments exist to reduce the number of androgens available. Androgens are produced both in the testes (95%) after stimulation with luteinizing hormone (LH) and luteinizing hormone-releasing hormone (LHRH) by the pituitary gland and in the adrenal glands (5%) after stimulation with adrenocorticotropic hormone (ACTH). Androgens produced by the adrenal glands are precursor hormones that are enzymatically converted to testosterone and DHT in the prostate and peripheral tissues. Since testosterone is a known etiological factor associated with prostate cancer, it follows that testosterone deficiency can be used as part of a treatment strategy. In practice, this can be achieved through surgical or medical castration, with the duration of hormonal control varying from a few months to several years.

Most research examining the neuropsychiatric effects of androgen use has primarily focused on behavioral issues, with a clear focus on violence and aggression. The researchers hypothesized that these behaviors might reflect changes in brain structures often associated with executive function and emotional control, including the prefrontal cortex (PFC), hippocampus, and amygdala. However, the mechanisms by which androgens influence changes in these structures and subsequent behavior are not well understood. In recent years, likely due to the ever-increasing number of older androgen users, there has been increasing research interest in long-term effects on neuronal and brain health. This review describes data published over the past year and a half on the effects of androgen use on the brain, including changes in neurobiology and neurochemistry, as well as cognitive deficits [34-37].

Aim of the research

Aim of the research was to study and analyze features of androgen hormone character of the development of normal physiological and pathohistological processes in male health.

Methodology

The main question of this article was to research and analyses features of androgen hormone character of the development of normal physiological and pathohistological processes in male health. We have searched and analyzed PubMed, Web of Sciences, Clinical key, Tomson Routers and Google Scholar mostly, using search terms bases, including the words to research and analyses features of androgen hormone character of the development of normal physiological processes in male patients. In addition to the desired subject understanding. Then, each article was discussed and an abstract of the total information gathered during the process was provided, aiming at easy understanding of the public. To establish these outcomes, over two hundred articles were investigated. We brought together all published data to comprehensively examine the effects in a systematic review, to define the roll out of the study of the research and analyses of the features of androgen hormone character of the development of normal physiological and pathohistological processes in male health.

Results and discussion

The level of testosterone in the blood serum in most men gradually decreases with age. Epidemiological and observational studies have shown that low testosterone levels are associated with an increased risk of cardiovascular disease. A meta-analysis of studies showed that patients with cardiovascular disease have significantly lower testosterone levels and higher 17-β-estradiol levels, which remain significant markers after adjusting for age and of body mass index. In longitudinal studies, baseline testosterone levels were lower in people with cardiovascular mortality.

Testosterone plays an important role in the treatment of true symptomatic hypogonadism in young and older men. There does not appear to be any major problem with testosterone use in otherwise healthy young men with specific indications for testosterone replacement therapy. Testosterone has a specific effect on the cardiovascular system. The use of testosterone in older men and patients with known coronary artery disease is controversial. Asymptomatic middle-aged and elderly men without a history of CVD should be informed of the uncertain CV risk. Randomized controlled trials are needed. Finally, in our opinion, patients with a recent myocardial infarction, revascularization, poorly controlled heart failure, or stroke within the past 6 months are not good candidates for starting or continuing cell replacement therapy. testosterone, given the uncertainty of cardiovascular risk.

Reduces or blocks the production of interstitial-cell stimulating hormone (ICSH). In adulthood, testosterone is essential for sperm production. In women, the ovaries produce two groups of steroid hormones: estrogen and progesterone. Estrogens, including estradiol, estrone and estriol are extreme in the general model, steroid hormones passively enter the cell and bind to the receptor, forming a receptor complex and releasing proteins in the process. Other proteins can also bind to the receptor complex, allowing them to interact with specific regions of DNA to effect transcription of sensitive genes. important for the development of secondary sex characteristics and the regulation of the menstrual cycle. Estrogens also affect libido and electrolyte and nitrogen metabolism, help maintain pregnancy, and prepare breasts for lactation. Progesterone, which is chemically similar to estrogen, helps regulate the changes that occur during menstruation and affects the development of the membranes and breasts during pregnancy. Three gonadotropic hormones produced by the pituitary gland regulate the secretion of estrogen and progesterone: follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. Some male and female hormones are actually secreted by

both sexes. Male hormones are secreted in greater quantities and are more effective when produced by men, and the same is true of female hormones when produced by women [38-41].

There are association between low levels of endogenous testosterone and atherosclerosis, coronary artery disease or cardiovascular events. Men with the highest level of testosterone and bioavailable testosterone had a higher relative risk of abdominal aortic atherosclerosis than men. In patients with coronary heart disease, testosterone levels were lower than in the control group. Serum testosterone levels and SHBG levels were inversely related to the incidence of serious adverse cardiovascular events. Lower testosterone levels in men with symptoms of coronary heart disease compared to controls. Some studies have shown a negative correlation between the degree of angiographic coronary artery disease and testosterone levels. There is an association between low serum testosterone levels and premature coronary heart disease in men. A negative correlation was found between carotid intima thickness and total testosterone concentration in middle-aged men with type 2 diabetes mellitus. Patients with low testosterone levels also more frequently experienced atherosclerotic plaques, endothelial dysfunction and higher levels of highly sensitive C-reactive protein. A significant negative correlation was observed between total testosterone levels and the Framingham risk score. Thus, many observational studies suggest an association between low testosterone levels and the presence of atherosclerosis, coronary heart disease and coronary events [42-44].

Testosterone is the main male sex hormone. As men age, testosterone levels usually drop. Symptoms of low testosterone include decreased libido, vasomotor instability, and decreased bone mineral density. Other symptoms may include depression, fatigue, erectile dysfunction, and decreased strength/muscle mass. Epidemiological studies show that low testosterone levels are associated with atherosclerosis, coronary heart disease, and cardiovascular disease. However, the treatment of hypogonadism in aging men has yielded conflicting results regarding its effect on cardiovascular events. New research suggests that testosterone may play a role in the treatment of heart failure, angina, and myocardial ischemia in the future. A large, long-term, prospective study of testosterone replacement therapy with a primary endpoint of a cluster of cardiovascular adverse events, including myocardial infarction, stroke, and/or cardiovascular death, is needed. The Food and Drug Administration recently placed additional labeling restrictions on testosterone -replacement therapy and called for more research to determine whether it is safe for the heart [45-46].

There are two main types of hypogonadism: Primary: This type of hypogonadism, also known as primary testicular failure, results from a testicular problem. Secondary: This type of hypogonadism indicates a problem in the hypothalamus or pituitary gland, the parts of the brain that signal the testicles to produce testosterone. The hypothalamus produces gonadotropin-releasing hormone, which signals the pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone. Luteinizing hormone then signals the testicles to produce testosterone. Both types of hypogonadism can be caused by an inherited (congenital) trait or by something that happens (acquired) later in life, such as an injury or infection.

Common causes of primary hypogonadism include: Klinefelter Syndrome: This condition is the result of a birth defect of the X and Y sex chromosomes. Males usually have one X chromosome and one Y chromosome. Two or more X chromosomes are also present in Klinefelter syndrome. Y chromosome The Y chromosome contains the genetic material that determines the sex and development of the child. The extra X chromosome present in Klinefelter syndrome causes abnormal development of the testicles, which in turn leads to insufficient production of testosterone. Before birth, the testicles grow inside the abdomen and usually descend to a permanent location in the

scrotum. Sometimes one or both testicles may not be paid at birth. This condition often corrects itself in the first years of life without treatment. If not corrected early in childhood, it can lead to testicular dysfunction and decreased testosterone production.

Testosterone supplementation is associated with a dose-dependent increase in muscle mass and a reciprocal decrease in fat mass in young and older men. The increase in muscle mass occurs due to the hypertrophy of type 1 (slow twitch) and type 2 (fast twitch) muscle fibers. Accordingly, testosterone treatment is associated with dose-dependent improvements in muscle strength and power, strength product and speed. abbreviations. However, androgens may not affect other aspects of muscle function, including fatigue and specific muscle tension or quality (ratio of muscle strength to size). The anabolic effects of androgens are achieved by acting on multiple cellular targets. Testosterone increases the replication and activation of satellite cells, the number of myonuclear and affects protein metabolism. In vitro studies suggest that androgens modulate the differentiation of pluripotent mesenchymal cells predominantly towards a myogenic rather than an adipogenic lineage. Multiple signaling pathways are involved in these androgen-dependent myogenic effects on cell differentiation and proliferation and turnover of muscle proteins. Androgen receptors in satellite cells, as well as several other types of muscle cells, are activated by androgens. Androgens binding to the androgen receptor promote translocation of β-catenin into the cell nucleus of mesenchymal pluripotent cells, leading to myogenic differentiation through follistatin signaling and inhibition of transforming growth factor-β. Similar mechanisms may be involved in the effects of androgens on satellite cell proliferation. Some studies also point to a role for Notch signaling in mediating the effects of androgens on satellite cell activation and proliferation. Other cellular mediators may include stimulation of protein synthesis via the Akt/4 target of rapamycin (mTOR) in mammals and inhibition of forkhead box mediated protein cleavage, as well as increased intramuscular signaling of insulin-like growth factor-1. The relative importance of these various subcellular mechanisms and their interaction with each other is currently not well defined.

Testosterone has a number of protective effects on cell growth and survival in the hippocampus, it is unclear whether testosterone can also stimulate neurogenesis. Adult neurogenesis involves a population of stem cells that multiply, migrate and differentiate into new neurons in the brain. In mammals, the sub granular zone in the dentate gyrus subregion of the hippocampal formation is a critical site for neurogenesis, which is highly sensitive to a variety of endogenous and environmental factors, particularly stress and antidepressant treatment. Two main components of hippocampal neurogenesis are commonly studied: the number of newly produced proliferating cells and the number of those new cells surviving at specific times. Since adult hippocampal neurogenesis is sexually dimorphic, such that females show higher cell proliferation than males and the survival rate of newly proliferating cells is higher in males than females, it is predictable that sex hormones affect these processes. The degree of hormonal regulation of hippocampal neurogenesis in depressive behavior has not yet been fully explored [47-49].

If a mumps infection involving the testicles in addition to the salivary glands (mumps orchitis) occurs during adolescence or adulthood, long-term testicular damage may occur. This may affect normal testicular function and testosterone production.

Chemotherapy or radiation therapy used to treat cancer can affect testosterone and sperm production. The effects of both treatments are often temporary, but permanent infertility can occur. While many men regain fertility within a few months of stopping treatment, many men consider storing sperm before beginning cancer treatment. Howell et al. reported that 30% of men with cancer had hypogonadism and 90% of these men had germinal epithelium deficiency.

Older men generally have lower testosterone levels than younger men. As men age, testosterone production slowly and steadily decreases. The rate of decrease in testosterone varies greatly from person to person. According to the American Association of Clinical Endocrinologists, up to 30 percent of men over the age of 75 have below-normal testosterone levels. Whether treatment is necessary remains controversial. An abnormality in the pituitary gland can alter the release of hormones from the pituitary gland to the testicles and interfere with normal testosterone production. A pituitary tumor or another type of brain tumor near the pituitary gland can lead to a lack of testosterone or other hormones. In addition, brain tumor treatments such as surgery or radiation therapy can impair pituitary function and cause hypogonadism [50-53].

Some inflammatory diseases such as sarcoidosis, histiocytosis, and tuberculosis affect the hypothalamus and pituitary gland and can impair testosterone production and cause hypogonadism. The HIV/AIDS virus can cause low testosterone levels by affecting the hypothalamus, pituitary gland, and testicles. The use of some medications, such as B. opioid pain relievers and some hormones, can impair testosterone production.

Significant obesity at any age can be associated with hypogonadism. Stress-Induced Hypogonadism Stress, excessive physical activity, and weight loss are associated with hypogonadism. Some attribute it to stress-induced hypercortisolism, which is believed to suppress hypothalamic function.

Throughout a man's life, testosterone plays an important role in sexual, cognitive, and physical development. During fetal development, testosterone helps determine sex. The most noticeable effects of elevated testosterone levels occur in the prepubertal period. At this time, body odor appears, the oiliness of the skin and hair increases, acne appears, accelerated growth occurs, early pubic, facial and armpit hair grows. Signs of puberty in men include enlarged sebaceous glands, enlarged penis, increased libido, more frequent erections, increased muscle mass, enlarged penis voice, increased height, bone maturation, hair loss on the head, and growth of the face, chest, legs, armpits and hair. Even in adulthood, the effects of testosterone are manifested in the form of libido, penile erection, aggression, mental and physical energy [54-58].

The cerebral cortex, the layer of the brain often referred to as gray matter, is the most developed part of the human brain. This part of the brain, which makes up about two-thirds of the mass of the brain, is responsible for processing information in the brain. Testosterone production starts in this part of the brain. The cerebral cortex signals the hypothalamus to stimulate testosterone production. To do this, the hypothalamus pulses to release gonadotropin-releasing hormone, which stimulates the pituitary gland, the part of the brain responsible for hormones involved in regulating growth, thyroid function, blood pressure, and other important bodily functions. When the pituitary gland is stimulated by gonadotropin-releasing hormone, it releases follicle-stimulating hormone and luteinizing hormone. Once released into the bloodstream, luteinizing hormone triggers the activity of Leydig cells in the testicles. In Leydig cells, cholesterol is converted to testosterone. When testosterone levels are adequate, the pituitary gland slows down the release of luteinizing hormone through a negative feedback mechanism, thereby slowing testosterone production. With such a complex process, there are many potential problems that can lead to low testosterone levels. Any changes in the testicles, hypothalamus, or pituitary gland can lead to hypogonadism. Such changes may be congenital or acquired, temporary or permanent [59-61].

Hypogonadism is characterized by a serum testosterone level of <300 ng/dl in association with at least one clinical sign or symptom. Signs of hypogonadism include absence or regression of secondary sex characteristics, anemia, muscle atrophy, decreased bone mass or bone mineral density, oligospermia, and abdominal obesity. Symptoms of post-pubertal hypogonadism include sexual

dysfunction (erectile dysfunction, decreased libido, decreased penile sensation, difficulty reaching orgasm, and decreased ejaculate), decreased energy and stamina, depressed mood, increased irritability, difficulty concentrating, changes in cholesterol levels, anemia, osteoporosis and tides. If prepubertal men are left untreated, the signs and symptoms are sparse body hair and delayed closure of the epiphyses.

Early diagnosis and treatment can reduce the risks associated with hypogonadism. Early detection in boys can help prevent problems related to delayed puberty. Early diagnosis in men helps protect against the development of osteoporosis and other diseases. The diagnosis of hypogonadism is based on symptoms and blood tests, particularly testosterone levels. Often the first step in diagnosis is the Androgen Deficiency Test in Aging Men (ADAM), a 10-item questionnaire designed to identify men with signs of low testosterone levels. Testosterone levels fluctuate throughout the day and are usually highest in the morning, so a blood test is usually done early in the morning. If low testosterone is confirmed, additional tests are done to determine if the cause is testicular, hypothalamic, or pituitary. These tests may include hormone testing, semen analysis, pituitary gland imaging, testicular biopsy, and genetic testing. After starting treatment, the patient can continue to measure testosterone levels to determine if the drug is helping to produce adequate levels of testosterone.

Testosterone is often referred to as the male hormone, in part because men have about ten times the concentration of testosterone than women, although women are actually more sensitive to testosterone. The gonads and adrenal cortex are the main sources of testosterone in most vertebrate species of both sexes. Peripheral testosterone can cross the blood-brain barrier and have a variety of effects on the brain. Additionally, small amounts of steroids, including testosterone, are synthesized de novo from cholesterol or steroid precursors in the brain and are termed neuro steroids and discussed in more detail below [62-65].

Cholesterol is the precursor to all steroid hormones, including testosterone. The rate-limiting step in steroid synthesis is the transport of cholesterol from the cytoplasm to the inner mitochondrial membrane where steroidogenic enzymes reside. A protein complex called trans nucleosomes forms on the mitochondrial outer membrane of the cells of the gonads and adrenal glands. The trans nucleosome includes the steroidogenic acute regulatory protein (StAR) as well as protein kinase A (PKA) and several other mitochondrial and cytosolic proteins. The process is initiated by the binding of luteinizing hormone (LH) or human chorionic gonadotropin (hCG; hCG in humans) to their G protein-coupled receptors, leading to the activation of cAMP PKA, which in turn phosphorylates and thereby activates StAR. StAR crosses the outer mitochondrial membrane, carries cholesterol at its hollow, hydrophobic C-terminus, and attaches to the inner mitochondrial membrane, where the enzyme desmolase, which cleaves the cholesterol side chain, resides.

Shown are a series of reactions starting with the cleavage of the side chain of carbon atoms by the enzyme desmolase to form pregnenolone, the obligate C21 steroid, and a prohormone for all other steroids. Pregnenolone can then be further processed either in the mitochondria or in the endoplasmic reticulum. Further, 17α-hydroxylase converts pregnenolone to 17α-hydroxypregnenolone, and in the adrenal cortex, 17,20-lyase catalyzes the conversion to dehydroepiandrosterone (DHEA), which circulates throughout the body, mainly in the more stable sulfated form (DHEA-S). However, small amounts of DHEA are also produced in the testicles and ovaries. DHEA is also synthesized in the brain as a "neurosteroid". From DHEA, 3β-hydroxysteroid dehydrogenase (3β-HSD) produces androstenedione, which is then converted to testosterone by 17β-hydroxysteroid dehydrogenase (17β-HSD). Testosterone has a number of biosynthetic pathways and

various metabolic pathways that determine its precise molecular mechanism of action. For example, the cytochrome P450 enzyme 5α-reductase can then reduce testosterone to the more potent androgen, dihydrotestosterone (DHT), which is converted by aldoketo-reductase (AKR1C2) to 5α-androstan-3α,17β-diol (abbreviated 3α). -diol) or with AKR1C1 to 5α-androstane-3β,17β-diol (3β-diol). 3α-diol binds to the androgen receptor with relatively low affinity, but acts as a neurosteroid GABA receptor agonist. Neurosteroids, including androstenediol, can act as allosteric modulators, increasing either the duration or frequency of opening of chloride channels in GABA receptors. Neuroactive steroids can cause these effects by binding to specific sites on the GABA receptor. 3β-diol exerts most of its effects through the estrogen receptor β (ERβ). Conversely, the P450 aromatase enzyme can aromatize testosterone to estradiol. Given the many pathways and diverse effects of testosterone and its metabolites, it is important to determine which biochemical factors, associated steroid receptors, and molecular pathways mediate the anxiolytic and antidepressant effects of testosterone.

Cardiovascular disease (CVD) remains the leading cause of death in the world today. There is a striking gender difference in cardiovascular disease, with men predisposed to earlier onset and more severe disease. Following a recent reassessment and ongoing debate regarding the estrogen protection hypothesis, and given the increasing use and abuse of androgens in our society, the alternative view that androgens may contribute to cardiovascular disease in men is gaining in importance. Whether androgens adversely affect cardiovascular disease in men or women remains a controversial issue in both the cardiovascular and endocrinology communities. This review draws on basic scientific research, animal studies, and clinical studies to outline our current understanding of the effects of androgens on atherosclerosis, a major cardiovascular disease, and the future directions of research on androgens associated with atherosclerosis direction [66-68].

Testosterone replacement therapy is the primary treatment for hypogonadism. Ideally, treatment should provide physiological levels of testosterone, typically between 300 and 800 ng/dL.Transdermal testosterone patches are available in India under the brand name Androderm. Transdermal patches deliver constant testosterone levels for 24 hours. Application site reactions are responsible for most side effects associated with transdermal patches, with older men being particularly prone to skin irritation. Local reactions include itching, blistering of the plaster, erythema, blistering, induration and allergic contact dermatitis. About 10% of patients discontinue patch treatment due to skin reactions. In one study, 60% of subjects stopped using the patch between weeks four and eight due to skin irritation. Headache, depression, and gastrointestinal bleeding may also occur in a small percentage of patients. Some patients report that the patch peels off easily and is difficult to remove from the packaging without sufficient dexterity. Transdermal patches are more expensive than injections, but their advantage is ease of use and maintenance of normal daily testosterone levels. Some patients report that the patch makes noise and is therefore stigmatized by its presence.

Two topical testosterone gels are currently available in India, Androgel and Testim. Morning use allows you to keep testosterone levels in line with the normal circadian rhythm. Topical testosterone gels also provide a longer-lasting increase in serum testosterone compared to transdermal patches. Like the patches, testosterone administered in gel form does not undergo first-pass metabolism. Side effects associated with treatment include headache, flushing, insomnia, increased blood pressure, acne, emotional lability, and nervousness. Although reactions will occur at the application site, gels are approximately 10 times less likely to cause skin irritation than transdermal patches. Benefits associated with the topical gel include maintaining normal daily testosterone levels and a

documented increase in bone density. Possible problems with the gel relate to the transferability of the gel from person to person and the cost.

The molecular mechanism mediating cellular responses to androgens is complex and involves both genomic and non-genomic effects that are still far from being clearly understood. The genomic effects of androgens are mediated by a specific receptor, the androgen receptor (AR). In response to androgen binding to AR, it switches to a transcription factor that regulates the expression of the target gene. The non-genomic effects of androgens appear independently of AR. Instead, it has been proposed that membrane-bound receptors trigger the rapid effects of androgens that result in second messenger signaling. This, in turn, triggers various cellular responses. These non-genomic pathways underlie the rapid vasodilation of the coronary arteries by testosterone [69-70].

Hypogonadism affects men of all ages, whether congenital or acquired. Patients with clinical symptoms associated with low testosterone levels should receive treatment to prevent sexual, cognitive, and physical changes. There are a variety of treatment options available that use a variety of dosage forms, allowing patients to choose the one that best suits their needs. Therefore, there is a clear need to educate the entire medical profession about hypogonadism, especially family doctors, who are often the first point of contact for the patient. In conclusion, clinicians should be aware of hypogonadism as a common clinical condition. Important triggers for clinicians to consider testing for hypogonadism include decreased libido, fatigue, osteoporosis and fractures, and erectile dysfunction.

Testosterone buccal tablets sold as a strain release testosterone in a pulsatile manner, similar to endogenous secretion. With this method, peak testosterone levels are reached quickly and steady state is achieved by the second dose after twice daily dosing. As with gels and transdermal products, buccal administration avoids first-pass metabolism. Food and drink do not affect the absorption of the drug. Although well tolerated, temporary gum irritation and bitter taste are the main side effects associated with this route. Irritated gums usually go away within the first week. Other side effects include dry mouth, toothache and stomatitis. Some patients find the oral tablet uncomfortable and worry that the tablet will move in the mouth when speaking.

Testosterone exerts an important regulation of cardiovascular function through genomic and nongenomic pathways. It produces several changes in cardiomyocytes, the main actor of cardiomyopathies, which are characterized by pathological remodeling, eventually leading to heart failure. Testosterone is involved in contractility, in the energy metabolism of myocardial cells, apoptosis, and the remodeling process. In myocarditis, testosterone directly promotes the type of inflammation that leads to fibrosis, and influences viremia with virus localization. At the same time, testosterone exerts cardioprotective effects that have been observed in different studies. There is increasing evidence that low endogenous levels of testosterone have a negative impact in some cardiomyopathies and a protective impact in others. This review focuses on the interrelationships between testosterone and cardiomyopathies and heart failure.

Intramuscular preparations are also available and are marketed as Depo-Testosterone (Testosterone Cypionate) and Delatestril (Testosterone Enanthate). Testosterone is suspended in oil to prolong absorption. Peak values are reached within 72 hours of administration, but intramuscular administration is associated with the most variable pharmacokinetics of all dosage forms. Superphysiological levels of testosterone are achieved during the first few days after administration and then subphysiological levels towards the end of the dosing interval. These changes are often associated with dramatic changes in mood, energy, and sexual function and are of concern to many patients. To reduce variability, lower doses and shorter dosing intervals (two weeks) are often used.

Injection site reactions are also common, but are rarely the reason for stopping treatment. Despite the fluctuations in testosterone levels, intramuscular injections offer an economical option and the convenience of dosing at two-to-four-week intervals. Disadvantages associated with injections include doctor visits, dosing visits, and lack of physiological models of testosterone.

The historical notion that elevated testosterone levels are responsible for the growth of prostate cancer was based on research. Current data indicate that high levels of endogenous androgens do not increase the risk of being diagnosed with prostate cancer. Similarly, testosterone therapy in testosterone-deficient men does not appear to increase the risk of prostate cancer or the likelihood of more aggressive disease at the time of diagnosis of prostate cancer. Androgen receptor saturation seems to explain this phenomenon. Men treated with testosterone therapy after treatment for localized prostate cancer did not experience higher relapse rates or worse outcomes; although research to date is limited. Early reports of testosterone-treated men did not show any progression adverse events under active surveillance/waiting.

Proven side effects of anabolic androgenic steroids include gonadal axis suppression and infertility, hirsutism and defeminization in women, and erythrocytosis. Alkylated anabolic androgenic steroids taken orally can cause liver disease. There is an association between the use of high-dose anabolic androgenic steroids and an increased risk of cardiovascular disease. Signs of anabolic androgenic steroid use are very low serum concentrations of high-density cholesterol and sex hormone-binding globulin and unexplained erythrocytosis. For high performance athletes, the biological passport (monitoring of blood or urine concentrations of androgens and androgen precursors after determining the athlete's baseline) is useful in demonstrating anabolic androgenic steroid use. For non-elite athletes, the best way to confirm anabolic androgenic steroid use is to do some research without judgement. Discontinuation of chronic anabolic androgenic steroid use is associated with anxious and depressive withdrawal syndrome.

Consistent effects on muscle mass in intervention studies, combined with associations observed in observational studies and increasingly well-characterized mechanistic pathways, suggest that testosterone is an important stimulator of muscle mass gain in older men. Thus, a decline in testosterone levels may contribute to the development of weakness, although declining strength with age involves many other mechanisms. As a result, the functional effects of testosterone are less clear. Much of the current research has been done with older, high-functioning men; more observational studies are needed as well as intervention trials in smaller populations. Current confusion regarding the putative syndromes of sarcopenia and weakness represents a limitation to the study design. A consensus on the most significant signs of physical deterioration will help determine etiology and plan future research. Focusing on specific areas, such as reduced mobility, may be preferable to current syndromic definitions. More sophisticated analysis of parallel changes in hormone levels, body composition, and functional outcomes over time will help unravel the direction of these relationships and thus the true role of androgens in functional decline. The development of SARMs could limit the side effects of testosterone, provide a more potent functional advance, and extend the use of androgen therapy to a wider population. A better understanding of the molecular mechanisms underlying the anabolic effects of androgens will facilitate the development of new non-steroidal drugs. The use of these agents in combination with well-designed training protocols represents an exciting new direction in this field [71-72].

Androgens have been shown to stimulate and suppress pro-atherogenic and pro-inflammatory effects on all cell types involved in atherogenesis. Based on current data, it would appear that the effects of androgens are dependent on cell type, dose, androgen type, and exposure time. For example, T

suppresses expression of vascular cell adhesion molecule-1 (VCAM-1) in human endothelial cells by an aromatase/estrogen receptor-dependent mechanism; however, DHT, a non-aromatizable androgen, induces VCAM-1 expression in human endothelial cells. Similarly, T has been shown to enhance reverse cholesterol transport, while DHT promotes the accumulation of cholesterol esters in monocyte-derived macrophages. Additionally, testosterone has been shown to inhibit nitric oxide release from monocytes through inhibition of inducible nitric oxide synthase. This decrease in NO potentially increases the risk of thrombosis due to increased platelet aggregation. In addition, testosterone has adverse effects by stimulating the proliferation of rat vascular smooth muscle cells, inducing the synthesis of proteoglycans and the elongation of glycosaminoglycan (GAG) chains on these proteoglycans, and testosterone increases apoptotic damage to cells vascular smooth muscle. Importantly, some of the effects on endothelial cells and MDM were sex-specific, occurred in cells derived from males but not females, and were associated with increased expression of AR in the cells of origin. male. This suggests that the stages of atherogenesis may differ significantly between sexes, mediated by androgen exposure and AR expression levels [36,42,64,68]

Therefore, testosterone and DHT may have effects that may lead to the development of atherosclerosis associated with human-dependent AR expression. However, testosterone may also exert an anti-atherogenic effect related to aromatization. Obviously, we need more work to understand how androgens work at the cellular level. One of the main questions that has arisen recently is whether flavoring is an important defense mechanism. There is a real need today to study and understand the metabolic activation pathways of testosterone in cell types associated with atherosclerosis, and to determine whether manipulation of these pathways can switch between atheroprotective and atherogenic effects. of testosterone.

Conclusion

So cardiovascular disease (CVD) remains the leading cause of death in the world today. There is a striking gender difference in cardiovascular disease, with men predisposed to earlier onset and more severe disease. Following a recent reassessment and ongoing debate regarding the estrogen protection hypothesis, and given the increasing use and abuse of androgens in our society, the alternative view that androgens may contribute to cardiovascular disease in men is gaining in importance. Whether androgens adversely affect cardiovascular disease in men or women remains a controversial issue in both the cardiovascular and endocrinology communities. This review draws on basic scientific research, animal studies, and clinical studies to outline our current understanding of the effects of androgens on atherosclerosis, a major cardiovascular disease, and the future directions of research on androgens associated with atherosclerosis direction. For men, exogenous testosterone treatment appears to be largely beneficial, at least in part due to the aromatization of testosterone to estradiol, especially when physiological testosterone levels are deficient. However, acetylsalicylic acid self-administration remains a significant cardiovascular safety issue, especially in light of reports of adverse effects on the lipid profile. While clinicians are considering using testosterone to treat age-related symptoms in men, data on the risk of cardiovascular disease with long-term testosterone use remains conflicting and poorly published. Current evidence suggests that, when treated with testosterone in aging women, androgen excess adversely affects risk factors for cardiovascular disease, especially in women with diabetes. Thus, knowledge of exogenous androgen treatment in men and women remains limited. Despite this, there is a growing use and abuse of androgens in our society, whether for therapeutic or recreational purposes. Whether androgens

adversely affect cardiovascular disease in men or women remains a controversial issue that urgently requires further research.

REFERENCES

1. AACE Hypogonadism Task Force. Medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients -2002 updated. Endocr Pract 2002;8:434-56.
2. Bhasin S, Cunningham GR, Hayes FJ. Testosterone therapy in adult men with androgen deficiency syndromes: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995- 2010.
3. Jordan JR. Allergy and topical irritation associated with transdermal testosterone administration: A comparison of scrotal and nonscrotal transdermal systems. Am J Contact Dermatol 1997;8:108-13.
4. Parker S, Armitage M. Experience with transdermal testosterone replacement therapy for hypogonadal men. Clin Endocrinol (Oxf) 1999;50:57-62.
5. Swerdloff RS, Wang C, Cunningham G. Long-term pharmacokinetics of transdermal testosterone gal in hypogonadal men. J Clin Endocrinol Metab 2000;85:4500-10.
6. Wang C, Swedloff RS, Iranmanesh A.Testosterone Gel Study Group. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypgonadal men. J Clin Endocrinol Metab 2000;85:2839-53.
7. Wang C, Swerdloff RS, Iranmanesh A. Effects of transdermal testosterone gel on bone turnover makers and bone mineral density in hypogonadal men. Clin Endocrinol (Oxf) 2001;54:739-50.
8. Arnold AP, Breedlove SM. Organizational and activational effects of sex steroids on brain and behavior: a reanalysis. Horm Behav. 1985;19:469–498.
9. Arnold AP, Gorski RA. Gonadal steroid induction of structural sex differences in the central nervous system. Annual review of neuroscience. 1984;7:413–442.
10. Auger CJ, Coss D, Auger AP, Forbes-Lorman RM. Epigenetic control of vasopressin expression is maintained by steroid hormones in the adult male rat brain. Proceedings of the National Academy of Sciences of the United States of America. 2011;108:4242–4247.
11. Aydogan U, Aydogdu A, Akbulut H, Sonmez A, Yuksel S, Basaran Y, Uzun O, Bolu E, Saglam K. Increased frequency of anxiety, depression, quality of life and sexual life in young hypogonadotropic hypogonadal males and impacts of testosterone replacement therapy on these conditions. Endocr J. 2012;59:1099–105.
12. Azcoitia I, Sierra A, Veiga S, Honda S, Harada N, Garcia-Segura LM. Brain aromatase is neuroprotective. Journal of neurobiology. 2001;47:318–329.
13. McGrath KC, McRobb LS, Heather AK. Androgen therapy and atherosclerotic cardiovascular disease. Vasc Health Risk Manag. 2008;4(1):11-21. PMID: 18629352; PMCID: PMC2464747.
14. Bale TL, Contarino A, Smith GW, Chan R, Gold LH, Sawchenko PE, Koob GF, Vale WW, Lee KF. Mice deficient for corticotropin-releasing hormone receptor-2 display anxiety-like behaviour and are hypersensitive to stress. Nat Genet. 2000;24:410–414.

15. Bao AM, Fischer DF, Wu YH, Hol EM, Balesar R, Unmehopa UA, Zhou JN, Swaab DF. A direct androgenic involvement in the expression of human corticotropin-releasing hormone. Mol Psychiatry. 2006;11:567–576.
16. Barden N. Implication of the hypothalamic-pituitary-adrenal axis in the physiopathology of depression. J Psychiatry Neurosci. 2004;29:185–193.
17. Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. The Journal of clinical endocrinology and metabolism. 1999;84:573–577.
18. Baulieu EE, Robel P. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) as neuroactive neurosteroids. Proc Natl Acad Sci U S A. 1998;95:4089–4091.
19. Baulieu EE, Robel P, Schumacher M. Neurosteroids: beginning of the story. Int Rev Neurobiol. 2001;46:1–32.
20. Becker C, Zeau B, Rivat C, Blugeot A, Hamon M, Benoliel JJ. Repeated social defeat-induced depression-like behavioral and biological alterations in rats: involvement of cholecystokinin. Mol Psychiatry. 2008;13:1079–1092.
21. Bekker MH, van Mens-Verhulst J. Anxiety disorders: sex differences in prevalence, degree, and background, but gender-neutral treatment. Gend Med. 2007;4(Suppl B):S178–193.
22. Benice TS, Raber J. Castration and training in a spatial task alter the number of immature neurons in the hippocampus of male mice. Brain research. 2010;1329:21–29.
23. Bennett NC, Gardiner RA, Hooper JD, Johnson DW, Gobe GC. Molecular cell biology of androgen receptor signalling. Int J Biochem Cell Biol. 2010;42:813–827.
24. Bingaman EW, Magnuson DJ, Gray TS, Handa RJ. Androgen inhibits the increases in hypothalamic corticotropin-releasing hormone (CRH) and CRH-immunoreactivity following gonadectomy. Neuroendocrinology. 1994;59:228–234.
25. McHenry J, Carrier N, Hull E, Kabbaj M. Sex differences in anxiety and depression: role of testosterone. Front Neuroendocrinol. 2014 Jan;35(1):42-57.
26. Wood RI, Stanton SJ. Testosterone and sport: current perspectives. Horm Behav. 2012 Jan;61(1):147-55.
27. Seney ML, Walsh C, Stolakis R, Sibille E. Neonatal testosterone partially organizes sex differences in stress-induced emotionality in mice. Neurobiology of disease. 2012;46:486–496.
28. Setalo G, Jr, Singh M, Nethrapalli IS, Toran-Allerand CD. Protein kinase C activity is necessary for estrogen-induced Erk phosphorylation in neocortical explants. Neurochem Res. 2005;30:779–790.
29. Shen CP, Tsimberg Y, Salvadore C, Meller E. Activation of Erk and JNK MAPK pathways by acute swim stress in rat brain regions. BMC Neurosci. 2004;5:36.
30. Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med. 2000;343:682–688.
31. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology. 2010;35:169–191.
32. Kaplan AL, Hu JC, Morgentaler A, Mulhall JP, Schulman CC, Montorsi F. Testosterone Therapy in Men With Prostate Cancer.

33. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, Bhasin S. Adverse events associated with testosterone administration. N Engl J Med. 2010 Jul 8;363(2):109-22.
34. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in en: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. 2007;82:29–39.
35. Fernández-Balsells MM, Murad MH, Lane M, et al. Clincal review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010;95:2560–2575.
36. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab. 2008;93:68–75.
37. Khaw K-T, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) prospective population study. Circulation. 2007;116:2694–2701.
38. Maggio M, Lauretani F, Ceda GP, et al. Relationship between low levels of anabolic hormones and 6-year mortality in older men: the Aging in the Chianti Area (InCHIANTI) study. Arch Intern Med. 2007;167:2249–2254.
39. Menke A, Guallar E, Rohrmann S, et al. Sex steroid hormone concentrations and risk of death in US men. Am J Epidemiol. 2010;171:583–592.
40. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2010;95:639–650.
41. Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH, Channer KS. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. Eur Heart J. 2006;27:57–64.
42. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study. J Am Coll Cardiol. 2009;54:919–927.
43. Kenny AM, Prestwood KM, Gruman CA, Fabregas G, Biskup B, Mansoor G. Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. 2002;57:M460–M465.
44. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. J Gerontol A Biol Sci Med Sci. 2003; 58:618–625.
45. Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab. 2009; 75:1092–1098.
46. Ferrando AA, Sheffield-Moore M, Yeckel CW, et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. Am J Physiol Endocrinol Metab. 2002;282:E601–E607.

47. Tan RS, Pu SJ. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. Aging Male. 2003; 6:13–17.
48. Brockenbrough AT, Dittrich MO, Page ST, Smith T, Stivelman JC, Bremner WJ. Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. Am J Kidney Dis. 2006; 47:251–262.
49. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA. 2006;296:2351–2361.
50. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95:2536–2559.
51. Johannsson G, Gibney J, Wolthers T, Leung KC, Ho KK. Independent and combined effects of testosterone and growth hormone on extracellular water in hypo-pituitary men. J Clin Endocrinol Metab. 2005; 90:3989–3994.
52. Quan A, Chakravarty S, Chen JK, et al. Androgens augment proximal tubule transport. Am J Physiol Renal Physiol. 2004;287: F452–F459.
53. Cieszynski, L.; Jendrzejewski, J.; Wisniewski, P.; Owczarzak, A.; Sworczak, K. Hair cortisol concentration in a population without hypothalamic-pituitary-adrenal axis disorders. Adv. Clin. Exp. Med. 2019, 28, 369–373.
54. Xiang, L.; Sunesara, I.; Rehm, K.E.; Marshall, G.D., Jr. Hair cortisol concentrations are associated with hair growth rate. Neuroimmunomodulation 2016, 23, 287–294.
55. Ehrmann, D.A.; Rosenfield, R.L.; Barnes, R.B.; Brigell, D.F.; Sheikh, Z. Detection of functional ovarian hyperandrogenism in women with androgen excess. N. Engl. J. Med. 2012, 327, 157–162.
56. Grymowicz M, Rudnicka E, Podfigurna A, Napierala P, Smolarczyk R, Smolarczyk K, Meczekalski B. Hormonal Effects on Hair Follicles. Int J Mol Sci. 2020 Jul 28;21(15):5342. doi: 10.3390/ijms21155342. PMID: 32731328; PMCID: PMC7432488.
57. Scarth M, Bjørnebekk A. Androgen abuse and the brain. Curr Opin Endocrinol Diabetes Obes. 2021 Dec 1;28(6):604-614. doi: 10.1097/MED.0000000000000675. PMID: 34709215; PMCID: PMC8631164.
58. Kloner RA, Carson C 3rd, Dobs A, Kopecky S, Mohler ER 3rd. Testosterone and Cardiovascular Disease. J Am Coll Cardiol. 2016 Feb 9;67(5):545-57. doi: 10.1016/j.jacc.2015.12.005. PMID: 26846952.
59. Anawalt BD. Diagnosis and Management of Anabolic Androgenic Steroid Use. J Clin Endocrinol Metab. 2019 Jul 1;104(7):2490-2500. doi: 10.1210/jc.2018-01882. PMID: 30753550; PMCID: PMC6517163.
60. O'Connell MD, Wu FC. Androgen effects on skeletal muscle: implications for the development and management of frailty. Asian J Androl. 2014 Mar-Apr;16(2):203-12. doi: 10.4103/1008-682X.122581. PMID: 24457838; PMCID: PMC3955329.
61. Mitnitski A, Rockwood K. Decrease in the relative heterogeneity of health with age: a cross–national comparison. Mech Ageing Dev. 2006;127:70–2.
62. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. J Am Geriatr Soc. 2005;53:2184–9.

63. Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. Mech Ageing Dev. 2006;127:494–6.
64. Abellan van Kan G, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. J Am Med Dir Assoc. 2008;9:71–2.
65. McGrath KC, McRobb LS, Heather AK. Androgen therapy and atherosclerotic cardiovascular disease. Vasc Health Risk Manag. 2008;4(1):11-21. PMID: 18629352; PMCID: PMC2464747.
66. Malkin CJ, Pugh PJ, West JN, et al. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. Eur Heart J. 2006;27:57–64.
67. Mukherjee TK, Dinh H, Chaudhuri G, et al. Testosterone attenuates expression of vascular cell adhesion molecule-1 by conversion to estradiol by aromatase in endothelial cells: implications in atherosclerosis. PNAS. 2002;99:4055–60.
68. Muller M, van den Beld AW, Bots ML, et al. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. Circulation. 2004;109:2074–9.
69. Nathan L, Shi W, Dinh H, et al. Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. Proc Natl Acad Sci USA. 2001;98:3589–93.
70. Ng M, Quinn CM, McCrohon JA, et al. Androgens up-regulate atherosclerosis-related genes in macrophages from males but not females: molecular insights into gender differences in atherosclerosis. J Am Coll Cardiol. 2003;42:1306–13.
71. Obasanjo IO, Clarkson TB, Weaver DS. Effects of the anabolic steroid nandrolone decanoate on plasma lipids and coronary arteries of female cynomolgus macaques. Metabolism. 1996;45:463–8. [PubMed] [Google Scholar]
72. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab. 2005;90:1502–10.

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

THE MANIFESTATION OF OVERALL MEDICATION OF CHRONIC PERIODONTITIS DISEASES BY USING OF PLASMA FLOW

Tamar Okropiridze[1], Nodar Sulashvili[2]
[1]MD, PhD, Doctor Medical Sciences, Professor of Teaching University Geomedy, Head of the Department of Dentistry, Tbilisi, Georgia.
[2]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Invited Professor/Lecturer of Tbilisi State Medical University, Tbilisi, Georgia.

ABSTRACT

The aim of the research was to study and analyze use of plasma flow in complex treatment of chronic periodontitis. We received 96 patients - 57 women and 39 men, aged 18 to 60 years - with a diagnosis of chronic apical periodontitis. 54 of them had chronic fibrous periodontitis, 42 had chronic granulating periodontitis. Both before treatment and after drug treatment of the canal and plasma therapy, we conducted a microbiological study of all patients. We took the material from the canals with disposable reams of paper. A total of 62 teeth were bacteriologically examined. We took the first sample before treatment, and the second one 48 hours after the start of treatment. We used a solid culture medium such as 5% blood agar in both sampling cases to isolate and identify cultures of microorganisms. The incubation time in a thermostat was 24 hours at 37°C, after which the colonies were selected. A smear was taken from a single colony, stained by Gram and examined under a microscope. With apical periodontitis, a mixed infection was detected, on average 4-6 types in one root canal. When using the anaerobic method, facultative and obligate anaerobic microorganisms were found in the endodont. We divided our patients into two groups: In group I, out of 54 patients with chronic fibrous periodontitis, group A (25 patients ~47%) and group B (29 patients ~53%) were distinguished. II. 2. In the group of 42 patients with chronic granulating periodontitis, subgroup C (20 patients, 47%) and subgroup D (22 patients, 53%) were identifiedSo, the application of microplazmatic scalpel – irradiator in complex treatment of chronicall periodontitis, where 96 patients undertook microplazmatic scalpel – irradiator in complex treatment. The therapy has shown positive results in chronic cases of periodontitis, which did not respond to the method of traditional treatment. We have used the microplazmatic scalpel– irradiator on the vestibular side of dental radix. Application of microplazmatic scalpel– irradiator is recommended for all the cases periodontitis except the granulomotosis form of chronicle periodontits. Evaluation of the clinical results of patients under our supervision showed us that in comparison with all other modern means of treatment, plasma irradiation has a great advantage. With its help, we significantly reduced the treatment time, while with the traditional method, tooth extraction was possible in three sessions in 33% of patients, with the inclusion of plasma therapy, we treated 25% of patients in three sessions; In two sessions - 22% of patients, in total - 47%, this figure is higher than the number of patients treated by the traditional method in the same time frame. Plasma therapy is economical and other expensive drugs are rarely used together with it; therefore, we consider it expedient to widely introduce this method into therapeutic dentistry. We did not use plasma flow treatment for chronic granulomatous periodontitis, since the stimulating effect of plasma flow can accelerate the proliferation of epithelial cells of the granuloma envelope and complicate the patient's condition. As a result of irradiation with a microplasma irradiator, part of the energy of electromagnetic radiation

of plasma of various wavelengths propagates from the surface layer of the skin to a depth of 10–12 cm. from the tools available so far in medicine, its effect on the human body is much more diverse and effective.

Keywords: Medication, chronic, periodontitis, diseases, using, plasma flow.

Introduction

The purpose of periodontitis treatment is to preserve, improve and care for natural teeth. Therapy includes manual, acoustic and/or ultrasonic instrumentation combined with supragingival plaque control. A systematic review of the literature investigated the effect of subgingival debridement in relation to bleeding on probing, pocket depth and probing tip height in patients with chronic periodontitis. Subgingival debridement has proven its worth be an effective treatment for reducing probing pocket depth and improving clinical attachment levels. The treatment leads to a reduction of pocket depth through recession and gingival reinforcement at the level of clinical affiliation. If the pocket depth is less than or equal to 5 mm, the treatment can be considered successful. On the success of the inactive surgical periodontal therapy. Patient-related factors such as disease severity and smoking status adversely affect periodontal treatment. Site-specific factors, e.g., B. Tooth type and endodontic treatment can also affect the outcome. Regarding the type of tooth, a distinction is made between single-rooted and multi-rooted teeth with possible furcation involvement, which makes successful treatment of molars difficult.

Impeccable treatment of periodontitis is one of the central problems of both dental practice and medicine in general. In chronic apical periodontitis, the luminous process is characterized mainly by proliferative phenomena (weakly expressed exudative and alteratory phenomena) and is often a symptom of acute periodontitis. It is poor in symptoms and does not cause pain unless aggravated. Clinically In apical periodontitis, the tooth is almost always discolored; in the presence of a carious defect in apical periodontitis, the pulp is always necrotic and gangrenous. Doesn't respond to percussion. In chronic periodontitis, changes are observed on the radiograph. Chronic periodontitis is characterized by an asymptomatic course as long as the immunological forces of the periodontium in the body are strong [1-2].

In chronic periodontitis, there is a thickening of the periodontal gap, which is accompanied by the development of connective tissue in fibrous periodontitis. With granulomatous periodontitis, connective tissue grows. Regeneration of cement and bone tissue. Along with the decomposition of soft and cool tissues [3-5]. The outcome of periodontitis depends on many factors, the virulence of microbes, the general condition of the body and treatment tactics. In the treatment of periodontitis, along with the traditional method, we for the first time included a completely new method in therapeutic dentistry - treatment with a microplasma scalpel [6-8].

The‘’plasmic scalpel’’ was modified for therapeutical proposes and was called ‘’plasma irradiator’’. Irradiation of injured tissue is performed from the distance of 7-12 cm from 3 nm. The treatment course consists of 3-10 seances, approximately. Plasma irradiation consists of the unity of whole specter of the sun and ozone. It has strong antimicrobial [bactericidal] effect. Plasma therapy speeds up the process of metabolism in the organism, improves microcirculation, stimulates processes of immunity and reparation regeneration [23-24]. One of the urgent problems of modern dentistry is the search for the most effective means and methods of bone grafting. These funds should optimize and at the same time stimulate the processes of reparative osteogenesis. Osteoplastic materials are used in the surgical treatment of dental diseases accompanied by bone tissue destruction: chronic periodontitis, periodontitis, jaw bone cysts [25-26].

Chronic periodontitis (CP) is characterized as a complex progressive chronic inflammatory process, which leads to the destruction of periodontal supportive tissue and a further loss of teeth. CP occurs when the magnitude effects of the pathogenic microbial load in the periodontal pocket are larger than that of the hosts immune response [9-10]. The basis of periodontal treatment is elimination or suppression of periodontal pathogens. The golden standard of which is mechanical debridement by scaling and root planing (SRP). However, large limitations of physical treatment have been observed due to the difficulty of accessing deep periodontal defects, which compromises the effectiveness of biofilm removal. The persistence of periodontal pathogens, such as Aggregatibacteractinomycetemcomitans and Porphyromonas gingivalis (P.g), were often found following SRP and can result in microbial re-colonization and the consequent destruction of periodontal tissue [11-12]. In regards to this issue, adjunctive systemic and localized antibiotics have been applied to compensate for the limitation of mechanical therapy. Despite the rapid development of a variety of adjunctive local periodontal treatments in recent years, such as metformin, antioxidants, photodynamic treatment and so on [13-14], chlorhexidine (CHX) remains one of the most effective local antimicrobial agents, and is widely used for the local treatment of periodontitis. Through the rapid attraction of the negatively charged bacterial cell surface to the cationic CHX molecule, CHX shows strong antibacterial activity in the periodontal pocket, along with a lack of toxicity, incompliance from patients and an emergence of resistance microorganisms. However, the high clearance of CHX from the periodontal pocket leads to subtherapeutic CHX concentrations in the local environment after only a short time of subgingival CHX application, which results in an insufficient treatment effectiveness. Given this limitation, CHX Gel with CHX concentration up to 15 times than liquid carriers were developed for periodontal treatment. In recent years, numerous of studies have reported the effectiveness of adjunctive CHX to nonsurgical periodontal treatment (NSPT). However, contrary results were presented [15–17], there is still no consensus on this issue. So far, only one systematic review without quantitative analysis indicated that the positive effect of local subgingival application of CHX Gel adjunctive to NSPT could be not justified as compared to NSPT alone [18-19]. Therefore, there is lack of strong evidence for support the beneficial effect of subgingival use CHX as adjunct to NSPT. Full-mouth disinfection (FMD) was proposed by Quirynen in 1995, with the aim of eradicating periodontal pathogens in a short time from all the oropharyngeal habitats (mucous membranes, tongue, tonsils and saliva) [20]. CHX gel as an adjunct was used in the FMD protocol, which was described as full-mouth scaling and root planing (FMSRP) in 1–2 sessions within 24 h combined with full-mouth subgingival irrigation with CHX gel, as well as a tongue brush and mouthwash by means of CHX. However, whether the use of antiseptics played a role in FMD is still unclear [21-22].

The aim of the research was to study and analyze medication of chronic periodontitis diseases by using of plasma flow.

Materials and methods

We received 96 patients - 57 women and 39 men, aged 18 to 60 years - with a diagnosis of chronic apical periodontitis. 54 of them had chronic fibrous periodontitis, 42 had chronic granulating periodontitis. Both before treatment and after drug treatment of the canal and plasma therapy, we conducted a microbiological study of all patients. We took the material from the canals with disposable reams of paper. A total of 62 teeth were bacteriologically examined. We took the first sample before treatment, and the second one 48 hours after the start of treatment. We used a solid

culture medium such as 5% blood agar in both sampling cases to isolate and identify cultures of microorganisms.
The incubation time in a thermostat was 24 hours at 37°C, after which the colonies were selected. A smear was taken from a single colony, stained by Gram and examined under a microscope. With apical periodontitis, a mixed infection was detected, on average 4-6 types in one root canal. When using the anaerobic method, facultative and obligate anaerobic microorganisms were found in the endodont. The latter is presented in the table:

Obligate Anaerobes	Facultative Anaerobes
Bacteroides Fusobacterium Wolinella Pertostreptococcus Eubacterium Bifidobacterium Propionibacterium Actinomyces	Streptococcus Lactobacillus Eikenella Capnocytophaga

The number of microorganisms isolated by paper straws in one root canal ranged from 102 to 107.

Results and discussion
We divided our patients into two groups:
In group I, out of 54 patients with chronic fibrous periodontitis, group A (25 patients ~47%) and group B (29 patients ~53%) were distinguished.
II. 2. In the group of 42 patients with chronic granulating periodontitis, subgroup C (20 patients, 47%) and subgroup D (22 patients, 53%) were identified.
a and b Patients in subgroup were treated with the conventional method, and each patient in subgroups b and d was treated with plasma flow along with the conventional method. The use of plasma flow leads to a significant stimulation of the body's immune system, has a pronounced antimicrobial (bactericidal) effect, anti-inflammatory, analgesic effect. The method leads to vasodilation, which in turn improves tissue trophism, enhances metabolism in the body, activates the synthesis of vitamins, and stimulates regeneration processes. The essence of the method lies in the so-called operation on a gas of a certain type of inert gas (in this case, argon). The use of such a therapeutic method, implemented with the help of a microplasmatron apparatus, which, due to broad-spectrum electromagnetic radiation accompanying the flow of low-temperature plasma created by the plasmatron, not only penetrates into the surface layers of the skin, but also deeply reaches the subcutaneous and deeper tissues and organs with a therapeutic effect. The length of the illuminated part of the plasma flow is on average one centimeter. From the side of the plasma flow, at a distance of two to three mm, the temperature does not exceed 30 degrees. At the same time, the plasma flow ahead quickly cools down, where only heat is felt at a distance of 7-12 cm. Plasma radiation includes the entire spectrum of solar radiation and a combination of ozone. It is important during treatment to pay attention to the selection of the optimal number of sessions and exposure time.
At the first stage, we prepared a carious cavity, treated it with medication, and expanded the orifices of the canals. At the entrance to the canal, a 1% solution of iodinol was injected to disinfect the necrotic pulp, then the contents of the canal were gradually removed with a pulp extractor. First, we

treated the canal with iodinol turundas, then with proteolytic enzymes, using trypsin, lysozyme, etc. Turunda, impregnated with a 0.1% solution of lysozyme, was left in the canal for two to three days under a temporary bandage. It was on these three days that we turned on the treatment base with the plasma flow. The number of sessions varied from two to five exposures of three minutes each for the entire surgical field. We used radiation to project the diseased tooth onto the skin of the face. The distance between the irradiator and the skin of the face was limited by the influence of the sensation of heat by the patient. The number of sessions varied depending on the severity of the disease. During the next treatment of the patient, after repeated drug treatment of the canals, we closed the top with Eugendent plastic reinforcing material. We checked the quality of the work performed with the help of X-rays, and we had cases when the tooth did not lend itself to the sealing of the closure. This problem has been brilliantly solved with the help of plasma flow.

So, the application of microplazmatic scalpel – irradiator in complex treatment of chronicall periodontitis, where 96 patients undertook microplazmatic scalpel – irradiator in complex treatment. The therapy has shown positive results in chronic cases of periodontitis, which did not respond to the method of traditional treatment. We have used the microplazmatic scalpel– irradiator on the vestibular side of dental radix. Application of microplazmatic scalpel– irradiator is recommended for all the cases periodontitis except the granulomotosis form of chronicle periodontits.

In the treatment of patients of the first group, the following data were obtained: 25 patients of subgroup A were treated in three sessions; Of the patients of subgroup B, we fixed the teeth of 12 patients in three sessions, 17 patients in two sessions.

Of the patients of the second group, in subgroup C, 13 patients with 65% were treated in five sessions. 7 patients in 3 sessions -35%. In subgroup d, teeth were fixed in 5 sessions in 6 patients ~ 27.4%, in 3 sessions in 12 patients ~ 54.5%, in 2 sessions in 4 patients ~ 18%.

So, from patients of subgroups A and C, in 5 sessions we fixed teeth in 13 patients, in 3 sessions - in 32 patients.

Of the patients in subgroups b and d, teeth were fixed in 6 patients in five sessions, in 24 patients in three sessions, in 21 patients in two sessions.

Evaluation of the clinical results of patients under our supervision showed us that in comparison with all other modern means of treatment, plasma irradiation has a great advantage. With its help, we significantly reduced the treatment time, while with the traditional method, tooth extraction was possible in three sessions in 33% of patients, with the inclusion of plasma therapy, we treated 25% of patients in three sessions; In two sessions - 22% of patients, in total - 47%, this figure is higher than the number of patients treated by the traditional method in the same time frame. Plasma therapy is economical and other expensive drugs are rarely used together with it; therefore, we consider it expedient to widely introduce this method into therapeutic dentistry.

We did not use plasma flow treatment for chronic granulomatous periodontitis, since the stimulating effect of plasma flow can accelerate the proliferation of epithelial cells of the granuloma envelope and complicate the patient's condition. As a result of irradiation with a microplasma irradiator, part of the energy of electromagnetic radiation of plasma of various wavelengths propagates from the surface layer of the skin to a depth of 10–12 cm. from the tools available so far in medicine, its effect on the human body is much more diverse and effective.

Conclusion

For successful medical treatment of chronic periodontitis, it is necessary that the root canals reach the apex. In this case, complete obturation of the canals and their disinfection as foci contributing to

the inflammatory process will be achieved. This can be done during endodontic and medical root canal treatment. Since there is no pain in chronic apical periodontitis, we treat the tooth painlessly. Evaluation of the clinical results of patients under our supervision showed us that in comparison with all other modern means of treatment, plasma irradiation has a great advantage. With its help, we significantly reduced the treatment time, while with the traditional method, tooth extraction was possible in three sessions in 33% of patients, with the inclusion of plasma therapy, we treated 25% of patients in three sessions; In two sessions - 22% of patients, in total - 47%, this figure is higher than the number of patients treated by the traditional method in the same time frame. Plasma therapy is economical and other expensive drugs are rarely used together with it; therefore, we consider it expedient to widely introduce this method into therapeutic dentistry.

LITERATURE

1. Chauhan AS, Bains VK, Gupta V, Singh GP, Patil SS. Comparative analysis of hyaluronan gel and xanthan-based chlorhexidine gel, as adjunct to scaling and root planing with scaling and root planing alone in the treatment of chronic periodontitis: a preliminary study. Contemp Clin Dent. 2013;4:54–61.
2. Matesanz P, Herrera D, Echeverría A, O 'Connor A, Gon-zález I, Sanz M. A randomized clinical trial on the clinical and microbiological efficacy of a xanthan gel with chlor-hexidine for subgingival use. Clin Oral Invest. 2013;17:55–66.
3. Verma A, Sanghi S, Grover D, Aggarwal S, Gupta R, Pandit N. Effect of insertion of xanthan-based chlorhexidine gel in the maintenance phase following the treatment of chronic periodontitis. J Indian Soc Periodontol. 2012;16:381–5.
4. Kranti K, Seshan H, Sameer Z. Clinical evaluation of topical subgingival application of biodegradable xanthan based 1.5% chlorhexidine gel for treatment on periodontal pockets. J Adv Dent Res. 2010;1:47–54.
5. O. Nemsadze, G. Asatiani, S. Jayani, Georgian patent for the invention: "Treatment of purulent-necrotic inflammatory processes with plasma radiation". Priority 21.01.97.
6. Dahlen G., Bergenholtz., Endocrine activity in teeth and pulp, J.Dent.Ges., 1999.
7. Sheltzer Sh., endodontologist, biological considerations in endodontic procedures, Mts. Greece, New York, 1999.
8. Haapasalo M., Bacteroides species in dental root canal infection, Endod. Dent. Traumatol., 1990, No. 5, 1-10.
9. Paolantonio M, D'Ercole S, Pilloni A, D'Archivio D, Lisanti L, Graziani F, et al. Clinical, microbiologic, and biochemical effects of subgingival administration of a xanthan-based chlorhexidine gel in the treatment of periodontitis: a randomized multicenter trial. J Periodontol. 2009;80:1479–92.
10. Gupta R, Pandit N, Aggarwal S, Verma A. Comparative evaluation of subgingivally delivered 10% doxycycline hyclate and xanthan-based chlorhexidine gels in the treatment of chronic periodontitis. J Contemp Dent Pract. 2008;9:25–32.
11. Oosterwaal PJ, Mikx FH, van 't Hof MA, Renggli HH. Short-term bactericidal activity of chlorhexidine gel, stannous fluoride gel and amine fluoride gel tested in periodontal pockets. J Clin Periodontol. 2011;18:97–100.

12. Perinetti G, Paolantonio M, Cordella C, D 'Ercole S, Serra E, Piccolomini R. Clinical and microbiological effects of subgingival administration of two active gels on persistent pockets of chronic periodontitis patients. J Clin Periodontol. 2004;31:273–81.
13. Goodson J. Pharmacokinetic principles controlling efficacy of oral therapy. J Dent Res. 2010;68:1625 –32.
14. Wade WG, Addy M. In vitro activity of a chlorhexidine containing mouthwash against subgingival bacteria. J Periodontol. 2009;60:521–5.
15. Rabe LK, Hillier SL. Effect of chlorhexidine on genital microflora, Neisseria gonorrhoeae, and Trichomonas vaginalis in vitro. Sex Transm Dis. 2000;27:74–8.
16. Slots J. Selection of antimicrobial agents in periodontal therapy. J Periodontal Res. 2002;37:389–98.
17. Manthena S, Ramesh A, Srikanth A, Ramoji Rao MV, Preethi PL, Samatha YP.
18. Comparative evaluation of subgingivally delivered chlorhexidine varnish and chlorhexidine gel in reducing microbial count after mechanical periodontal therapy. J Basic Clin Pharm. 2014;6:24–8.
19. Boia S, Stratul Ş-I, Boariu M, Ursoniu S, Goţia SL, Boia ER, et al. Evaluation of
20. antioxidant capacity and clinical assessment of patients with chronic periodontitis treated with non-surgical periodontal therapy and adjunctive systemic antibiotherapy. Romanian J Morphol Embryol. 2018;59:1107–13.
21. Almeida ML, Duarte PM, Figueira EA, et al. Effects of a full-mouth disinfection protocol on the treatment of type-2 diabetic and non-diabetic subjects with mild-to-moderate periodontitis: one-year clinical outcomes. Clin Oral Investig. 2019. https://doi.org/10.1007/s00784-019-02927-8
22. Pockpa AD, Soueidan A, Louis P, Coulibaly NT, Badran Z, Struillou X. Twenty Years of Full-Mouth Disinfection: The Past, the Present and the Future. Open Dent J. 2018;12:435–42.
23. Santuchi CC, Cortelli JR, Cortelli SC, Cota LO, Fonseca DC, Alencar CO, et al.
24. Scaling and root Planing per quadrant versus one-stage full-mouth disinfection: assessment of the impact of chronic periodontitis treatment on quality of life—a clinical randomized, controlled trial. J Periodontol. 2016;87:114–23.
25. Quirynen M, Mongardini C, De Soete M, Pauwels M, Coucke W, van Eldere J,et al. The role of chlorhexidine in the one-stage full-mouth disinfection treatment of patients with advanced adult periodontitis. Long-term clinical and microbiological observations. J Clin Periodontol. 2000;27:578–89.
26. Matesanz-Pérez P, García-Gargallo M, Figuero E, Bascones-Martínez A, Sanz M, Herrera D. A systematic review on the effects of local antimicrobials as adjuncts to subgingival debridement, compared with subgingival debridement alone, in the treatment of chronic periodontitis. J Clin Periodontol. 2013;40:227
27. Webdocument. RECORD-statement; http://www.record-state ment.org/. Accessed September 25, 2018.
28. Van der Velden U. Purpose and problems of periodontal disease classification. Periodontol. 2000;2005(39):13-21.
29. Van der Velden U. Diagnosis of periodontitis. J Clin Periodontol. 2000;27:960-961.

30. Joyston-Bechal S, Smales FC, Duckworth R. Effect of metronida-zole on chronic periodontal disease in subjects using a topically applied chlorhexidine gel. J Clin Periodontol. 1984;11(1):53-62.
31. Chapple I, Mealey BL, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: consensus report of workgroup 1 of the 2017 World Workshop on the classification of periodontal and peri-implant diseases and conditions. J Clin Periodontol. 2018;45(Suppl 20):S68-S77.
32. Baelum V, Lopéz R. Defining and predicting outcomes of non-surgical periodontal treatment: a 1-yr follow-up study. Eur J Oral Sci. 2016;124:33-44.
33. Kolakovic M, Held U, Schmidlin PR, Sahrmann P. An estimate of pocket closure and avoided needs of surgery after scaling and root planing with systemic antibiotics: a systematic review. BMC Oral Health. 2014;14:159.
34. Preus HR, Gunleiksrud TM, Sandvik L, Gjermo P, Baelum V. A randomized, double-masked clinical trial comparing four periodontitis treatment strategies: 1-year clinical results. J Periodontol. 2013;84:1075-1086.
35. Sanz M, Bäumer A, Buduneli N, et al. Effect of professional mechanical plaque removal on secondary prevention of prevention of periodontitis and the complications of gingival and periodontal preventive measures: consensus report of group 4 ofthe 11th European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases. J Clin Periodontol. 2015;42:214-220.
36. Mestnik MJ, Feres M, Figueiredo LC, et al. The effects of adjunctive metronidazole plus amoxicillin in the treatment of generalized aggressive periodontitis: a 1-year double-blinded, placebo-controlled, randomized clinical trial. J Clin Periodontol. 2012;39:955-961.
37. Teughels W, Durukan A, Ozcelik O, Pauwels M, Quirynen M, Haytac MC. Clinical and microbiological effects of Lactobacillus reuteri probiotics in the treatment of chronic periodontitis: a randomized placebo-controlled study. J Clin Periodontol. 2013;40:1025-1035.

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

THE PERSPECTIVES OF ARTIFICIAL INTELLECT IN SERVICE OF PHARMACY, MEDICINE AND PUBLIC HEALTH

Nato Alavidze[1], Nodar Sulashvili[2]
[1]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia.
[2]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Invited Professor/Lecturer of Tbilisi State Medical University, Tbilisi, Georgia.
Email:

ABSTRACT

Aim of the research was to study and analyze the perspectives of artificial intellect in service of pharmacy, medicine and public health. Digital health is largely shaped by experts outside of the health sector and this provides an opportunity for interdisciplinary collaboration to develop the foundation of digital health education. Education in pharmacy and pharmaceutical sciences must be needs-based to meet the current and changing demands of digital health. These requirements should reflect the needs of all members in all sectors and career levels in pharmacy and pharmaceutical sciences, from clinical pharmacist to drug research. Digital medicine-The digital drug system currently contains four main components: an inert sensor embedded in an inert tablet, a non-medicated sensor (patch) worn by the patient, a mobile application and a web-based dashboard. Upon interaction with gastric fluids, the ingestible sensor is activated and connects to a wearable sensor that sends a signal to a mobile device where it can be viewed by patients or subsequently viewed by healthcare providers and caregivers using secure mobile-based and cloud-based applications. based software. It also has the ability to record other behavioral and physiological parameters, such as physical activity, heart rate, skin temperature, sleep and digital therapeutics. Aspiring pharmacists, pharmaceutical scientists and healthcare professionals. Students are most involved in the era of digital transformation. Their participation in digital health education processes is an important opportunity as they support the adoption and promotion of these digital health technologies. Several studies have been conducted to understand digital health skills, knowledge and competencies among pharmacy students. Since most of the research conducted is done in countries such as the US, UK and Australia, the global state of digital health in pharmacy schools is not fully understood. The vast amount of health data provides the opportunity to use more artificial intellect and machine learning in the practice of pharmacy to solve important issues related to medication management and use. Trend analysis in large data sets can reveal individual patient risk of adverse events, behavioral aspects, compliance profiles, etc. A pharmacist is a professional expert who can augment a data scientist's expertise to create services. Understanding the terminology and concepts used in artificial intellect will help pharmacists engage constructively with data scientists and collaborate with them to develop models that enhance patient care. Digital health systems can also empower and engage patients, making them co-designers of care. Shared decision-making between healthcare workers and patients requires trust, a sense of partnership and transparency in their interactions. Healthcare professionals become collaborators on the patient's journey to health, yet still provide empathy and a human touch to support patients' well-being.

Keywords: Perspectives, artificial intellect, service, pharmacy, medicine, public health.

Introduction

The term "telemedicine" was introduced in the 1960s and has expanded to include all forms of communication technology to provide health care and public education in rural and remote areas and educate students about telepharmacy. The International Federation of Pharmacists defines telemedicine as “the use of information and. Communication Technology (ICT) Delivery Telepharmacy is a relatively recent development in the health care industry that enables the provision of high quality pharmacy services in rural and remote areas. It has attracted a lot of attention during the COVID-19 pandemic. Digital health technologies save lives, improve health and well-being, expand access to health care, and help build effective health systems and healthy populations. With increasing health conditions and an aging population, digital health can be the key to meeting many unmet needs for health and related services [1-3].

Digital health is a key priority for mainstream policy and health organizations involved in implementing digital health and raising digital literacy standards. The World Economic Forum stressed that “few industries have the potential for such profound digital transformation as healthcare [4-5].

Recent technological advances have revolutionized clinical practice, from prevention to diagnosis, monitoring and treatment of disease, and have generated unprecedented public interest and engagement in self-care and health [6-7].

The COVID-19 pandemic has accelerated digital health. Industry has the potential to be transformed by digital technologies as profoundly as healthcare. Recent technological advances have revolutionized clinical practice, from prevention to diagnosis, monitoring and treatment of disease, and have generated unprecedented public interest and engagement in self-care and health. The COVID-19 pandemic has accelerated the transformation of digital healthcare, which will have a long-term impact on healthcare services. There are important lessons to be learned from this digital healthcare transformation [8-10].

Many digital health technologies rely heavily on understanding and proper use by healthcare professionals. There is a clear need for greater focus, concerted action and investment in education, training and skills development to ensure that healthcare professionals understand and use digital health to realize the expected benefits. Universities and education providers provide digital medical education, with most programs focusing on certificate delivery models. There is a lack of digital medical education and training, and an initiative focused on the national or professional level could be an incentive to integrate into education [11-12].

Pharmacy as a profession is historically associated with information technology. Hence, it has the ideal abilities and competencies to provide more digital healthcare services to patients. Realizing the full potential of digital health requires a confident, capable, agile and digitally savvy pharmaceutical workforce. Only with improved education and training will the pharmaceutical workforce be able to keep pace with the digital transformation of healthcare [13-14].

Digital health is largely shaped by experts outside of the health sector and this provides an opportunity for interdisciplinary collaboration to develop the foundation of digital health education. Education in pharmacy and pharmaceutical sciences must be needs-based to meet the current and changing demands of digital health. These requirements should reflect the needs of all members in all sectors and career levels in pharmacy and pharmaceutical sciences, from clinical pharmacist to drug research [15-16].

Aspiring pharmacists, pharmaceutical scientists and healthcare professionals. Students are most involved in the era of digital transformation. Their participation in digital health education

processes is an important opportunity as they support the adoption and promotion of these digital health technologies. Several studies have been conducted to understand digital health skills, knowledge and competencies among pharmacy students. Since most of the research conducted is done in countries such as the US, UK and Australia, the global state of digital health in pharmacy schools is not fully understood [17-18].

Aim of the research

Aim of the research was to study and analyze the perspectives of artificial intellect in service of pharmacy, medicine and public health.

Methodology

The main question of this article was to research and analyses the perspectives of artificial intellect in service of pharmacy, medicine and public health. We have searched and analyzed PubMed, Web of Sciences, Clinical key, Tomson Routers and Google Scholar mostly, using search terms bases, including the words to research and analyses the perspectives of artificial intellect in service of pharmacy, medicine and public health. Then, each article was discussed and an abstract of the total information gathered during the process was provided, aiming at easy understanding of the public. To establish these outcomes, over two hundred articles were investigated. We brought together all published data to comprehensively examine the effects in a systematic review, to define the roll out of the study of the research and analyses of the perspectives of artificial intellect in service of pharmacy, medicine and public health.

Results and discussion

A large number of pharmacy schools and departments do not offer digital medical education. Similarly, only a small proportion of the students and practitioners surveyed have received education or training in digital health as part of their continuing education. There is a misconception among students and faculty interviewed that digital medical education and online education are considered interchangeable terms. Digital health education still has a long way to go to create ready and flexible pharmaceutical education to meet the rapid changes in digital health. Integrating digital health into undergraduate pharmaceutical education is a critical strategy for improving digital health. “Much remains to be done to create ready and flexible pharmaceutical education to keep up with the rapid changes in digital healthcare. About half of the educators agreed that their students have the competencies to deliver digital health services, and their individual schools can easily identify and add new digital health skills to the curriculum as they emerge in practice. While this finding shows the potential for progress overall as it is likely to promote digital health awareness and lifelong learning. Pharmacists were more likely to receive digital medical education as part of continuing professional development if pharmacists had previously received digital medical education in school. The most common digital health education issues reported by schools and departments were lack of experience followed by lack of resources [19-20].

Practitioners' responses indicated that they were not familiar with new digital health technologies such as blockchain technology, bots, digital medicine and artificial intellect. A key gap in digital medical education is the skills and knowledge on how to use technology to solve existing clinical problems and improve care. Practitioner expectations of the clinical benefits of digital health in practice remained low. This may be because the introduction of digital health tools into clinical

care has been one of the least likely concepts to be included in pharmaceutical education, from the point of view of academics. Existing digital medical education appears to be more focused on providing administrative and functional competencies to facilitate business processes and improve operational efficiency [21-22].

Pharmacists, pharmaceutical schools, educators, students, and practitioners indicated the need to support national organizations, schools, workplaces, and student associations to provide guidance, training, infrastructure, and educational resources for digital health.

Training in the implementation of digital health tools was a key need cited by students and practitioners. The lack of enabling policies, the availability of digital health tools and data, and technical limitations were identified as the biggest challenges in implementing digital health in practice.

This report is the first of its kind global review of digital health in pharmaceutical education that examines the readiness and responsiveness of pharmaceutical education and identifies gaps in knowledge and skills among the pharmacy workforce. We believe this report will encourage further research and development in this area to expand digital healthcare with a pharmaceutical workforce [23-24].

Digital health is a key priority for mainstream policy and health organizations involved in implementing digital health and raising digital literacy standards. Recent technological advances have revolutionized clinical practice, from prevention to diagnosis, monitoring and treatment of disease, and have generated unprecedented public interest and engagement in self-care and health [25-26].

The COVID-19 pandemic has accelerated the transformation of digital healthcare, which will have a long-term impact on healthcare services. There are important lessons to be learned from this digital healthcare transformation. New digital health technologies must be people-centered, high quality, evidence-based, efficient, workable for providers and consumers alike, sustainable, inclusive, fair and reliable so that they can be integrated into practice [27].

Many digital health technologies rely heavily on their use and proper use by healthcare professionals. It has become necessary for healthcare professionals to equip themselves with digital health skills to deliver new and evolving models of healthcare services.

Pharmacy has historically used information technology. Hence, it has the ideal abilities and competencies to provide more digital healthcare services to patients.

According to the World Health Organization (WHO), digital health is “a field of knowledge and practice related to the development and use of digital technologies to improve health”. Technology and digital transformation are rapidly changing information ecosystems and the design of healthcare systems. The use of various digital technologies, such as artificial intellect and machine learning, offers great opportunities to improve health services, access to care, health workforce and health outcomes.

Although digital health has been around for a long time with technologies focused on e-health (electronic health records), the rapid growth of technology in the past few years has led to exciting new areas of digital health, including mobile health applications (mHealth) and wearable technologies. Telehealth and telemedicine, artificial intellect, advanced robotics and genomics. Digital health also includes other digital health uses such as the Internet of Things, advanced computing, and big data analytics. While they can provide significant benefits, there are also risks, especially in terms of health disparities, data privacy, and the limitations of artificial

intellect. Digital health is a broad term and its definition will change as new medical technologies emerge [28-29].

Although digital health has been around for a long time with technologies focused on e-health (electronic health records), the rapid growth of technology in the past few years has led to exciting new areas of digital health, including mobile health applications (mHealth) and wearable technologies. Telehealth and telemedicine, artificial intellect, advanced robotics and genomics. Digital health also includes other digital health uses such as the Internet of Things, advanced computing, and big data analytics. While they can provide significant benefits, there are also risks, especially in terms of health disparities, data privacy, and the limitations of artificial intellect. Digital health is a broad term and its definition will change as new medical technologies emerge [30-31].

An electronic health record (EHR) is a digital version of a patient's paper chart. EHRs are real-time, patientcare records that make information available instantly and securely to authorized users. While an EHR does contain the medical and treatment histories of patients, an EHR system is built to go beyond standard clinical data collected in a provider's office and can be inclusive of a broader view of a patient's care. EHRs can: contain a patient's medical history, diagnoses, medications, treatment plans, immunization dates, allergies, radiology images, and laboratory and test results; allow access to evidence-based tools that providers can use to make decisions about a patient's care.; and automate and streamline provider workflow [32-33].

An electronic health record (EHR) is a digital version of a patient's paper chart. EHRs are real-time, patient-centric records that make information available instantly and securely to authorized users. Although EHRs contain patients' medical and treatment histories, an EHR system is designed to go beyond the standard clinical data collected in a provider's office and can encompass a broader view of patient care.

An EHR can: contain a patient's medical history, diagnoses, medications, treatment plans, immunization dates, allergies, radiology images, and lab and test results; Allow access to evidence-based tools that providers can use to make decisions about patient care.; and automating and streamlining provider workflow [34-35].

One of the key features of an EHR is that health information can be created and managed by authorized providers in a digital format capable of being shared with other providers across more than one healthcare organization. EHRs are built to share information with other healthcare providers and organizations — such as laboratories, specialists, medical imaging facilities, pharmacies, emergency facilities, and school and workplace clinics — so they contain information from all clinicians involved in a patient's care [36-37].

One of the key features of HR is that health information can be created and managed by authorized providers in a digital format that can be shared with other providers across multiple healthcare organizations. EHRs are designed to share information with other health care providers and organizations such as laboratories, specialists, medical imaging facilities, pharmacies, emergency care facilities, and schools and workplace clinics, so they contain information from all physicians involved in caring for patient [38-39].

Pharmacists provide care to patients across the healthcare continuum and should be active participants in the EHR, seeking and documenting information. EHR use and implementation are driven by funding and policy changes, and pharmacists need to be part of the design and implementation teams. As health information technology proliferates and EHRs are designed and implemented in the healthcare setting, it is imperative that pharmacists' workflow and

information needs are met within EHRs to optimize medication therapy quality and patient outcomes. While pharmacists use many different advanced functions in the EHR, the literature describes three main uses: documentation, medication reconciliation, and patient evaluation and monitoring [40-41].

Pharmacists provide continuous medical care to patients and should be active participants in the electronic health record, information retrieval and documentation. The use and implementation of the EHR is driven by changes in funding and policy, and pharmacists should be part of the development and implementation teams. As healthcare information technology proliferates and eHealth records are developed and implemented in the healthcare environment, it is essential that the workflows and information needs of pharmacists are met in eHealth records to optimize the quality of drug therapy and patient outcomes. Although pharmacists use many different advanced features of electronic health records, three main areas of their application are described in the literature: documentation, drug reconciliation, and patient evaluation and monitoring [42-43].

E-Prescribing and e-dispensing- e-Prescribing is a prescriber's ability to electronically send an accurate, error-free and understandable prescription directly to a pharmacy from the point of care. It is an important element in improving the quality of patient care. e-Dispensing is defined as the act of electronically retrieving a prescription and giving out the medicine to the patient as indicated in the corresponding e-prescription. Once the medicine is dispensed, the dispenser reports via software information about the dispensed medicine(s). The benefits of both technologies include enhanced patient safety, reduced drug costs, increased access to patient prescription records, and improved pharmacy workflow [44-45].

Electronic prescribing and electronic dispensing- is the ability for a prescriber to electronically submit an accurate, error-free, and understandable prescription directly from the point-of-care pharmacy. This is an important element in improving the quality of patient care. Electronic dispensing is defined as receiving a prescription electronically and dispensing a drug to a patient as specified in the corresponding electronic prescription. Once a drug is dispensed, the dispenser provides the program with information about the dispensed drugs. The benefits of both technologies include improved patient safety, lower drug costs, increased access to patient prescription records, and improved pharmacy efficiency.

A blockchain is a continuously growing list of records, called blocks, that are linked and secured through the use of cryptography. A blockchain can serve as "an open, distributed ledger" or "shared record book" that can record transactions between multiple parties efficiently and in a verifiable and permanent way. Once blockchain enters the pharmaceutical environment, a number of pharmacists' activities may be further automated, such as patient record management, patient information distribution, and reimbursement management [46-47].

A blockchain is an ever-growing list of records, called blocks, that are linked and secured using cryptography. A blockchain can be an "open, distributed ledger" or a "shared ledger" that can record transactions between multiple parties in an efficient, verifiable, and permanent manner. As blockchain enters the pharmaceutical landscape, a number of activities for pharmacists can be further automated, such as patient record management, patient information dissemination, and reimbursement management.

An online pharmacy is an online merchant that sells medicines and can function as an independent internet site, "AGUs", which are partnerships between pharmacies. From a consumer perspective, online pharmacies seem to offer a lot of potential value, though not necessarily on price. For patients who are at home, the possibility of ordering and delivering medicines from

home is obvious. For those who live in remote areas and for consumers who are short on time and have difficulty getting to the pharmacy, ordering online has clear advantages. There are also those who seek personal products and prefer anonymity [48-49].

Wearable medical device refers to technology that can be correctly placed by the user on the body and can track important aspects of health in accordance with the current standard. These devices can collect data by non-invasively monitoring physiological parameters, or sense substrates from areas of the body in a minimally invasive way. These technologies could open the way to empowering pharmacists to monitor drugs to improve clinical outcomes and patient safety [50-51].

A bot (also known as a web robot or internet bot) is a software application that uses steps or scripts to automate a task. Through a variety of toolkits available, chatbots utilize Natural Language Understandings (NLU) services. With NLU, chatbots focus on the use of a conversational interface, one that permits a user to interact using their natural form of speaking. After adding clinical triage and medical content into a bot framework, the resultant virtual personal health assistants can interact with the user on topics regarding wellbeing, experienced health, questions on diseases, and information about healthcare interventions. Bots may help optimize adherence by answering drug-related questions, by telling a patient what to expect during the first weeks a medicine is taken, or by reducing the potential for the medicine to be taken other than as prescribed [52-53].

A bot (also known as a web robot or internet bot) is software that uses steps or scripts to automate a task. With various tools available, chatbots use natural language understanding (NLU) services. Chatbots with NLU focus on using a conversational interface that allows the user to interact using a natural form of conversation.18 After adding clinical triage and medical content to the bot framework, the resulting virtual personal health assistants communicate with the user about well-being, experienced health, disease questions, and health care interventions. Bots can help optimize compliance by answering drug-related questions, telling patients what to expect during the first few weeks of taking a drug, or reducing the potential for taking a drug other than as prescribed [54-55].

Digital medicine-The digital drug system currently contains four main components: an inert sensor embedded in an inert tablet, a non-medicated sensor (patch) worn by the patient, a mobile application (app); and a web-based dashboard. Upon interaction with gastric fluids, the ingestible sensor is activated and connects to a wearable sensor that sends a signal to a mobile device where it can be viewed by patients or subsequently viewed by healthcare providers and caregivers using secure mobile-based and cloud-based applications. based software.20 It also has the ability to record other behavioral and physiological parameters, such as physical activity, heart rate, skin temperature, sleep and digital therapeutics [56-57].

Digital therapy (DTx) is a new treatment modality in which digital systems such as smartphone applications, digital sensors, wearable devices, certain virtual reality or artificial intellect devices are used as regulatory approved, prescribed therapeutic interventions for medical prevention, management or treatment. conditions. DTx products have a range of different potential functions, including modifying the use of medications, changing patient behavior independent of pharmaceutical product use, and treating a medical condition or influencing a patient's underlying physiological response. Many also have the opportunity [58].

Remote patient monitoring (RPM) uses digital technologies to collect health data from individuals in one location, such as a patient’s home, and electronically transmit the information

to healthcare providers in a different location for assessment and recommendations. Community pharmacist services are traditionally linked to a product, but pharmacists are skilled in medication management, disease state evaluation and patient counselling, which are skills that can contribute to an elevated RPM program [59].

Remote patient monitoring (RPM) uses digital technologies to collect health data from individuals in one location, such as the patient's home, and transmit the information electronically to health care providers elsewhere for evaluation and recommendations. Community pharmacist services are traditionally product-related, but pharmacists are skilled in medication management, in disease assessment and patient counseling, which are skills that can contribute to an enhanced RPM program.

Online/remote (patient) counselling, and telemedicine/ telehealth/ virtual care: Tele pharmacy has many recognizable benefits such as the easy access to healthcare services in underserved, remote and rural locations, economic benefits, patient satisfaction as a result of effective patient counselling, and minimal scarcity of local pharmacist and pharmacy services.

Online/remote (patient) consultations and telemedicine/telemedicine/virtual assistance: Telepharmacy has many clear benefits such as easy access to medical services in underserved, remote and rural areas, economic benefits, patient satisfaction through effective patient counseling, and minimal shortage of local pharmacists and pharmaceutical services [60].

Artificial intellect (AI) is a field of computer science that aims to mimic human intelligence with computer systems. This mimicry is accomplished through iterative, complex pattern matching, generally at a speed and scale that exceed human capability.[28] AI can strongly influence and shift our focus from the dispensing of medicines toward providing a broader range of patient-care services.[29] Improvements in budgeting, lower operational costs, and improved overall organizational efficiency will be seen as positive results of AI data analysis.[30] AI is set to revolutionize pharmaceutical care through connecting different pharmaceutical data sets, analyzing platforms of medical and pharmaceutical records, designing holistic treatment plans, or signaling adverse events or non-adherence. Also, AI may help automate repetitive pharmacy tasks, such as checking prescriptions or reviewing poly-pharmaceutical drug profiles (signaling, for example, overconsumption or interactions) [61].

Artificial intellect (AI) is a branch of computer science that aims to imitate human intelligence with computer systems. This mimicry is achieved by matching repetitive, complex patterns, generally at a speed and scale that exceeds human capacity. AI can have a powerful impact and shift our focus from dispensing medicine to providing a broader range of patient care services. Improved budgeting, lower operational costs and improved organizational efficiency are seen as positive outcomes of AI data analysis. or reporting adverse events or failure to comply. Also, AI can help automate repetitive tasks in the pharmacy, such as checking prescriptions or reviewing polypharmacy drug profiles (alarming, for example, overdose) [62].

Big data can be defined as digital data that are generated in high volume and high variety and that accumulate at high velocity, resulting in datasets too large for traditional data-processing systems.[31] Data science can be defined as the set of fundamental principles that support and guide the principled extraction of information and knowledge from data.[32] The pharmaceutical facet of healthcare is full of data. Large quantities of patient information are regularly collected and shared between providers and pharmacy staff to ensure that patients receive the care that they need. While these data have traditionally been used simply to ensure that the right prescription in the correct dosage is distributed to the proper patient, key stakeholders are finding that the

information can also be leveraged to improve several other important areas of pharmacy practice. Specifically, data use is affecting pharmacy practice in terms of managing healthcare plan expenditures, monitoring consumer use of prescription drugs and advancing research and development efforts [63].

Mobile applications can help people manage their own health and wellness, promote healthy living, and provide access to useful information when and where people need it. These tools are being adopted almost as quickly as they can be developed. Through the use of mobile applications, pharmacists can stay up to date with disease state guidelines, maintain adequate pharmacy stock inventories, access drug information systems, review patient health information and use tools to calculate individual drug doses and to accurately convert between units of measurement. Mobile devices may also assist pharmacists by converting smartphones into point-of-care diagnostic tools, such as otoscopes or blood pressure monitors. Mobile applications can also help patients manage disease states, improving their medication adherence and logging important health history [64].

The coronavirus disease (COVID-19) pandemic has been a powerful stimulus in catalyzing the use of technology. In the era of digital health technologies, the focus on new models has shifted to virtual visits, virtual care, remote patient monitoring, and websites and chatbots (for risk assessment, screening, triage).[36] This pandemic has showed the usefulness of digital health solutions and constitutes an opportunity to insert these solutions into our healthcare systems. Digital technologies and distant care became embedded more than ever in our everyday lives and, importantly, within healthcare roles. As a result, the digitalization of healthcare practices is growing exponentially [65].

Under its National Health Plan for COVID-19, the Australian Government has accelerated the delivery of electronic prescriptions. Australian pharmacists have been able to undertake different remunerated services (Meds Checks, Diabetes Meds Checks, Home Medicine Reviews and Residential Medication Management Reviews) via telehealth.

The impact of digitization of healthcare services has been profound and is expected to be even more profound in the future. To appreciate this, a broader perspective must be taken. Achieving broader health system goals, including quality, access, efficiency, and equity, is the goal against which new digital health services should be evaluated.

Decisions to adopt new digital health services, at different levels of the healthcare system, are ideally based on evidence regarding their performance considering health system goals. These goals in a broad sense are unaltered by the process of digitalization. Governance should be designed and tailored in such a way to capture all relevant changes in an adequate way [66-67].

Many digital health technologies strongly depend on their uptake and appropriate use by healthcare professionals. This may lead to new healthcare professions, as well as to existing healthcare professionals acquiring new skills and competencies to work with new digital health services. Co-creation in developing new digital health services can be useful to increase acceptability and user friendliness, also in practice. Professionals' experiences with using the technologies are also crucial to monitor and consider in any evaluation.[43] If digital health technologies are understood, designed and implemented well, health professionals can co-exist with them, which has the potential to ease some of the burden to allow more time with patients or carrying out lifesaving research [68].

Digital health systems can also empower and engage patients, making them co-designers of care. This shared decision-making between health workers and patients demands trust, a sense of

partnership and transparency in their interactions. Healthcare professionals become collaborators in a patient's journey to health, while still providing empathy and a human touch in support of patients' well-being.

Digital health systems can also empower and engage patients, making them co-designers of care. Shared decision-making between healthcare workers and patients requires trust, a sense of partnership and transparency in their interactions. Healthcare professionals become collaborators on the patient's journey to health, yet still provide empathy and a human touch to support patients' well-being.

Interventions for clients: Clients are members of the community who are potential or current users of health services, including health promotion activities. This group also includes caregivers of clients receiving health services. Interventions for health care providers: Health care providers are members of the health care workforce who deliver health care services. Interventions for health system or resource managers: Health system and resource managers are involved in the administration and supervision of public health systems. Interventions in this category reflect managerial functions related to supply chain management, health financing, and human resource management. Interventions for data services: Data services consist of cross-functional functions to support a wide range of activities related to the collection, management, use and exchange of data.

In many countries, pharmacists were among the first healthcare providers to adopt all four pillars of information technology systems mentioned above to optimize pharmaceutical care services. Managing thousands of drugs in stock, checking for drug-drug interactions, and facilitating sequencing by analyzing refill rates are some of the reasons why, often before doctors using electronic prescription systems, pharmacists are already used to working with computers. Pharmacists demonstrate a structured mindset that stems from a rigorous educational path. They like to analyze data and support decision tools derived from reliable data systems.

The pharmacy profession is clearly one that has a certain technical aura. Hence, it has the ideal aptitude and competencies to provide more digital healthcare services to patients.

Some of the key areas in which digital technologies will impact the pharmacy profession can be summarized as follows: Integrating Wearables Data into Decision Making: As more wearables are able to monitor increasing amounts of patient health and wellness data, this data can be used as digital biomarkers in pharmaceutical decision making. Digital biomarker data can be described as objective, quantitative data collected by wearables, portable devices, or even implanted or digestive health tracking devices. Think smart watches with proven ECG apps that can support the pharmacist in determining the effectiveness and safety of cardiac treatments. Or a meditation device that provides data on a patient's mental relaxation status, which can help improve the effectiveness of potential migraine treatments. There are many examples here where pharmacists can ask themselves how they can use this data to improve their services by predicting outcomes, adverse events and patient satisfaction. Once pharmacists have access to this data, they can interpret patients' vital signs in real time and provide them to a primary care or specialty physician to optimize pharmaceutical care as needed. Nowadays, such access should be possible, but not widespread.

Health App Use: As healthcare moves to phone-based access models, patients will have access to increasing amounts of digital biomarker data 24 hours a day. The global interoperability of these data is increasing due to the increasing standardization of health data. This, along with the fact that computers are getting faster and mobile phones are becoming more powerful, will make the

patient's mobile environment the center of care information. As with the impact of wearables, pharmacy information and communication technology systems should ideally be able to connect to these patient environments, exchange informed consent patient data, and process them into valuable tools for delivering digital pharmaceutical care through the health applications the patient already uses. . This ultimately becomes important as digital therapy (DTx) becomes more integrated into the standard of care. DTx delivers evidence-based therapeutic interventions to patients guided by high-quality software programs for the prevention, management or treatment of a wide range of physical, mental and behavioral conditions[69-70].

Robotic Support-Automated dispensing processes with robots, packaging systems to create individualized dosages, and chatbot information technology to answer frequently asked questions are all examples of robotics that can improve the efficiency of the pharmaceutical process. Robotics can also reduce the number of dispensing errors, resulting in avoided hospitalizations, deaths and costs in healthcare systems.

Conclusion

The vast amount of health data provides the opportunity to use more artificial intellect and machine learning in the practice of pharmacy to solve important issues related to medication management and use. Trend analysis in large data sets can reveal individual patient risk of adverse events, behavioral aspects, compliance profiles, etc. A pharmacist is a professional expert who can augment a data scientist's expertise to create services. Understanding the terminology and concepts used in artificial intellect will help pharmacists engage constructively with data scientists and collaborate with them to develop models that enhance patient care. Digital health systems can also empower and engage patients, making them co-designers of care. Shared decision-making between healthcare workers and patients requires trust, a sense of partnership and transparency in their interactions. Healthcare professionals become collaborators on the patient's journey to health, yet still provide empathy and a human touch to support patients' well-being.

REFERENCES

1. National Association of Boards of Pharmacy. Model state pharmacy act and model rules of the national association of boards of pharmacy 2018. https://nabp.pharmacy/publications-reports/resource-documents/model-pharmacy-act-rules. Accessed November 28, 2018.
2. Sherman J. Telepharmacy? A promising alternative for rural communities. Pharmacy Times 2007. https://www.pharmacytimes.com/publications/issue/2007/2007-02/2007-02-6296. Accessed Dec 17, 2019.
3. Tzanetakos G, Ullrich F, Mueller K. Telepharmacy rules and statutes: a 50-state survey. Am J Med Res 2017;(2017):1–4.
4. Scott DM, Friesner DL, Rathke AM, Peterson CD, Anderson HC. Differences in medication errors between central and remote site telepharmacies. J Am Pharm Assoc 2012;52(5):e97-e104.
5. Friesner DL, Scott DM, Rathke AM, Peterson CD, Anderson HC. Do remote community telepharmacies have higher medication error rates than traditional community pharmacies? Evidence from the North Dakota Telepharmacy Project. J Am Pharm Assoc (2003) 2011;51(5):580–90. 10.1331/JAPhA.2011.10115.

6. Steckler T. Telepharmacy: controversy and promise. J Pharm Technol 2016;32(6):227–9. 10.1177/8755122516670415.
7. Centers for Medicare & Medicaid Services. Medicare 2018 part C and D star ratings technical notes 2017. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/Downloads/2018-Star-Ratings-Technical-Notes-2017_09_06.pdf. Accessed May 15, 2020.
8. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. http://ep.yimg.com/ty/cdn/epill/pdcmpr.pdf. Accessed February 16, 2019.
9. McGinley P. National Quality Forum endorses measures to improve medication safety and quality. Healthcare Finance News 2009. https://www.healthcarefinancenews.com/press-release/national-quality-forum-endorses-measures-improve-medication-safety-and-quality. Accessed April 14, 2020.
10. United States Department of Agriculture. USDA Economic Research Service rural-urban continuum codes. https://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx. Accessed April 9, 2019.
11. US Department of Housing and Urban Development. HUD USPS ZIP code crosswalk files. https://www.huduser.gov/portal/datasets/usps_crosswalk.html. Accessed April 9 2016.
12. Schmittdiel JA, Raebel MA, Dyer W, Xu S, Goodrich GK, Schroeder EB, et al. Prescription medication burden in patients with newly diagnosed diabetes: a SUrveillance, PREvention, and ManagEment of Diabetes Mellitus (SUPREME-DM) study. J Am Pharm Assoc (2003) 2014;54(4):374–82. 10.1331/JAPhA.2014.13195.
13. Halli-Tierney AD, Scarbrough C, Carroll D. Polypharmacy: evaluating risks and deprescribing. Am Fam Physician 2019;100(1):32–8.
14. Hudd TR, Tataronis GR. The impact of an urban telepharmacy on patient medication adherence in a federally qualified health center. J Pharm Technol 2011;27(3):117–22. 10.1177/875512251102700304.
15. Health Care Payment Learning & Action Network. Measuring progress: adoption of alternative payment models in commercial, Medicaid, Medicare advantage, and Medicare fee-for-service programs, 2018. https://hcp-lan.org/2018-apm-measurement/. Accessed Dec 9, 2019.
16. Pednekar P, Peterson A. Mapping pharmacy deserts and determining accessibility to community pharmacy services for elderly enrolled in a State Pharmaceutical Assistance Program. PLoS One 2018;13(6):e0198173. 10.1371/journal.pone.
17. Qato DM, Daviglus ML, Wilder J, Lee T, Qato D, Lambert B. 'Pharmacy deserts' are prevalent in Chicago's predominantly minority communities, raising medication access concerns. Health Aff (Millwood) 2014;33(11):1958–65. 10.1377/hlthaff.2013.
18. Howarth HD, Peterson GM, Jackson SL. Does rural and urban community pharmacy practice differ? A narrative systematic review. Int J Pharm Pract 2020;28(1):3–12. 10.1111/ijpp.12567
19. Crilly P, Kayyali R. A systematic review of randomized controlled trials of telehealth and digital technology use by community pharmacists to improve public health. Pharmacy. 2020. 8(3):137. doi: 10.3390/pharmacy8030137
20. Alexander E, Butler C, Darr A, et al.. ASHP statement on telepharmacy. Am J Health-Syst Pharm. 2017;74(9):e236-e241. doi: 10.2146/ajhp170039

21. Telemedicine and Telehealth. HealthIT.gov. https://www.healthit.gov/topic/health-it-health-care-settings/telemedicine-and-telehealth. Published September 24, 2020. Accessed September 14, 2021.
22. Omboni S, Tenti M, Coronetti C. Physician–pharmacist collaborative practice and telehealth may transform hypertension management. J Hum Hypertens. 2019;33(3):177-187. doi: 10.1038/s41371-018-0147-x.
23. Badowski ME, Walker S, Bacchus S, et al.. Providing comprehensive medication management in telehealth. Pharmacotherapy. 2018;38(2):e7-e16. doi: 10.1002/phar.2071
24. Bellfi L, Young J, Pratt L, Patel A, Mei D, Chan J. Sustained virologic response with peginterferon plus ribavirin in the Illinois prison population infected with hepatitis C virus through telemedicine: a retrospective chart review: 29. Pharmacotherapy. 2016;36(12).
25. Shane-McWhorter L, Lenert L, Petersen M, et al.. The Utah remote monitoring project: improving health care one patient at a time. Diabetes Technol Ther. 2014;16(10):653-660. doi: 10.1089/dia.2014.0045.
26. McFarland M, Davis K, Wallace J, et al.. Use of home telehealth monitoring with active medication therapy management by clinical pharmacists in veterans with poorly controlled type 2 diabetes mellitus. Pharmacotherapy. 2012;32(5):420-426. doi: 10.1002/j.1875-9114.2011.01038.x
27. Shafiee Hanjani L, Caffery L, Freeman C, Peeters G, Peel N. A scoping review of the use and impact of telehealth medication reviews . Res Social Adm Pharm. 2020;16(8):1140-1153. doi: 10.1016/j.sapharm.2019.12.014
28. Kosmisky D, Everhart S, Griffiths C. Implementation, evolution and impact of ICU telepharmacy services across a health care system. Hosp Pharm. 2019;54(4):232-240. doi: 10.1177/0018578719851720.
29. Smith A, Thomas E, Snoswell C, et al.. Telehealth for global emergencies: Implications for coronavirus disease 2019 (COVID-19). J Telemed Telecare. 2020;26(5):309-313. doi: 10.1177/1357633X20916567.
30. Koonin LM, Hoots B, Tsang CA, et al.. Trends in the use of telehealth during the emergence of the COVID-19 pandemic--United States, January-March 2020. MMWR Morb Mortal Wkly Rep. 2020;69(43):1595-1599. doi: 10.15585/mmwr.mm6943a3
31. Skoy E, Eukel H, Frenzel J, Schmitz T. Performance and perceptions: evaluation of pharmacy students' consultation via telepharmacy. J Pharm Tech. 2015;31(4):155-160. doi: 10.1177/8755122514568123.
32. Beal J, Weber Z, Isaacs A, Illingworth Plake K, Zillich A, Woodyard J. Pharmacy student preferences and perceptions of in-person versus video evaluations in pharmacy skills-based laboratory courses. Am J Pharm Educ. 2020;84(11):7976. doi: 10.5688/ajpe7976
33. Begley K, O'Brien K, Packard K, et al.. Impact of interprofessional telehealth case activities on students' perceptions of their collaborative care abilities. Am J Pharm Educ. 2019;83(4):6880. doi: 10.5688/ajpe6880.
34. Rutledge C, Kott K, Schweickert P, Poston R, Fowler C, Haney T. Telehealth and ehealth in nurse practitioner training: current perspectives. Adv Med Educ Pract. 2017;8:399-409. doi: 10.2147/AMEP.S116071.
35. Proceedings of the 2016 annual meeting of the American Medical Association house of delegates. https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-

browser/public/about-ama/councils/Council%20Reports/council-on-medical-education/a16-cme-reports-v2.pdf. Published 2016. Accessed September 14, 2021.
36. Poudel A, Nissen L. Telepharmacy: a pharmacist's perspective on the clinical benefits and challenges. Integr Pharm Res Pract. 2016;5:75-82. doi: 10.2147/IPRP.S101685.
37. Chwistek M. "Are you wearing your white coat?": telemedicine in the time of pandemic . JAMA. 2020;324(2):149. doi: 10.1001/jama.2020.10619.
38. Haney T, Kott K, Fowler C. Telehealth etiquette in home healthcare: the key to a successful visit. Home Healthcare Now. 2015;33(5):254-259. doi: 10.1097/NHH.0000000000000228
39. Hyder MA, Razzak J. Telemedicine in the United States: An Introduction for Students and Residents. J Med Internet Res. 2020 Nov 24;22(11):e20839. doi: 10.2196/20839. PMID: 33215999; PMCID: PMC7690251.
40. WHO Guideline: Recommendations on Digital Interventions for Health System Strengthening. Geneva, Switzerland: World Health Organization; 2019. URL: https://apps.who.int/iris/bitstream/handle/10665/311941/9789241550505-eng.pdf?ua=1
41. American Telemedicine Association. Telehealth: Defining 21st Century Care. Arlington, VA: ATA; 2020. URL: https://www.americantelemed.org/resource/why-telemedicine/.
42. Kane CK, Gillis K. The use of telemedicine by physicians: still the exception rather than the rule. Health Aff (Millwood) 2018 Dec;37(12):1923-1930.
43. Link MM. Space Medicine in Project Mercury. NASA SP-4003. NASA Special Publication. Washington, DC: Office of Manned Space Flight, National Aeronautics and Space Administration; 1965. URL: http://articles.adsabs.harvard.edu/full/1965NASSP4003.....L [accessed 2020-11-16]
44. Li HK. Telemedicine and ophthalmology. Surv Ophthalmol 1999;44(1):61-72.
45. Aita MC, Nguyen K, Bacon R, Capuzzi KM. Obstacles and solutions in the implementation of telestroke: billing, licensing, and legislation. Stroke 2013 Dec;44(12):3602-3606.
46. Ward MM, Jaana M, Natafgi N. Systematic review of telemedicine applications in emergency rooms. Int J Med Inform 2015 Sep;84(9):601-616.
47. Weinstein RS, Lopez AM, Joseph BA, Erps KA, Holcomb M, Barker GP, et al. Telemedicine, telehealth, and mobile health applications that work: opportunities and barriers. Am J Med 2014 Mar;127(3):183-187.
48. Burute N, Jankharia B. Teleradiology: the Indian perspective. Indian J Radiol Imaging 2009 Feb;19(1):16-18 [FREE Full text]
49. Hasselberg MJ. The digital revolution in behavioral health. J Am Psychiatr Nurses Assoc 2020;26(1):102-111.
50. Starren J, Hripcsak G, Sengupta S, Abbruscato CR, Knudson PE, Weinstock RS, et al. Columbia University's Informatics for Diabetes Education and Telemedicine (IDEATel) project: technical implementation. J Am Med Inform Assoc 2002;9(1):25-36 [FREE Full text]
51. Kvedar J, Coye MJ, Everett W. Connected health: a review of technologies and strategies to improve patient care with telemedicine and telehealth. Health Aff (Millwood) 2014 Feb;33(2):194-199.
52. Kulshreshtha A, Kvedar JC, Goyal A, Halpern EF, Watson AJ. Use of remote monitoring to improve outcomes in patients with heart failure: a pilot trial. Int J Telemed Appl 2010;2010:870959 [FREE Full text]

53. Darkins A, Ryan P, Kobb R, Foster L, Edmonson E, Wakefield B, et al. Care Coordination/Home Telehealth: the systematic implementation of health informatics, home telehealth, and disease management to support the care of veteran patients with chronic conditions. Telemed J E Health 2008 Dec;14(10):1118-1126.
54. Mann DM, Chen J, Chunara R, Testa PA, Nov O. COVID-19 transforms health care through telemedicine: evidence from the field. J Am Med Inform Assoc 2020 Apr 23;27(7):1132-1135 [FREE Full text]
55. Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. N Engl J Med 2020 Mar 11;382(18):1679-1681.
56. Dizon R. 2018 in review: state & federal telehealth policy.: National Consortium of Telehealth Resource Centers; 2019. URL: https://www.telehealthresourcecenter.org/2018-in-review-state-federal-telehealth-policy/ [accessed 2020-11-16]
57. Ladika S. Telehealth overview: the reality check, please. Manag Care 2017 Apr;26(4):16-18
58. Antoniotti NM, Drude KP, Rowe N. Private payer telehealth reimbursement in the United States. Telemed J E Health 2014 Jun;20(6):539-543.
59. Rogove H, Stetina K. Practice challenges of intensive care unit telemedicine. Crit Care Clin 2015 Apr;31(2):319-334.
60. Data.HRSA.gov. Medicare Telehealth Payment Eligibility Analyzer. Rockville, MD: Health Resources & Services Administration URL: https://data.hrsa.gov/ [accessed 2020-11-16]
61. National policy: Telehealth and Medicare. West Sacramento, CA: Center for Connected Health Policy; 2019. URL: https://www.cchpca.org/telehealth-policy/telehealth-and-medicare [accessed 2020-11-16]
62. Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020, Public law 116-123-Mar 6, 2020, HR 6074, 116th Congress. 2020. URL: https://www.govinfo.gov/content/pkg/PLAW-116publ123/pdf/PLAW-116publ123.pdf
63. Medicare.gov. Medicare & coronavirus. Woodlawn, MD: U.S. Centers for Medicare & Medicaid Services URL: https://www.medicare.gov/medicare-coronavirus.
64. Resneck JS, Abrouk M, Steuer M, Tam A, Yen A, Lee I, et al. Choice, transparency, coordination and quality among direct-to-consumer telemedicine websites and apps treating skin disease. JAMA Dermatol 2016 Jul 01;152(7):768-775.
65. Greenhalgh T, Wherton J, Shaw S, Morrison C. Video consultations for covid-19. BMJ 2020 Mar 12;368:m998.
66. Kaplan B, Litewka S. Ethical challenges of telemedicine and telehealth. Camb Q Healthc Ethics 2008;17(4):401-416.
67. Haluza D, Naszay M, Stockinger A, Jungwirth D. Prevailing opinions on connected health in Austria: results from an online survey. Int J Environ Res Public Health 2016 Aug 11;13(8) [FREE Full text]
68. Geronimo A, Wright C, Morris A, Walsh S, Snyder B, Simmons Z. Incorporation of telehealth into a multidisciplinary ALS clinic: feasibility and acceptability. Amyotroph Lateral Scler Frontotemporal Degener 2017 Nov;18(7-8):555-561.
69. Ward MM, Ullrich F, Potter AJ, MacKinney AC, Kappel S, Mueller KJ. Factors affecting staff perceptions of tele-ICU service in rural hospitals. Telemed J E Health 2015 Jun;21(6):459-466.

70. Adler-Milstein J, Kvedar J, Bates DW. Telehealth among US hospitals: several factors, including state reimbursement and licensure policies, influence adoption. Health Aff (Millwood) 2014 Feb;33(2):207-215.

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

THE SCIENTIFIC DISCUSSION OF CHARACTERISTICS OF REGULAR PHARMACEUTICS AND PHARMACISTS' PRINCIPLES AND SOPHISTICATED EMISSION OUTLET DISPUTES, APPARITION BY HEALTH CARE EXPERTS IN GEORGIA

Nodar Sulashvili[1], Nana Gorgaslidze[2], Tamar Lobjanidze[3], Vasil Tkeshelashvili[4], Natia Kvizhinadze[5], Luiza Gabunia[6], Nato Alavidze[7], Ketevani Gabunia[8], Nino Abuladze[9], Marina Giorgobiani[10], Irine Zarnadze[11], Shalva (Davit) Zarnadze[12]

[1]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Invited Professor/Lecturer of Tbilisi State Medical University, Tbilisi, Georgia; Professor of The School of Health Sciences, The University of Georgia, Tbilisi, Georgia.
[2]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Tbilisi State Medical University, Head of The Department of Social and Clinical Pharmacy, Tbilisi, Georgia.
[3]Professor, Dean of The School of Health Sciences, The University of Georgia, Tbilisi, Georgia.
[4]MD, PhD, Doctor of Medical Sciences, Professor, Academician, Head of The Doctoral Educational Study Program, The University of Georgia, School of Health Sciences, Tbilisi, Georgia.
[5]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Tbilisi State Medical University, Department of Social and Clinical Pharmacy. Tbilisi, Georgia.
[6]MD, PhD, Doctor of Medical Sciences, Professor, Director of the Scientific Research-Skills Center at Tbilisi State Medical University, Professor of the Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia.
[7]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia.
[8]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia.
[9]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia.
[10]MD, PhD, Doctor of Medical Sciences, Professor of Tbilisi State Medical University, Department of Hygiene and Medical Ecology, Tbilisi, Georgia.
[11]MD, PhD, Doctor of Medical Sciences, Professor of Tbilisi State Medical University, Department of Public Health, Health Care Management, Policy and Economy, Tbilisi, Georgia.
[12]MD, PhD, Doctor of Medical Sciences, Professor of Tbilisi State Medical University, Head of the Department of Nutrition, Aging Medicine, Environmental and Occupational Health, Tbilisi, Georgia.
Email: n.sulashvili@tsmu.edu

ABSTRACT

The main goal of the research was to study and analyze characteristics of regular pharmaceutics and pharmacists' principles and sophisticated emission outlet dispute, apparition by health care experts in Georgia. The study was a quantitative investigation and analysis of the characteristics of regular pharmaceutics and pharmacists' principles and sophisticated emission outlet dispute, apparition by health care experts in Georgia by using questionnaires. Were conducted a survey study. Questionnaires were for public health specialists; 307 public health specialists were interviewed. Were used methods of systematic, sociological (surveying, questioning), comparative, mathematical-statistical, graphical analysis. The data were processed and analyzed with the SPSS program. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. We defined $p < 0.05$ as significant for all analyses.

According to the study results, Clinical Pharmacy defines that as the health specialty that characterizes the activities of clinical pharmacists and the provision of health services, clinical pharmacists promote and develop rational and appropriate pharmacotherapy, the rational use of pharmaceutical manufacturing and medical devices. The practice of clinical pharmacy includes knowledge of pharmacotherapy, pharmaceutical care and first aid; it combines leadership in health care with specific therapeutic knowledge, understanding, cognition, learned habits and assessment to ensure rational and optimal treatment outcomes for patients. Likewise, pharmaceutical care and clinical pharmacy are closely related concepts, although there are differences between professional development structures that determine specificity. Clinical pharmacy includes the theoretical knowledge and understanding, practical skills, values and attitudes needed by pharmacists to promote healthcare and pharmaceutical services to individual patients and populations to provide contribution and assistance in teaching of patients to understand the prescribed drugs intake rules, pharmacists need in deep knowledge in basics of medicine, pharmacology, pharmacotherapy, pharmaceutical chemistry, pharmaceutical care, clinical pharmacy and other pharmaceutical disciplines. Properly educated pharmacists have great importance and value for the provision higher quality health care services, for the provision higher quality pharmaceutical care and very essential for patient's safety. About half part of the respondents considered that pharmacist is not responsible for registration of adverse effects of the drugs, while less than a third part of them considered pharmacist to be responsible for that. By legislation one of the functions of pharmacist is to register the side effects of drugs, what is very essential for patients' safety. It should increase the awareness of pharmacist as the health professional.

Keywords: Characteristics, regular, pharmaceutics, pharmacists', principles, sophisticated, dispute, health care, experts, Georgia.

Introduction

The pharmacists hold the great condition to satisfy the necessity for health care vocational to ensure effective and safe using of medicines. To do this, pharmacists should suppose higher liability than they at the present time do for the monitoring of pharmacotherapy for the customers, consumers and patients they are serving [1-2]. That liability goes completely behind the traditional distributing and dispensing practices that have long been the maintenance of the pharmacy activities. Ppharmacists liability should be enlarged conclude controlling of the pharmacotherapeutic progression and thereby improve therapeutic outcomes and patients' life quality, advising with doctor prescribers and consolidating with different health care workers and practicians on behalf of patients [3-4]. Pharmacists' involvement into pharmaceuticals may consist in drug storage, drug supply, dispensing, manufacturing, formulation, distribution, marketing, quality warranty, licensing, information management, monitoring, development, education, and research. Drug supply and medicine information management system is the main part of pharmaceutical services and proceeds forming the basement of pharmacy activities. The higher pharmaceutical schooling and education hold an appropriate duty and responsibility to generate post-graduate professionals who are qualified and authorized to provide the pharmaceutical care services. Sufficiency results promote to quality warranty by provided that easily approachable working standards [5-7].

Pharmaceutical care and clinical pharmacology are a professional discipline that combines fundamental pharmacology and clinical medicine. The Clinical Pharmacist offers invaluable support in developing the final prescription with improved patient care and increased safety. Its development began in the early 1950s, largely thanks to the efforts of Harry Gold. The introduction of pharmacists into hospital

services began as early as 1957. Pharmacotherapy became more and more complex. The clinical pharmacist has pioneered a new role for pharmacists in hospital services. The role of clinical pharmacists underwent significant changes from the 1960s to the 1990s as their involvement in direct patient care improved. In the early 1970s, federal funding helped significantly expand the clinical pharmacy teaching staff at pharmacy colleges. Pharmaceutical Education has discussed the place of clinical pharmacy in pharmaceutical education. With clinical pharmacists overwhelmed with patient numbers and the emergence of new drugs, doctors are increasingly turning to pharmacists for drug information, especially in institutions [8-10].

The clinical pharmacist often takes a slightly different approach to drug use and can provide valuable additional information, such as interactions, in the clinician's decision-making process for potential drug changes and monitoring. The concept of pharmaceutical care emphasizes the responsibility of pharmacists to seek the best possible outcomes for patients from a therapeutic regimen. They possess an in-depth knowledge of medicines that is combined with a fundamental understanding of the biomedical, pharmaceutical, socio-behavioral and clinical sciences. Clinical pharmacists follow evidence-based treatment guidelines, advancing science, the latest technology, and appropriate legal, ethical, social, cultural, economic and professional prescriptions to achieve their desired therapeutic goals. Consistently, clinical pharmacists take responsibility and accountability for the management of drug therapy in a direct patient care setting, whether they practice on their own, in consultation, or in collaboration with other healthcare professionals. Their functions include comprehensive drug management (ie, prescribing, monitoring and adjusting drugs), non-drug counseling, and coordination of care. Interdisciplinary collaboration enables pharmacists to provide direct patient care or telecommuting in a variety of clinical settings, including disease management, primary care, or specialty care. A clinical pharmacist can take responsibility for chronic or acute diseases related to the endocrine, cardiovascular, respiratory, gastrointestinal, or other systems. Clinical pharmacist researchers generate, disseminate and apply new knowledge to drive improvement. In the healthcare system, clinical pharmacists are experts in the therapeutic use of drugs. A clinical pharmacist usually provides patients and healthcare professionals with drug treatment reviews and approvals. Clinical pharmacists are the primary source of scientifically reliable / scientifically logical information and advice on the safe, appropriate and economical use of medicines. They obtain a medical history and medication history, check for medication errors including prescribing, dosing and administering errors, identify drug interactions, track adverse reactions, suggest individual dosing regimen, advise patients, etc. They also provide information on medication use. and medical devices such as an inhaler, insulin pen, eye drops, nasal sprays, etc. [11-14].

For the majority of respondent patients', mostly significant factors, while choosing a pharmacy are: Service culture, wide range of products, reasonable prices. For less than half of respondent patients, mostly significant factors, while choosing a pharmacy are: Possibility to receive consultation about drugs with a physician or a pharmacist, convenient location of the pharmacy, high qualification of pharmacist personnel [15-17].

The majority of the patients determined the main factor while drug choosing process to be recommendation of a physician. Less than half part of respondents determined the main factor while choosing the drugs to be the doctor's prescription and advice of a pharmacist. Therefore, the role of pharmacist is significant in the healthcare system. For the higher quality healthcare and pharmaceutical services, the pharmacist's appropriate education level is of crucial importance. It was shown that the health of patients was directly related to the professional education level of pharmacist. Therefore, pharmacist should have eligible higher pharmaceutical education [18-20].

The massive political, economic, public, national and civil situation influencing of the health care system division in many countries, which also should have positive or negative effects on the pharmaceutical care practice. Due to modern demands, it is quite obvious, higher pharmaceutical education systems are needed deep and radical changes. The function, duty and role of pharmacists and pharmaceutical personnel demand to re-evaluated and overestimated [21-22]. Higher pharmaceutical institutions, universities higher pharmacy schools and colleges should be created according to modern medical demands globally. It is very important to establish and estimate new practical models, which should make use within developing modern health care surroundings. Higher pharmaceutical educational programs must be focused on the demands of the purpose public and audience [23-24]. Higher pharmaceutical programs, curriculum, program goals, methods for attaining learning outcomes, study results, study program, teaching process characteristics, course content and syllabuses, teaching methods, study materials, learning resources, reading materials, participant type of assessment, course assessment and quality assurance should be in modern standards [25-26].

Pharmacists hold scientifically educated understanding, with deep pharmaceutical and medical knowledge; they are post-graduate healthcare occupational and high skilled expert specialists in all the viewpoints of the delivering and using medicines. Pharmacists ensure to accession cost-effective, safe and high-quality medicines. The levers for the modification of the higher institutional pharmaceutical schooling and education are multiply ranged, with growing in format, character, nature and depth [27-28].

According to the modern challenges, the higher pharmaceutical educational institutions need to develop pharmacy faculty study programs curriculum, which should obviously determine learning and education results. Current study results will aid to lead pharmacy program and curriculum enhancement [29-30]. The institutional educational modification, revision and restructure would demand not only a comprehensive pharmacy program curriculum, but also a majority obligation to pharmaceutical faculty perfection and enhancement. Also, pharmacy programs' syllabuses need modernization according to modern health care and pharmaceutical care challenges in the worldwide. Therefore, should train and prepare new types of tutors and mentors to educate pharmacy faculty students and pharmacists via various types of informative, experiential and practical skill materials. Properly distributed and allocated institutional educational opportunities, possibilities, potentials, capacities and study resources need modification [31-32].

The higher pharmaceutical educational results could make use of as renewed educational institutional framework to such an extent consolidates and integrates pharmaceutical and medical sciences, occupational characteristics, professional practical skills, inter professional working practice, and high professionalism at new main division of pharmaceutical care direction, public health and health care systems governance and whole modern pharmacy practice [33-38].**Goal:** Main aim of the study was to analyze the characteristics of regular pharmaceutics and pharmacists' principles and sophisticated emission outlet dispute, apparition by health care experts in Georgia.

Materials and methods

We conducted survey study. Research objectives are materials of sociological research: The study was quantitative investigation and analysis of characteristics of regular pharmaceutics and pharmacists' principles and sophisticated emission outlet dispute, apparition by health care experts in Georgia, by using survey (Questionnaire). Surveys were for public health specialists; 307 public health specialists were interviewed. Were used methods of systematic, sociological (surveying,

questioning), comparative, mathematical-statistical, graphical analysis. The data was processed and analyzed with the SPSS program. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. We defined $p < 0.05$ as significant for all analyses. The study's ethical items. In order to provide the study's ethical character each participant of it was informed about the study's goal and suggested of willingness of the work to be done. So, the respondents' written or oral compliance was got on that issue. All the studies were carried out by the selected organizations administrations' previous compliance. Were used Informed consent form for each respondent to participate in an anonymous survey. During the whole period of research, the participants incognita was also provided. For the international rules and criteria' conformity this human subject comprising given study was discussed and confirmed on the Bioethics Committee sessions of the YSMU. In order to meet the objectives, set in the research we also used the results obtained through analysis of available official information, studies and opinions about pharmacists, as well as the methods of quantitative studies. The research implementation required the following sub studies: characteristics of regular pharmaceutics and pharmacists' principles and sophisticated emission outlet dispute, apparition by health care experts in Georgia.

Results and Discussions

On the basis of performed study results the following have been founded:

First time were complex studied professional peculiarities of the pharmacists per vision by pharmacists specialists, professional peculiarities of the employed pharmacist-student, professional peculiarities of the pharmacists by vision of the chief -pharmacist, peculiarities of professional for pharmacists via per vision of the health-care specialist, pharmacists' professional features as per view of the patients, professional peculiarities of the young pharmacist- specialists, professional peculiarities of the pharmacist-student. To reveals influencing factors for the specificities of the role, achievements, innovations, professional and enhancement prospects of pharmacists in health care sector. In result of the study and evaluation of the pharmacist's professional peculiarities news, objectively reasoned comprehension of the problems in this field has been adopted, which became a base for developing recommendations. In particular, for the first time the following have been studied and established: the peculiarities of professional and career improvement strategy for pharmacists, pharmacist specialist's professional features, specificities of the role, achievements, innovations, professional and enhancement prospects of pharmacists in health care sector globally. First time the process of professional formation of pharmacists in the scope and context of pharmaceutical care, including the stages of professional development was studied and scientifically established. First time the most influence factors for the pharmacist's professional formation were identified. Deepen defined the role of pharmacist and the specific features for the pharmaceutical specialists' formation at various stages were studied and identified. On the bases of comprehensive studied was revealed, that pharmacist specialists in contradistinction to other medical specialists like physicians, dentists etc. Pharmacists do not have continuous education, periodic certification and licensing. Pharmacists' profession removed from the regulated and certified health professional members' team.

The respondents' vast majority considered that the issues to for pharmacists were in need of the further regular studies or trainings in the following fields: new medications, issues of pharmacotherapy of certain diseases, pharmacology and pharmacotherapy, drugs toxicity. From the

study results it is obvious that in the higher pharmaceutical institutions' pharmaceutical educational programs and curriculum need upgrade, renewal, modernization and adaptation to the new modern medical challenges. Therefore, continuous pharmaceutical educational programs should be created. These programs should be more focused on new medications, pharmacotherapy, pharmacology, drugs toxicity and dosage, routes of drug administration, selection of OTC drugs, cost-effectiveness and cost-benefits of drugs [39-41].

The respondents' large majority considered necessity of provision of cooperation between pharmacists and physicians on the issues of pharmacotherapy. The pharmacist must provide information to doctor about new drugs pharmacotherapy, the generic replacement drugs, the cost-effectiveness and cost-benefits of drugs, drugs' generic, chemical and brand names. In our opinion and vision cooperation between pharmacists and physicians on the issues of pharmacotherapy is positively reflected on patients' health and has great importance for provision higher quality health care service for patients' safety. The respondents' vast majority considered that the issues to for pharmacists were in need of the further regular studies or trainings in the following fields: new medications, issues of pharmacotherapy of certain diseases, pharmacology and pharmacotherapy, drugs toxicity. From the study results it is obvious that in the higher pharmaceutical institutions' pharmaceutical educational programs and curriculum need upgrade, renewal, modernization and adaptation to the new modern medical challenges. Therefore, continuous pharmaceutical educational programs should be created. These programs should be more focused on new medications, pharmacotherapy, pharmacology, drugs toxicity and dosage, routes of drug administration, selection of OTC drugs, cost-effectiveness and cost-benefits of drugs [42-46].

The respondents' large majority considered necessity of provision of cooperation between pharmacists and physicians on the issues of pharmacotherapy (See fig.1). The pharmacist must provide information to doctor about new drugs pharmacotherapy, the generic replacement drugs, the cost-effectiveness and cost-benefits of drugs, drugs' generic, chemical and brand names. In our opinion and vision cooperation between pharmacists and physicians on the issues of pharmacotherapy is positively reflected on patients' health and has great importance for provision higher quality health care service for patients' safety [47-49].

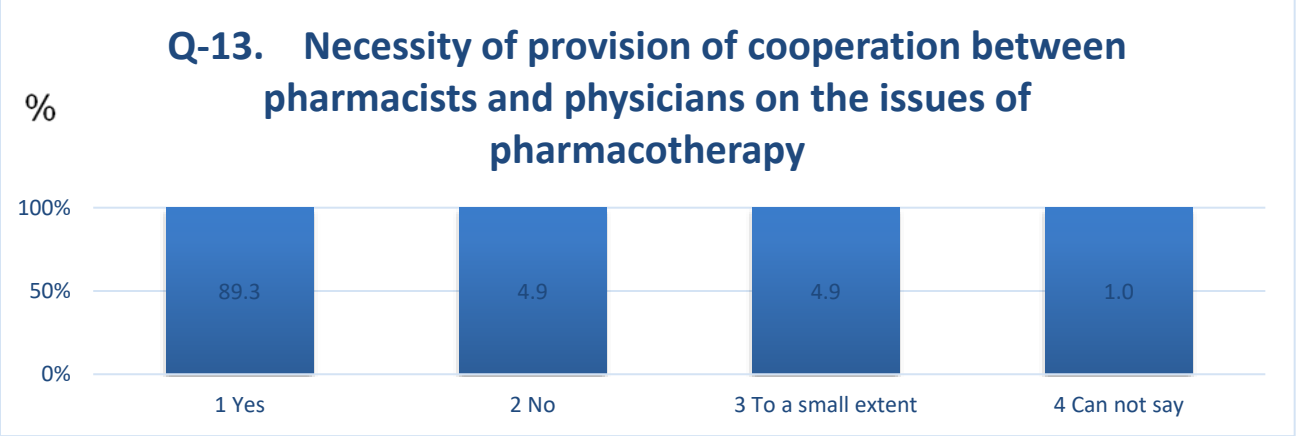


Figure 1. The respondents' opinion about the necessity to provide cooperation between pharmacists and physicians on the issues of pharmacotherapy.

More than half part of the respondents considered that pharmacist is not in charge of treatment as a physician, meanwhile about a quarter of the public health specialists considered a pharmacist to be in charge of that (See fig.2). Properly educated pharmacist can minimize and reduce the mistakes made by a doctor in the recipe. That has a great importance and value for provision higher quality health care service for patients' safety [50-51].

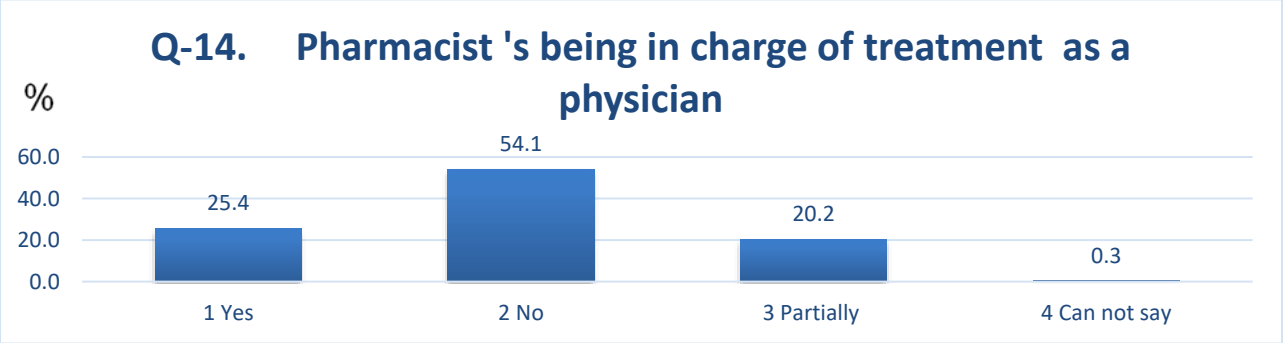


Figure 2. The respondents' (public health specialists) opinion about pharmacist's being in charge of treatment as a physician.

The respondents' vast majority considered that pharmacist should provide assistance in teaching patients to understand the prescribed drugs intake rules (See fig.3). According to that higher quality pharmaceutical service could be only provided by the pharmacists of higher pharmaceutical education, graduated from the authorized, accredited and licensed by the state higher education institutes and universities [52-53].

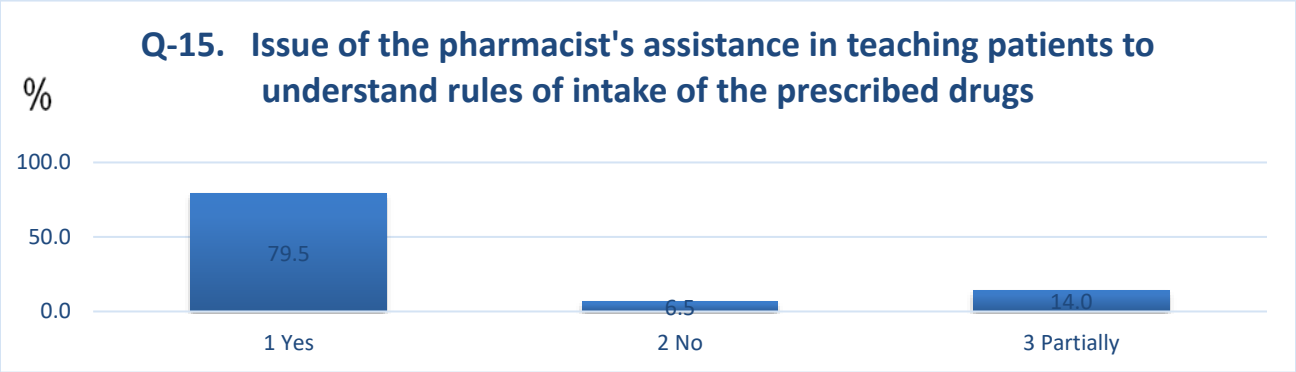


Figure 3. The respondents' (public health specialists) opinions about providing assistance by pharmacist in teaching patients to understand rules of intake of prescribed drugs.

To provide contribution and assistance in teaching of patients to understand the prescribed drugs intake rules, pharmacists need in deep knowledge in basics of medicine, pharmacology, pharmacotherapy, pharmaceutical chemistry, pharmaceutical care, clinical pharmacy and other pharmaceutical disciplines. Properly educated pharmacists have great importance and value for the provision higher quality health care services, for the provision higher quality pharmaceutical care and very essential for patient's safety [54-56].

About half part of the respondents considered that pharmacist is not responsible for registration of adverse effects of the drugs, while less than a third part of them considered pharmacist to be responsible for that. By legislation one of the functions of pharmacist is to register the side effects of drugs, what is very essential for patients' safety. It should increase the awareness of pharmacist as the health professional [57-59].

The respondents' majority considered that importance in work of pharmacist was in personal realization as a specialist, receiving remuneration and provision of necessities of life. The respondents' minority considered it to be in relief of pain in suffering of people (See fig.4).

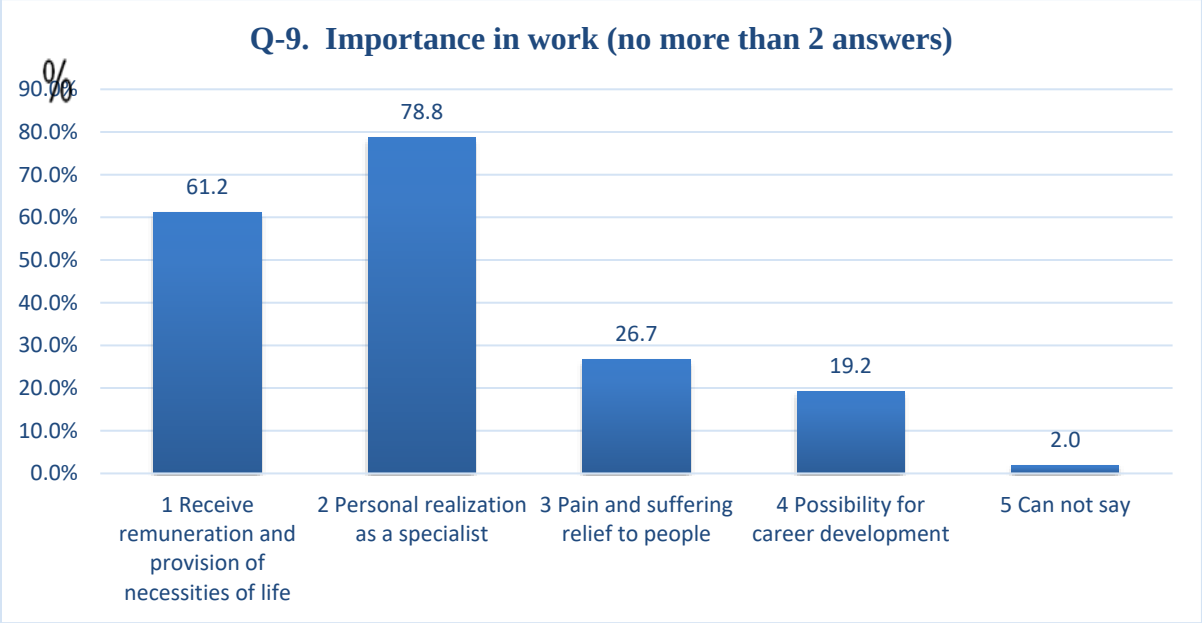


Figure 4. Important issues in work for the respondents' (public health specialists)

Less than half part of the respondents considered that the level of basic training of pharmacists was not corresponding to the contemporary requirements (See fig.5). According to the sociological study results of the public care specialists it is obviously, that all pharmacists should have higher pharmaceutical education from the state recognized and accredited higher education institutions and universities. Pharmacists' specialty should become a regulated health care profession. According to that Government should make certification, licensing and accreditation of pharmacist professionals [60-62].

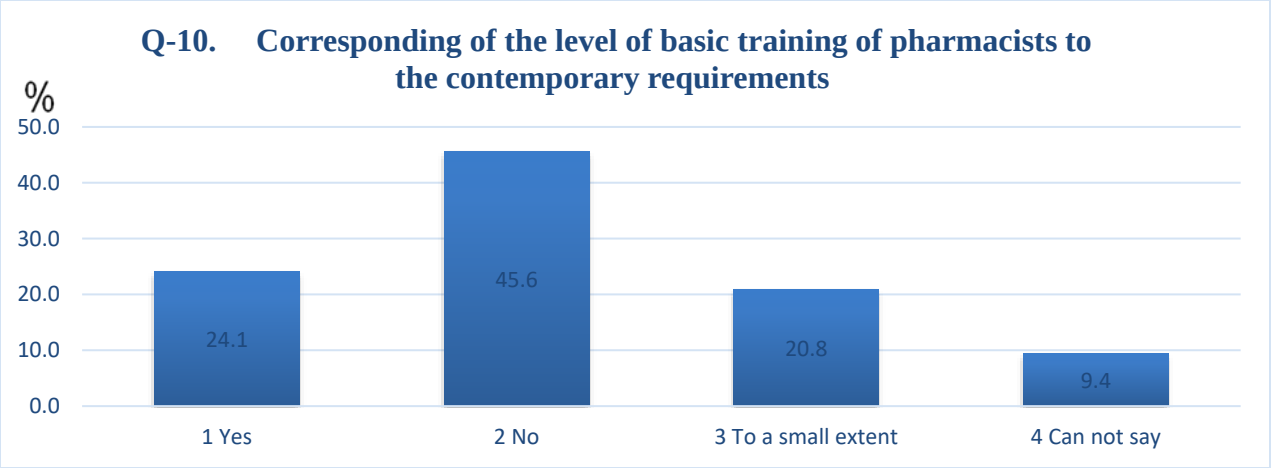


Figure 5. The respondents' opinion about pharmacists' basic training level correspondence to the contemporary requirements

The respondents' vast majority considered that the issues to for pharmacists were in need of the further regular studies or trainings in the following fields: new medications, issues of pharmacotherapy of certain diseases, pharmacology and pharmacotherapy, drugs toxicity (See tabl.1). From the study results it is obvious that in the higher pharmaceutical institutions' pharmaceutical educational programs and curriculum need upgrade, renewal, modernization and adaptation to the new modern medical challenges. Therefore, continuous pharmaceutical educational programs should be created [66-68]. These programs should be more focused on new medications, pharmacotherapy, drugs toxicity and dosage, routes of drug administration, selection of OTC drugs, cost-effectiveness and cost-benefits of drugs [63-65].

Table 1. The respondents' (public health specialists) opinions about the issues for pharmacists necessary for the further regular studies or trainings.

Q-11. The issues for pharmacists necessary for the further regular studies or trainings (several answers were possible)	Count	Percent %
1. New drugs	187	60.9
2. Psychology of communication with customers	103	33.6
3. Issues of pharmacotherapy of certain diseases	197	64.2
4. Safety and effectiveness of drugs	154	50.2
5. Pharmacology and pharmacotherapy	224	73.0
6. Normative legal regulation of pharmaceutical activity	94	30.6
7. Drugs toxicity	164	53.4
8. Drugs dosage	112	36.5
9. Routes of drug administration	110	35.8
10. Drug forms	61	19.9
11. Drug design	43	14.0

12. Rules of drug administration	123	40.1
13. Drugs generic, chemical and brand names	57	18.6
14. Selection of OTC drugs	108	35.2
15. Cost-effectiveness and cost-benefits of drugs	96	31.3

Approximately half part of the respondents was not familiar to the concept of pharmaceutical care; while more than a quarter of the public health specialists were well familiar to the concept of pharmaceutical care (See fig.6).

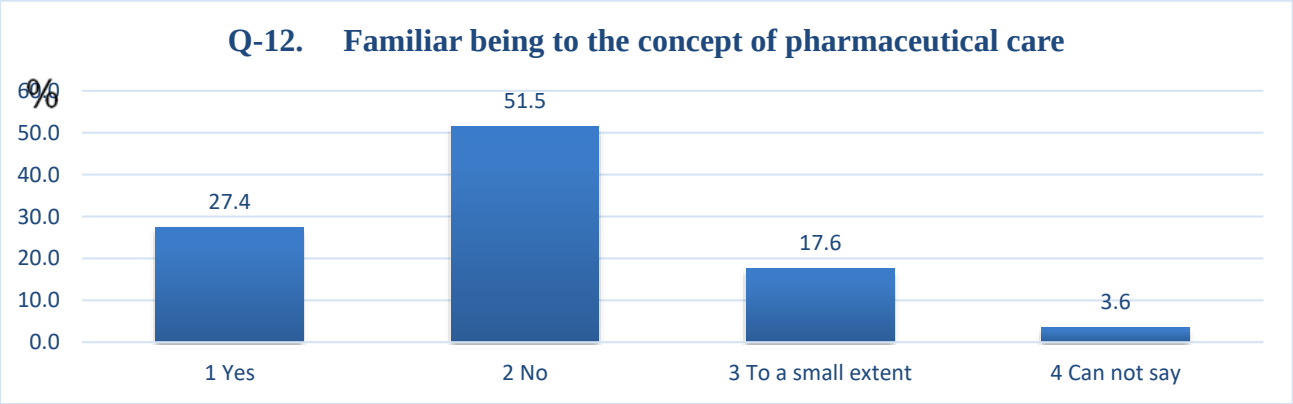


Figure 6. The respondents' (public health specialists) cognition of the concept of pharmaceutical care.

The respondents' majority considered that the pharmacists' functions in a pharmacy consisted in realization of drugs and instruments of medical purpose and providing information about drugs to the population. Less than half part of the respondents considered it to be in ultimate care about the patients' health and wellness, the drugs dosage and dispensing. About one third part of the public health specialists considered it to be in creation, development, production and sale of drugs, medical devices, instruments for medical purposes and healthcare products. About one third of the health specialists considered the pharmacists to be experts of drugs; about one third of them – to be inform of customers in cost-effectiveness and cost-benefits of drugs, the rest part of them considered that pharmacists help in selection of analogue of drugs (See tabl.2). According to that pharmacist job should become regulated and more authorized in health care system [66-67].

Table 2. The public health specialists' opinion about the pharmacist's functions in pharmacy.

Functions performed by pharmacists in pharmacy (no more than 5 answers)	Count	Percent %
1. Realization of drugs and tools (instruments) of medical purpose	164	53.4
2. Creation, development, production and sale of drugs, medical devices, instruments for medical purposes and healthcare products	110	35.8
3. Providing information about drugs to the population	165	53.7
4. Pharmaceutical care	77	25.1
5. Experts of drugs	102	33.2

6. Ultimate care about the patients' health and wellness	131	42.7
7. Dosage and dispensing of drugs	124	40.4
8. Informing the customers in pharmacotherapy direction	107	34.9
9. Informing the customers in cost-effectiveness and cost-benefits of drugs	88	28.7
10. Helping customers in offering or selection of OTC drugs	77	25.1
11. Informing the customers about drug design and drug forms	37	12.1
12. Informing the customers about drugs' generic, chemical and brand name	39	12.7
13.Informing the customers about drugs' effectiveness, safety and toxic effects	66	21.5
14. Informing customers about routes of drug administration	30	9.8
15. Informing customers about rules of drug administration	35	11.4
16. Helping in selection of analogue of drugs	97	31.6

Clinical Pharmacy defines that as the health specialty that characterizes the activities of clinical pharmacists and the provision of health services, clinical pharmacists promote and develop rational and appropriate pharmacotherapy, the rational use of pharmaceutical manufacturing and medical devices. The practice of clinical pharmacy includes knowledge of pharmacotherapy, pharmaceutical care and first aid; it combines leadership in health care with specific therapeutic knowledge, understanding, cognition, learned habits and assessment to ensure rational and optimal treatment outcomes for patients. Likewise, pharmaceutical care and clinical pharmacy are closely related concepts, although there are differences between professional development structures that determine specificity. Clinical pharmacy includes the theoretical knowledge and understanding, practical skills, values and attitudes needed by pharmacists to promote healthcare and pharmaceutical services to individual patients and populations [68-71].

Conclusion

To provide contribution and assistance in teaching of patients to understand the prescribed drugs intake rules, pharmacists need in deep knowledge in basics of medicine, pharmacology, pharmacotherapy, pharmaceutical chemistry, pharmaceutical care, clinical pharmacy and other pharmaceutical disciplines. Properly educated pharmacists have great importance and value for the provision higher quality health care services, for the provision higher quality pharmaceutical care and very essential for patient's safety. About half part of the respondents considered that pharmacist is not responsible for registration of adverse effects of the drugs, while less than a third part of them considered pharmacist to be responsible for that (See fig.7). By legislation one of the functions of pharmacist is to register the side effects of drugs, what is very essential for patients' safety. It should increase the awareness of pharmacist as the health professional.

REFERENCES

1. N. Kvizhinadze, D. Tophuria, N. Intskirveli, N. Sulashvili; Study of Factors Affecting on Population's Health Improvement.Caucasus Journal of Health Sciences and Public Health; E ISSN 2449-2450; ISSN 2449-2647; The University of Georgia Publishing House. www.caucasushealth.ge; Official Journal of the University of Georgia and Iv. Javakhishvili Tbilisi State University with Support of the Arctic University of Tromsø/Norway. Volume 4, Supplement 8, July 20-24, 2020; Pp 42-45.

2. Sulashvili, N., Beglaryan M. Professional features for employed pharmacy faculty students in Georgia. // The New Armenian Medical Journal Supplement. YSMU Science Week 2017 Conference. November 27-December 1, Vol.11, №3, 2017, Yerevan, Armenia, p. 40.
3. Sulashvili, N., Beglaryan M. Vocational peculiarities of young pharmacist professionals// International scientific journal Intellectual. №35, 2018. Tbilisi, Georgia. pp. 96-104.
4. Sulashvili, N., Beglaryan M., Gogashvili M., Matoshvili M. Occupational particularities and strategy of Pharmacy faculty students. // Experimental and Clinical Medicine, Scientific-Practical Journal. №3, 2018. Tbilisi, Georgia. pp. 15-24.
5. Sulashvili, N., Beglaryan M., Matoshvili M. Occupational features of pharmaceutical workers, viewed by the chief pharmacists// Caucasus Journal of Health Sciences and Public Health. Volume 2, Issue 2, June 2018.Tbilisi-Georgia. pp.56-61.
6. Sulashvili, N., Beglaryan M., Sulashvili M. Personal features, capabilities and skills of job adaptation for pharmacist specialists. //Tbilisi David Agmashenebeli University Periodical Scientific Journal №13, 2018. Tbilisi, Georgia. pp. 231-236.
7. Sulashvili N., Beglaryan M., Kvijinadze N., Matoshvili M. Vocational training and activity of pharmacists in Georgia. // Georgian Medical News. № 5 (278), May 2018. Tbilisi - New York. pp.199-206.
8. N. Sulashvili, M. Beglaryan; Pharmacist Occupational Features, Regulations Framework and Profession Enhancement Challenges of Pharmaceutics.Caucasus Journal of Health Sciences and Public Health; E ISSN 2449-2450; ISSN 2449-2647; The University of Georgia Publishing Official Journal of the University of Georgia and Iv. Javakhishvili Tbilisi State University with Support of the Arctic University of Tromsø/Norway. Volume 4, Supplement 8, July 20-24, 2020; Pp 31-36.
9. N. Kvizhinadze, D. Tophuria, N. Intskirveli, N. Sulashvili; Study of Factors Affecting on Population's Health Improvement.Caucasus Journal of Health Sciences and Public Health; E ISSN 2449-2450; ISSN 2449-2647; The University of Georgia Publishing House. www.caucasushealth.ge; Official Journal of the University of Georgia and Iv. Javakhishvili Tbilisi State University with Support of the Arctic University of Tromsø/Norway. Volume 4, Supplement 8, July 20-24, 2020; Pp 42-45.
10. Characteristics of pharmacist activity, viewed by the customer's / N. Sulashvili. M. Beglaryan //International Science and Innovation Festival 2017. Conferences "Healthy Lifestyle-Scientific Evidence and Controversial issues" and "Innovation in Medicine" Tbilisi State Medical University. September 2017. Tbilisi, Georgia, p. 30-31.
11. Professional features for employed pharmacy faculty students in Georgia / N. Sulashvili, M. Beglaryan // The New Armenian Medical Journal Supplement. YSMU Science Week 2017 Conference. November 27-December 1**,** Vol.11, №3 2017, Yerevan, Republic of Armenia, p. 40.
12. Nodar Sulashvili. Peculiarities Of Professional And Career Improvement Strategy For Pharmacists Republic of Armenia Ministry Of Education And Science; Yerevan State Medical University After M. Heratsi; Abstract of The Dissertation For The Scientific of PhD In Pharmaceutical Sciences; On Specialty 15.00.01 – Pharmacy; The Specialized Council 026 "Theoretical Medicine" of The Supreme Certifying Committee Of The Republic Of Armenia At The Yerevan State Medical University. YEREVAN – 2019; Pp 1-26.
13. N. Sulashvili, N. Alavidze, N. Abuladze, N. Kvizhinadze, M. Gogashvili, M. Beglaryan. Pharmaceutical professional and organizational issue aspects in Georgia. Materials of 12th

Scientific and Practical Internet Conferences, The National University of Pharmacy, Scientific and Practical Internet-Conference: «Pharmacoeconomics in Ukraine, Condition and Development Prospects», (Kharkiv, Ukraine, May 22, 2020 Year). Pp 11-20.

14. N. Sulashvili; PECULIARITIES OF PROFESSIONAL AND CAREER IMPROVEMENT STRATEGY FOR PHARMACISTS REPUBLIC OF ARMENIA MINISTRY OF EDUCATION AND SCIENCE; YEREVAN STATE MEDICAL UNIVERSITY AFTER M. HERATSI; ABSTRACT of the dissertation for the scientific degree of Ph.D. in Pharmaceutical Sciences; On specialty 15.00.01 – Pharmacy; The Specialized Council 026 "Theoretical Medicine" of the Supreme Certifying Committee of the Republic of Armenia at the Yerevan State Medical University. YEREVAN – 2019; Pp 1-26.
15. N. Sulashvili; PECULIARITIES OF PROFESSIONAL AND CAREER IMPROVEMENT STRATEGY FOR PHARMACISTS REPUBLIC OF ARMENIA MINISTRY OF EDUCATION AND SCIENCE; YEREVAN STATE MEDICAL UNIVERSITY AFTER M. HEARTS; DISSERTATION; Dissertation for the Scientific Degree of Ph.D. in Pharmaceutical Sciences; On specialty 15.00.01 – Pharmacy; YEREVAN – 2019; Pp 1-175;
16. N. Sulashvili, M. Beglaryan, I. Zarnadze, Sh. Zarnadze, N. Alavidze, N. Abuladze, J. Cheishvili, N. Kvizhinadze.VOCATIONAL PERSPECTIVES AND THE MAIN PROFESSIONAL OPPORTUNITIES AND CHALLENGES OF PHARMACY FACULTY STUDENTS IN GEORGIA.УДК: 615.014.2:615.2 НФаУ, 2020. Scientific Publication. The collection of MATERIALS of the V International Scientific and Practical conference- "TECHNOLOGICAL AND BIOPHARMACEUTICAL ASPECTS OF DRUGS DEVELOPING WITH DIFFERENT ORIENTATION OF ACTION"; MINISTRY OF HEALTH OF UKRAINE, National University of Pharmacy, Department of drug technology. 26 of November, Kharkiv, Ukraine-2020.Pp 35-51.
17. Characteristics of pharmacist activity, viewed by the customer's / N.Sulashvili. M. Beglaryan // International Science and Innovation Festival 2017. Conferences "Healthy Lifestyle-Scientific Evidence and Controversial issues" and "Innovation in Medicine" Tbilisi State Medical University. September 2017. Tbilisi, Georgia, p. 30-31.
18. Professional features for employed pharmacy faculty students' in Georgia / N.Sulashvili, M.Beglaryan // The New Armenian Medical Journal Supplement. YSMU Science Week 2017 Conference. November 27-December 1**,** Vol.11, №3 2017, Yerevan, Republic of Armenia, p. 40.
19. Schnipper JL, Kirwin JL, Cotugno MC, et al. Role of pharmacist counseling in preventing adverse drug events after hospitalization.Arch Intern Med. 2016.
20. Sulashvili N., Beglaryan M. Shashiashvili G. Medical Professional's job Satisfaction and pharmaceutical organization issues viewed by Drug Dispensers in Georgia// ISSN 1987-863X, 8th Eurasian Multidisciplinary Forum, EMF 2018, 6-7 September. Tbilisi, Georgia. pp.42-55.
21. National Matching Services. Summary results of the match for positions beginning in 2014. https://www.natmatch.com/ashprmp/ stats/2014applstats.html. Accessed March 24, 2014
22. Hassell K. Centre for Pharmacy Workforce Studies (CPWS) briefing paper: GPhC register analysis2011.http://www.pharmacy.regulation.org/sites/default/files/Analysis%20of%20GPhC%20Pharmacist%20Register%202011.pdf. Accessed April 9, 2014.

23. Pharmacist's professional features and work gratification/ N. Sulashvili; M. Beglaryan // Black sea scientific journal of academic research multidiscipline journal. (Medicine, Pharmacy sciences) Volume 29. March-April 2016. Tbilisi, Georgia, p.62-68.
24. Pharmacists' professional features, viewed by the customer's (customer's) eyes in Georgia/ N. Sulashvili, M. Beglaryan // Scientific-Practical Journal. Experimental and Clinical Medicine, №4, 2017. Tbilisi, Georgia, p. 22-25.
25. Franklin B. D.& van Mil J. W., Defining clinical pharmacy and pharmaceutical care // Pharm World Science 2005;27(3): p. 137-144.
26. N. Sulashvili; Peculiarities of professional and career improvement strategy for pharmacists' republic of Armenia ministry of education and science; Yerevan state medical university; Dissertation; Dissertation for the Scientific Degree of PhD in Pharmaceutical Sciences; On specialty 15.00.01 – Pharmacy; YEREVAN – 2019; Pp 1-175;
27. N. Sulashvili, M. Beglaryan, N. Alavidze, L. Gabunia, I. Pkhakadze, T. Okropiridze, M. Sulashvili, G. Pkhakadze; Legal and regulatory scope, and identify the main challenges and opportunities of Georgian pharmacists.REPUBLIC OF ARMENIA ISSN 1829-040X, ORCID: 0000-0001-9263-6791, BULLETIN OF THE MEDICAL INSTITUTE AFTER MEHRABYAN, VOL. 9 TOM, YEREVAN 2020, Pp 88-104.
28. Graf J, von den Driesch A, Koch K-C, Janssens U. Identification and characterization of errors and incidents in a medical intensive care unit. Acta Anaesthesiol Scand 2005;49(7):930—9.
29. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers Y-M. Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. Drug Saf 2018;41(10):919—31.
30. García-Gil M, Velayos-Amo C. Hospital pharmacist experience in the intensive care unit: plan COVID. Farm Hosp 2020;44(7):32—5.
31. Shane P. Desselle, David P. Zgarrick, Greg Alston; Pharmacy Management: Essentials for All Practice Settings // Fourth Edition; 2016,pp. 329-347.
32. Sulashvili N. The Features of Professional Career Improvement Strategy and Job Satisfaction among pharmacists // Business-Engineering Journal. - Business Engineering in Pharmacy. №2, 2014. Tbilisi, Georgia, pp. 195-199.
33. Sulashvili N., Kvizhinadze N., Maisuradze I. Pharmacist professional features in Georgia. // Conference of young scientists. Thesis collection. Georgian National Academy of Sciences. 18-19 May 2015. Tbilisi, Georgia, pp. 81-82.
34. Sulashvili N., M Beglaryan. Pharmacist mission gratification and profession improvement strategy. // Black sea scientific journal of academic research conference newsletter. (Medicine, Pharmacy sciences). Volume 26. November 2015. Tbilisi, Georgia, pp. 10-12.
35. Sulashvili, N., Beglaryan M. Pharmacist's professional features and work gratification. // Black sea scientific journal of academic research multidiscipline journal. (Medicine, Pharmacy sciences) Volume 29. March-April 2016. Tbilisi, Georgia, pp. 62-68.
36. Sulashvili, N., Beglaryan M. Pharmacists' professional features, viewed by the customer's (customer's) eyes in Georgia. // Experimental and Clinical Medicine, Scientific-Practical Journal, №4, 2017. Tbilisi, Georgia, pp. 22-25.
37. Sulashvili, N. Peculiarities of professional for pharmacists, viewed by the health-care specialists in Georgia// Experimental and Clinical Medicine, Scientific-Practical Journal. №4 2017. Tbilisi, Georgia, pp.47-51.

38. Sulashvili, N., Beglaryan M. Characteristics of pharmacist activity, viewed by the customer's//
39. International Science and Innovation Festival 2017. Conf.-es "Healthy Lifestyle-Scientific Evidence and Controversial issues" and "Innovation in Medicine" Tbilisi State Medical University. September 2017. Tbilisi, Georgia. pp. 30-31.
40. N. Sulashvili, M. Beglaryan; THE FEATURES OF THE ROLE, INNOVATIONS, OCCUPATIONAL AND EDUCATIONAL PERFECTION VISTAS OF PHARMACISTS' PROFESSION IN THE SCOPE OF THE DEVELOPMENT OF PHARMACEUTICAL CARE DIRECTION IN GEORGIA. ISSN 2521-3261 (Online); ISSN 2521-3253 (Print); DOI 10.37057/2521-3261; https://journalofresearch.eu/index.php/jreu; (EJR) European Journal of Research, Volume 7, Issue 1, 2022; Published 19-01-2022. Pages 14-25.
41. N. Sulashvili, M. Beglaryan, J. Cheishvili, I. Zarnadze, Sh. Zarnadze, T. Tsintsadze; CURRENT SCIENTIFIC RESEARCH DISCOVERY OUTCOMES OF HIGHER PHARMACY EDUCATIONAL PERSPECTIVES AROUND ON MULTIPURPOSE PHARMACIST' OCCUPATION TOWARDS MEDICINE, PHARMACEUTICS AND PUBLIC HEALTH;УДК [37:61]:001.895(063); MATERIALS OF THE ALL-UKRAINIAN SCIENTIFIC AND PRACTICAL CONFERENCE- "INNOVATIONS IN MEDICAL EDUCATION: PERSPECTIVES, CHALLENGES AND OPPORTUNITIES" WITH INTERNATIONAL PARTICIPATION; MINISTRY OF HEALTH OF UKRAINE ZAPORIZHZHYA STATE MEDICAL UNIVERSITY, 21 of January, 2022. ZAPORIZHZHYA, UKRAINE-2022; Pp:194-212.
42. N. Sulashvili, A. Aznauryan, A. T-Markosyan, N. Gorgaslidze, S. Kocharyan, I. Zarnadze, B. Yenokyan, T. Chikviladze, N. Chichoyan, L. Gabunia, Sh. Zarnadze, M. Beglaryan; MODERN SCIENTIFIC DISCUSSION OF SPECIFICITES OF THE ROLE, ACHIEVEMENTS, INNOVATIONS, PROFESSIONAL AND ENHANCEMENT PROSPECTS OF PHARMACISTS IN THE CONTEXT OF THE DEVELOPMENT OF HEALTH CARE SECTOR GLOBALLY.ISSN 1512-0392; E-ISSN 2667-9736; SCIENTIFIC-PRACTICAL JOURNAL of Experimental and Clinical Medicine №5-6; 9 of October, 2021, Tbilisi-Georgia. Pp: 38-42.
43. Thomas R. Brown; By Thomas R. Brown - Handbook of Institutional Pharmacy Practice//4th (fourth) Edition; American Society of Health-System Pharmacists (December 1, 2006); pp. 65-71.
44. Ashley W. Ells (Author), Justin Sherman; Community and Clinical Pharmacy Services // A step by step approach.; McGraw-Hill Education/Medical; 1 edition (April 30, 2013); pp. 45-156.
45. Kenneth R. Baker; Medication Safety: Dispensing Drugs Without Error // Delmar Cengage Learning; 1 edition (May 10, 2012); pp. 12-35.
46. Moore T.J., Furberg C.D., Mattison D.R., Cohen M. R. Completeness of serious adverse drug event reports received by the US Food and Drug Administration in 2014. // Pharmacoepidemiology, Drug Safety. 2016; 25(6): pp. 713–718;
47. Robert P. Navarro; Managed Care Pharmacy Practice 2nd Edition // Jones & Bartlett Learning; 2 edition (December 25, 2008); pp. 336-389.
48. World Health Organization; Quality Assurance of Pharmaceuticals 2017: WHO Guidelines, Good Practices, Related Regulatory Guidance and GXPs Training Materials // World Health Organization; 2017 edition (January 11, 2018); pp. 51-59.

49. Jeri J. Sias and Susana V. James; Spanish for the pharmacy professional (English and French Edition) // American Pharmacists Association; 1st edition (January 30, 2009); pp. 35-79.
50. The Role of the Pharmacist in Patient Care: Achieving High Quality, Cost-Effective and Accessible Healthcare Through a Team-Based, Patient-Centered Approach Paperback – July 7, 2020; pp 435-486.
51. Pharmacotherapy: Improving Medical Education Through Clinical Pharmacy Pearls, Case Studies, and Common-Sense Audible Audiobook – Unabridged Eric Christianson (Author); 2015, pp 8-29
52. Community and Clinical Pharmacy Services: A step by step approach. 1st Edition, Kindle Edition by Ashley W. Ells (Author), Justin Sherman (Author) Format: Kindle Edition;2013, pp 187-219.
53. N. Sulashvili., M. Beglaryan., O. Gerzmava., I. Zrnadze., Sh .zarnadze., N. kvijhinadze; Modern features and challenges of the pharmacist profession, viewed by the patients and public health specialists via pharmaceutical care direction in public health settings; bulletin of the medical institute after Mehrabian, vol. 9, Yerevan 2020, pp 105-120.
54. Atkinson J., Rombaut B., The 2011 PHARMINE report on pharmacy and pharmacy education in the European Union // Pharm. Pract. 2011;9: pp. 169–187.
55. Herbert K. E., Urmie J. M., Newland B. A, Farris K. B.. Prediction of pharmacist intention to provide Medicare medication therapy management services using the theory of planned behavior // Res Social Adm Pharm. 2006;2(3): pp. 299–314.
56. N. Sulashvili, M. Beglaryan, M. Sulashvili, N. Kvizhinadze, N. Kiknavelidze.JOB SATISFACTION PROPOSALS AND CHALLENGES OF GEORGIAN PHARMACISTS; UDC 001.1; ISBN 978-92-9472-197-6; Collection of scientific articles of the scientific and practical publication; Abstracts of II International Scientific and Practical Conference" THE WORLD OF SCIENCE AND INNOVATION". London, United Kingdom, 16-18 September 2020. Pp 175-190.
57. General Pharmaceutical Council. Future Pharmacists: Standards for the Initial Education and Training of Pharmacists // London: GPhC; pp. 2011.
58. Roberts A. S., Benrimoj S., Chen T.F., Williams K. A., Aslani P. Implementing cognitive services in community pharmacy: A review of facilitators used in practice change // Int. J. Pharm. Pract. 2006;14: pp. 163–170.
59. N. Sulashvili; Peculiarities of professional and career improvement strategy for pharmacists' republic of Armenia ministry of education and science; Yerevan state medical university; Dissertation; Dissertation for the Scientific Degree of PhD in Pharmaceutical Sciences; On specialty 15.00.01 – Pharmacy; YEREVAN – 2019; Pp 1-175;
60. Fred Weissman, James Pinder, Mark Berns; Pharmacy practice and tort Law,Mc Graw-Hill Education / Medical; 1 edition (February 8, 2016); pp.125-197.
61. The Role of the Pharmacist in the Health Care System. (2016). Retrieved from http://apps.who.int/medicinedocs/en/d/Jh2995e/1.3.html A World Health Organization resource.
62. Marialice S. Bennett; How to Implement the Pharmacists' Patient Care Process // American Pharmacists Association; 1 edition (March 15, 2015); pp. 38-54.
63. Kimberly A. Galt Pharm. D. FASHP, Michael Galt; Patient-Centered Care for Pharmacists; //American Society of Health-System Pharmacists; 2 editions (February 20, 2012); pp. 94-136.

64. International Pharmaceutical Federation and World Health Organization. joint FIP/ WHO guidelines on good pharmacy practice: standards for quality of pharmacy services // The Hague and Geneva: International Pharmaceutical Federation and World Health Organization, 2011.
65. Rutter P. Role of community pharmacists in patients' self-care and self-medication // Integrated Pharmacy Research and Practice. 2015; 4: pp. 57-65.
66. Michael Ira Smith, Albert I. Wertheimer, Jack E. Fincham; Pharmacy and the US Health Care System; Pharmaceutical Press // 4th Revised edition edition (April 15, 2013);pp. 402-426.
67. Kimberly A., Galt Pharm. D. FASHP and Michael Galt // Patient-Centered Care for Pharmacists; (Feb 20, 2012); pp.123-129.
68. Isett's BJ, Schondelmeyer SW, Artz MB, et al. Clinical and economic outcomes of medication therapy management services: the Minnesota experience. J Am Pharm Assoc (2003). 2018.
69. Westerlund T., Björk H.T. Pharmaceutical care in community pharmacies: Practice and research. // Ann. Pharmacother. 2006; 40: pp.1162–1169.
70. Chisholm-Burns M. A, Lee J. K, Spivey C. A, et al. U.S. pharmacists' effect as team members on patient care: systematic review and meta-analysis // Med Care. 2010; 48(10): pp. 923-33.
71. Colleen Doherty Lauster, SnehaBaxiSrivastava; Fundamental Skills for Patient Care in Pharmacy Practice // Jones & Bartlett Learning; 1 edition (April 8, 2013). pp. 115-157.

THE SPECIFICITIES ON PHARMACOLOGICAL EFFECTS OF U-II RECEPTOR ANTAGONIST – PALOSURAN EFFECTING ON SERUM ELECTROLYTES, SYSTEMIC BLOOD ARTERIAL PRESSURE AND CARDIAC MYOCARDIAL TISSUE IN LABORATORY RATS WITH EXPERIMENTAL HYPERTENSION

Albina Kajaia[1] , Luiza Gabunia[2], Ketevan Ghambashidze[3], Levan Ratiani[4], Nodar Sulashvili[5], Nino Gogokhia[6], Makrine Mirziashvili[7]

[1]MD, PhD Student of Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia;
[2]MD, PhD, Doctor of Medical Sciences, Professor, Director of the Scientific Research-Skills Center at Tbilisi State Medical University, Professor of the Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia;
[3]MD, PhD, Doctor of Medical Sciences, Professor of Department of Pathological Physiology at Tbilisi State Medical University, Invited Professor-Lecturer of Scientific Research-Skills Center of Tbilisi State Medical University Tbilisi, Georgia;
[4]MD, PhD, Doctor of Medical Sciences, Professor, General Director of the First University Clinic of Tbilisi State Medical University, Head of the Department of Emergency Medicine, Reanimatology and Anesthesiology at Tbilisi State Medical University, Tbilisi, Georgia;
[5]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Invited Professor-Lecturer of Scientific Research-Skills Center of Tbilisi State Medical University, Tbilisi, Georgia; Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Associate Professor of Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Tbilisi, Georgia; Invited Professor of the University of Georgia, School of Health Sciences, Tbilisi, Georgia.
[6]MD, PhD, Doctor of Medical Sciences, Professor, Head of the Laboratory of the First University Clinic of Tbilisi State Medical University, Tbilisi, Georgia;
[7]MD, PhD, Doctor of Medical Sciences, Assistant Professor of Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia, Tbilisi, Georgia;
Email: n.sulashvili@ug.edu.ge

ABSTRACT

This article discusses the effect of treatment with the U-II receptor antagonist palosuran on systemic blood pressure and myocardial tissue in hypertensive laboratory rats using the Goldblatt method (2 kidneys + 1 clamp). Palosuran was administered intraperitoneally (10 mg/kg once daily) 4 and 8 weeks after hypertension modeling. The blood pressure was measured non-invasively (in the tail) according to the Till-Zeff method using a blood pressure measuring system-systole. For the morphological examination, paraffin spots of the myocardial tissue were stained with hematoxylin and eosin. It has been shown that palosuran has an antihypertensive effect in both healthy and hypertensive rats, which is explained by its antagonistic effect on urotensin II receptors and thus a vasodilating effect. With early treatment, no left ventricular hypertrophy was detected in the myocardium of the hypertensive rat compared to the myocardium of the untreated rat, while with late treatment the left ventricular hypertrophy was mild. We can say that treatment with palosuran together with lowering blood pressure in rats significantly reduces the stress on the myocardium and thus the expected complications. Based on the results obtained, we can say that palosuran shows an antihypertensive effect in both healthy and hypertensive rats. With early treatment, no left ventricular hypertrophy was detected in the myocardium of the hypertensive rat compared to the myocardium of the untreated rat, while with late treatment the left ventricular hypertrophy was mild, then treatment with Palosuran Lab. Rats. Together with lowering the blood pressure in rats, it significantly reduces the stress on the myocardium and thus the complication to be expected. Based

on the results of the experiments it could be concluded that palosuran shows a blood pressure lowering effect in the laboratory in the early stages of hypertension. Rats with renovascular hypertension caused significant changes in serum Na^+ and K^+ levels, with the exception of serum Ca $^{++}$ concentration. Palosuran significantly reduced the concentration of Na + and K + in the blood serum of rats with hypertension. The Na^+ and K^+ concentrations were maintained within normal limits even after administration of L-NAME, with the exception of late initiation of treatment. It is known that palosuran has an antagonistic effect on urotensin-II (U-II) receptors, which leads to a decrease in the vasoconstrictor effect of U-II. As shown in the literature, U-II induces active NO production in low doses (by activating NO synthase) and therefore causes vasodilation as an endothelin-dependent vasodilator. This phenomenon can explain the pronounced decrease in SBP in all groups of experimental animals examined. In treatment started at a late stage of arterial hypertension, the antihypertensive effects of palosuran were less pronounced, which is explained by the fact that the hypertensive effect on the blood vessels increases the production of U-II and enhances the endothelial independent vasoconstrictors effect of Urotensin. After treatment with palosuran, blood pressure decreased significantly in all study groups. The antihypertensive effect of palosuran was demonstrated in both cases, both with early treatment (start after 4 weeks of modeling renovascular hypertension) and with relatively late treatment (start after 8 weeks of modeling renovascular hypertension). hypertension) of rats with high blood pressure.
Keywords: Pharmacological, U-II receptor antagonist, cardiac, hypertension, palosuran, myocardium, rats.

Introduction

The goals of antihypertensive treatment are to prevent the onset/progression/ recurrence of cardiovascular disease associated with persistent high blood pressure, reduce mortality, and help high blood pressure patients lead a normal life like healthy people [1,2]. Prescribing antihypertensive drugs to achieve the recommended target blood pressure remains the most important step in the management of patients with high blood pressure. Medicines targeting blood pressure must be well tolerated, economically available, and easy to take in order to maintain long-term resistance [3,4,5].

There are currently four main classes of antihypertensive drugs: diuretics, calcium channel blockers, renin-angiotensin system (RAS) inhibitors, and beta blockers [6,7]. Despite their ability to lower blood pressure, dramatically improve the long-term prognosis of the patient, and reduce cardiovascular outcomes, it is important to consider the safety profile of antihypertensive drugs, as safety is a key factor in compliance with long term and side effects [8,9,10]. For example, diuretics/thiazides can cause hyponatremia, hypokalemia, hyperuricemia, high cholesterol and LDL cholesterol, serum creatinine / urea, and risk of diabetes. Patients may experience weakness, muscle cramps, impotence, and gout attacks [11,12]. Anti-aldosterone diuretics can cause dizziness, drowsiness, allergic reactions, sexual dysfunction, nausea, vomiting, and hyperkalemia. ACE inhibitors cause persistent dry cough, angioedema, dry mouth, nausea, rash, hyperkalemia, increased serum creatinine levels [13,14,15]. Hyperkalemia, elevated serum creatinine, nausea, dry mouth, and abdominal pain are common manifestations of angiotensin receptor antagonists. Calcium/dihydropyridine antagonists cause peripheral edema, headache, flushing, palpitations, constipation, nausea, and gingival hyperplasia. Beta-blockers increase the risk of diabetes, increase triglycerides, lower HDL cholesterol, worsen asthma, cause fatigue, insomnia, nightmares, decreased exercise, rash, and weight seizures [16,17,18]. Thus we can say that the problem of effective

treatment of arterial hypertension has not lost its relevance and its solution in a given clinical situation often remains very difficult [19,20].

Analyzes the effect of treatment with the U-II receptor antagonist palouran on systemic blood pressure and myocardial tissue in hypertensive laboratory rats using the Goldblatt method (2 kidneys + 1 clamp). Palosuran was administered intraperitoneally (10 mg/kg once daily) 4 and 8 weeks after modeling hypertension. Blood pressure was measured noninvasively (on the tail) using the Till-Zuff method using the Systola sphygmomanometer system. For morphological examination, paraffin stains of myocardial tissue were stained with hematoxylin and eosin. Palosuran has been shown to have an antihypertensive effect in normal and hypertensive rats, which is explained by its antagonistic effect on urotensin II receptors and therefore its vasodilating effect. With early treatment, no left ventricular hypertrophy was detected in the myocardium of hypertensive rats compared to untreated rats, whereas with late treatment left ventricular hypertrophy was mild. It can be said that treatment with palosuran, together with lowering blood pressure in rats, significantly reduces the load on the myocardium and, consequently, the expected complications.

Vasoconstriction is mediated by smooth muscle cell receptors (SMCs) and appears to be variable and highly dependent on the vascular bed, while vasodilation is mediated by the endothelium [21-22]. However, in a painful state of chronic heart failure or essential hypertension, U-II loses its ability to expand [23]. It is clear that this loss and dysfunction of endothelial cells contributes to a contractile response to relaxation [24,25].

Elevated U-II levels and overexpression of urotensin receptors (UTRs), which are found in high blood pressure, heart failure, diabetes, portal hypertension, and kidney failure, suggest that the U-II / UTR system plays an essential role in their appearance. Diseases could play a role. [26,27]. In this regard, the study of UTR antagonists in the treatment of hypertension and other conditions associated with hypertension appears interesting and promising [28,29].

Palosuran, a promising non-peptide UTR antagonist for drug development, was developed to inhibit U-II calcium accumulation and mitogen-activated protein kinase phosphorylation. Data on the use of palozuran in hypertensive patients are scarce in the literature and are mutually exclusive [30,31]. In rat models of acute renal failure and diabetes, palozuran significantly improved renal function, reduced tubular and tubulointerstitial damage, and improved survival [32,33,34].

The interaction between U-II and UT leads to the activation of phospholipase C and the release of inositol (1,4,5) triphosphate [Ins (1,4,5) P3]. Interact with Ins (1,4,5) P3 a receptor located in the endoplasmic / sarcoplasmic reticulum for the release of Ca^{2+} from intracellular deposits, leading to tissue-dependent reaction [35,36,37]. In the cardiovascular system, yes the receptor is located in the cardiomyocytes, increased Contractility is expected. In the vascular system, Constrictor and expander responses were re-recorded. the receptor is located on a vascular or smooth muscle cell Endothelium or endothelial activation Nitric oxide synthase Ca2-dependent increase Nitric oxide, which penetrates the blood vessels gently [38,39].Vasodilation muscle. In contrast to most transport molecules the binding of U-II to its receptor is essentially irreversible; this has been reported for recombinants and native UT. This restrictive irreversibility is probably related to in the presence of a highly conserved cyclic hexapeptide Basic [40]. The irreversibility of the link has important consequences for regulating receiver-controlled signals. Under "normal" Under certain conditions it is likely that the receptor peptide system functionally noiseless [41,42].

The non-peptide UT-II antagonist palosuran was developed to inhibit calcium accumulation and phosphorylation of U-II-induced mitogen-activated protein kinase. Data on the use of palosuran in people with high blood pressure are rare and mutually exclusive [43,44].

The study was designed to investigate the effect of the urotensin-2 receptor antagonist palosuran on blood pressure and serum electrolytes in laboratory rats with renovascular hypertension (2 kidneys + 1 clamp) and to determine possible changes in sodium, potassium and calcium levels [45,46].

Studies have shown that palosuran lowers mean arterial pressure in renovascular hypertensive rats. The vasodilator effect of palosuran is superior to the inhibitory effect of L-NAME on NO and the endothelium-independent vasoconstrictor effect induced by urotensin, especially in the early stages of hypertension [47,48]. The antihypertensive effects of palosuran were less pronounced when treatment was started relatively late. It is believed that the damaging effect of high blood pressure on blood vessels increases the production of U-II and enhances the endothelial-independent vasoconstrictive effect of urotensin [49,50].

Elevated U-II levels and over expression of the urotensin receptor (UTR) found in high blood pressure, heart failure, diabetes, portal hypertension, and kidney failure suggest that the U-II / UTR system has a critical role in the development of these Diseases could play [51,52,53]. With this in mind, the study of UTR antagonists in the treatment of hypertension and other conditions associated with hypertension appears to be interesting and promising. Palosuran is a non-peptidic UTR antagonist with drug discovery potential designed to inhibit calcium accumulation by U-II and the phosphorylation of mitogen-activated protein kinase. The literature data on the use of palosuran in patients with hypertension are rare and mutually exclusive [54,55,56]. In rat models of acute kidney failure and diabetes [57,58].

The U-II / U system can be involved in the pathogenesis of these diseases [59]. However, its role is not fully understood. It is logical and interesting to study the effect of antagonists of the U-II / UT system as effective antihypertensive agents and complications caused by arterial hypertension (myocardial hypertrophy, heart and kidney failure) [60,61].

In recent years, researchers' interest in the cyclic vasoactive neuropeptide urotensin-II (U-II) has increased significantly. As a regulator of vascular tone, U-II is involved in many physiological and pathological processes [62,63,64]. U U-II binds to the U receptor (U), activates the G protein (GP-14) and induces the activation of the inositol triphosphate cycle by activating phospholipase C [65,66]. U-II is a more potent vasoconstrictor than endothelin-1, vasopressin, and vasoconstrictor prostaglandins. U-II acts as an endothelium-independent vasoconstrictor and endothelium-dependent vasodilator [67,68]. However, in the case of pathology, this vasodilator-vasoconstrictor balance is disturbed, therefore U-II is considered a potential trigger for the development of pathological processes [69,70].

According to the World Health Organization, arterial hypertension is the most common disease of the cardiovascular system worldwide, killing around 26% of the population and making 64 million people disabled every year. Despite the wide range of antihypertensive drugs available on the global pharmaceutical market, the treatment of arterial hypertension remains an urgent problem due to the side effects of existing antihypertensive drugs, all of which are the basis for the development of new drugs with fundamentally different mechanisms of action [70,71,73].

The results obtained showed a significant difference between healthy rats with and without hypertension in the blood electrolytes. In the early stages of modeling the disease, Palosuran significantly reduced serum Na + concentration and increased K + concentration in hypertensive rats. The Na + and K + concentrations were also kept within normal limits after administration of L-NAME, with the exception of a late start on treatment. In conclusion, palosuran may represent a new treatment option for people with early-stage hypertension. In view of all of this, we found it

interesting to investigate the effect of the UTG antagonist palosuran on the heart and kidney tissue in laboratory rats under conditions of experimental arterial hypertension.

High blood pressure is a serious disease that greatly increases the risk of heart, brain, kidney and other diseases. Today, high blood pressure is considered the most common cause of cardiovascular disease in the world. An estimated 1.13 billion people worldwide have high blood pressure, most of whom (two-thirds) live in low-and middle-income countries [74,75,76].

Despite the efficacy of currently available antihypertensive drugs, there is still a need for new treatment strategies that are more effective in certain groups of hypertensive patients.

It has been suggested that the urotensine system plays an important role in the pathophysiology of arterial hypertension. Urotensin II, as the most potent known vasoconstrictor in mammals [77], is activated in arterial hypertension. Plasma urotensin II was increased in hypertensive patients compared to a control group with normal blood pressure and was directly related to systolic blood pressure. These data increase the likelihood that urotensin II (U-II) may play an etiologic role in hypertension and its complications [76,78].

Materials and methods

The studies were carried out on male laboratory rats (Wistar breed, weight - 200-250 g). To obtain an experimental model of arterial hypertension, we used the so-called renovascular. H. Goldblatt's method (2 kidneys + 1 clamp).

Under general anesthesia (Nembutal - 50 mg/kg) the left kidney was exposed in the retroperitoneal area; Then we separated the renal artery from the vein and nerve. Renal ischemia was induced by a chrome clip with dosed ligation of the artery (diameter 0.2 mm).

Intraperitoneal administration of Palosuran at a dose of 10 mg/kg once a day for 4 weeks was started in the studied rats 4 and 8 weeks after the development of the model of hypertension. The animals were divided into 3 groups: I - group (healthy, intact rats); Group II (rats with arterial hypertension, in which the intraperitoneal administration of Palosuran was started 4 weeks after the development of the hypertension model); Group III (diseased rats in which Palosuran was administered 8 weeks after model development).

In rats, systemic blood pressure was measured once a week for 12 weeks using a non-invasive (tail) tail-cuff method using a systolic blood pressure measurement system. After that, mean arterial pressure was calculated.

Tissue samples were examined in a 10% solution of neutral formalin to examine the morphological picture of the myocardium. 3-5 microns. The thicknesses of the paraffin lumps were stained with hematoxylin and eosin. The samples were examined under a digital microscope.

The data obtained were processed with a statistical program - SPSS-20. The Student t-test was used to compare the control and experimental group data. Reliability coefficient $p < 0.05$.

Research results and discussion

Based on the experiments carried out on laboratory rats at different stages of renovascular arterial hypertension, a change in mean arterial pressure (MAP) was revealed in comparison with the normal values (Table N1). In particular, 1 week after modeling arterial hypertension, SBP did not change statistically significantly; after 2 weeks, SBP increased statistically significantly by 24% ($P < 0.05$); After 4 weeks - statistically increased by 42% ($p < 0.02$); After 8 weeks, there was a statistically significant increase in SBP by 44% ($p < 0.02$), and after 12 weeks - by 53% ($p < 0.001$);

In healthy rats, the SBP decreased statistically significantly by 33% after administration of palosuran (p <0.02); Under the influence of LNAME, against the background of palosuran, there was a tendency towards an increase in SBP of 23% compared to rats that received only palosuran, while a decrease that was not statistically significant when compared to healthy rats that received no treatment of the SBP by 17%.

In rats with hypertension as a result of 4 weeks of treatment starting 4 weeks later, 8 weeks after disease modeling, the effects of palosuran resulted in a statistically significant decrease in SBP of 32% (p <0.001).

Under the influence of L-NAME against the background of palosuran, an increase in SBP of 18% was observed compared to rats that received only palosuran, while it was statistically significantly reduced by 20% compared to untreated rats (p <0, 02).

In rats with arterial hypertension, against the background of a 4-week treatment begun in the 8th week, in the 12th week after the modeling of the disease, under the influence of palosuran, the SBP was reduced relatively less, but statistically significant - by 23% (p <0.02). Against the background of palosuran under the influence of L-NAME, there was a tendency for the SBP to increase by 16% compared to rats given only palosuran, while the blood pressure was statistically insignificant by 10% compared to the data obtained in treated rats.

Table 1. Changes in mean arterial pressure (MAP) in healthy and hypertensive rats against the background of the action of palosuran at different stages after modeling the disease.

N	Experimental groups	SBP	
		Untreated	P|+ Palosuran
1	Healthy rats	95 ±3,1	64±3,0**
2	1 week after hypertension modeling	97±3,5	
3	2 weeks after hypertension modeling	118±4,1*	-
4	3 weeks after hypertension modeling	101 ±9,2	-
5	4 weeks after modeling hypertension	135 ± 10,0**	-
6	5 weeks after hypertension modeling	137± 8,3**	93 ± 5,5***
7	6 weeks after hypertension modeling	145 ± 10,0***	112± 7,2**

*- p<0.05; **- p<0.01; ***- p<0.001

As the results of the study show, after 1 week after modeling hypertension, only a tendency towards an increase in SBD was observed, while after 2 weeks a statistically significant increase in pressure was observed. After 4 weeks there was a stable, reliable and progressive increase in blood pressure - arterial hypertension developed.

The rise in blood pressure in renovascular hypertension is caused by ischemia, hypoxia, activation of the renin-angiotensin-aldosterone system (RAA) in the clipped kidney and consequent severe peripheral vasoconstriction and water retention. After the first manifestation of an increase in blood pressure after about 2 weeks, the transient normalization of blood pressure is probably associated with the activation of compensatory mechanisms of the second kidney, which implies a change in the renin concentration and an inhibition of the RAAS. After 4 weeks, however, laboratory rats developed severe hypertension due to the complex action of the RAS and activation of the sympathetic nervous system. The latter further increases renin production and peripheral vasoconstriction.

A statistically significant decrease in blood pressure was observed in all groups examined under the influence of palosuran. The antihypertensive effect of palosuran was shown both in early treatment (after 4 weeks of modeling) and in a relatively late stage of treatment (8 weeks of modeling).
It is known that palosuran has an antagonistic effect on urotensin-II (U-II) receptors, which leads to a decrease in the vasoconstrictor effect of U-II. As shown in the literature, U-II induces active NO production in low doses (by activating NO synthase) and therefore causes vasodilation as an endothelin-dependent vasodilator. This phenomenon can explain the pronounced decrease in SBP in all groups of experimental animals examined [16].
In treatment started at a late stage of arterial hypertension, the antihypertensive effects of palosuran were less pronounced, which is explained by the fact that the hypertensive effect on the blood vessels increases the production of U-II and enhances the endothelial independent vasoconstrictors effect of Urotensin [19, 18;].
After treatment with palosuran, blood pressure decreased significantly in all study groups. The antihypertensive effect of palosuran was demonstrated in both cases, both with early treatment (start after 4 weeks of modeling renovascular hypertension) and with relatively late treatment (start after 8 weeks of modeling renovascular hypertension). hypertension) of rats with high blood pressure.
Palosuran is known to have an antagonistic effect on U-II receptors, which reduces the vasoconstrictor effect of U-II. According to the literature, low doses of U-II induce active production of NO (by activating NO synthase) and therefore vasodilation as an endothelium-dependent vasodilator. This phenomenon may explain the decrease in SBP in all groups of laboratory animals examined [30].

Table 2. Effects of Palosuran and L-NAME on serum electrolytes (mmol/L) in healthy and hypertensive rats at different stages of hypertension

.

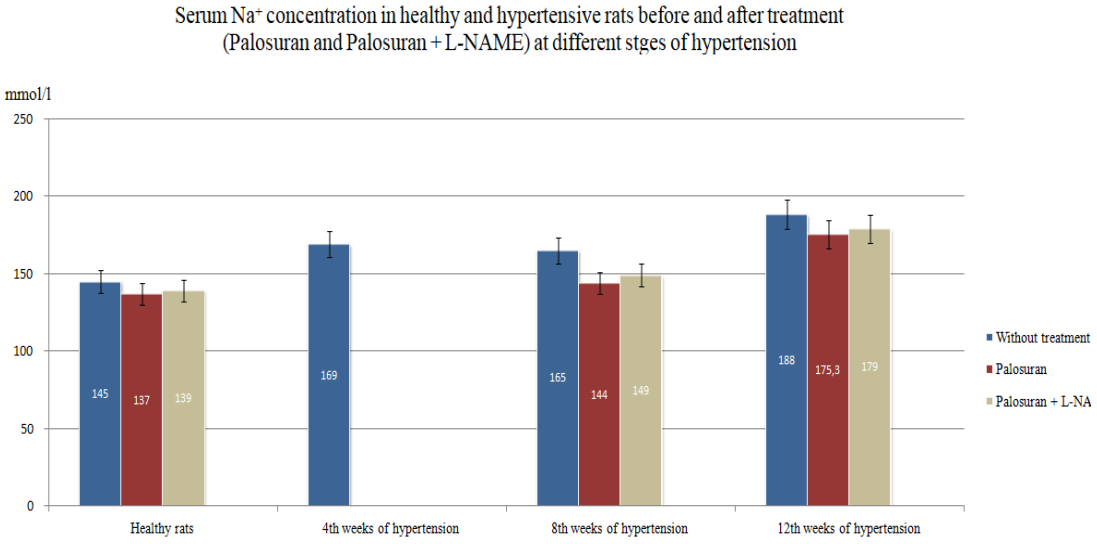
	Groups	Without treatment			+ Palosuran			Palosuran + L-NAME		
		Na^+	K^+	Ca^{++}	Na^+	K^+	Ca^{++}	Na^+	K^+	Ca^{++}
1	Healthy rats	145,2	4,5	9,2	137,0	4,9	9,24	139,1	5,0	9,25
2	4th week of hypertension	169,1**	4,1	9,0	-	-	-	-	-	-
3	8th week of hypertension	165,0**	4,3	9,1	144,1**	4,88*	9,25	149,0*	4,6	9,22
4	12th week of hypertension	188,1***	3,0**	9,22	175,3	3,2	9,22	179,1	3,1	9,24

-** $p<0.05$; * -** $p<0.01$; ***** -** $p<0.001$

In healthy rats after administration of Palosuran decrease in serum Na^+ by 6,5% was not statistically significant. The same, unreliable alterations in Na^+ concentrations were detected in rats treated with Palosuran after administration of L-NAME. Serum Na^+ was increased by 1,5% and compared with the results of untreated rats serum Na^+ was decreased by 4,1% ($p>0,05$).
Administration of L-NAME in Palosuran treated animals revealed tendency of increase in Na^+ by 2%. It was not statistically different also compared to the results of untreated rats and significantly increased by 28,8% ($p<0,001$) compared to the results of healthy group animals.

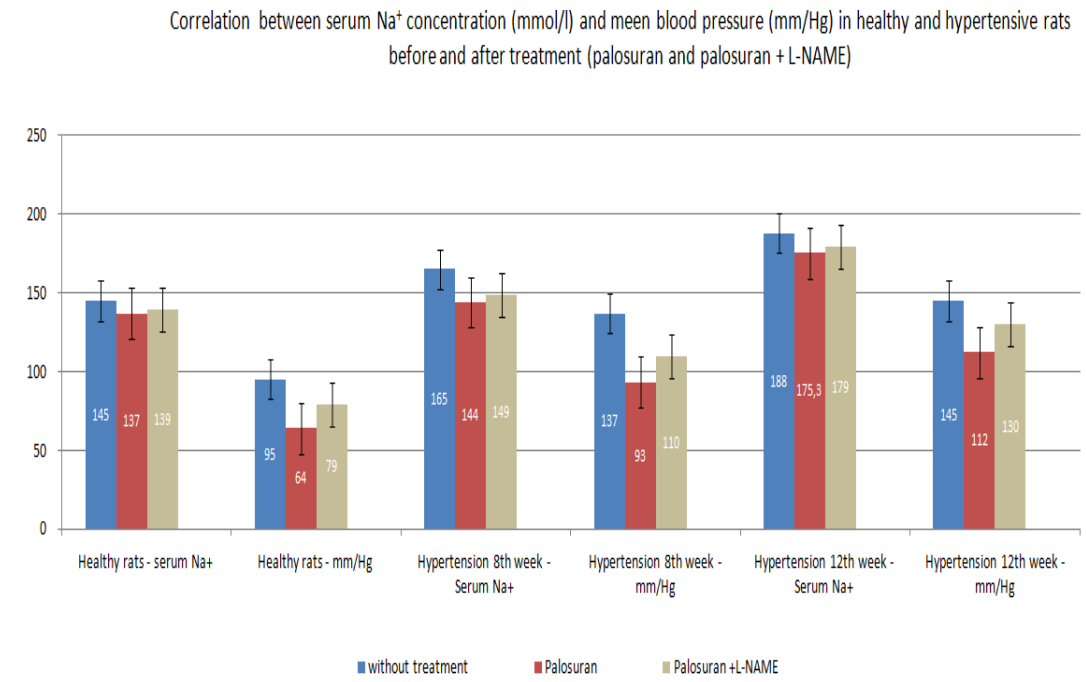
In healthy rats, a 6.5% decrease in serum Na + after administration of palozuran was not statistically significant. Similar unreliable changes in Na + concentrations were observed in palosuran-treated rats following administration of L-NAME. Serum Na + increased by 1.5%, and compared to results obtained in untreated rats, serum Na + decreased by 4.1% (p> 0.05).
After 4, 8 and 12 weeks of disease modeling in rats with essential hypertension, there was a gradual and significant increase in serum Na + levels of 17%, 14% (p <0.01) and 30 % (p <0.001), respectively. data from healthy rats. Although the serum Na + level increased by 14% (p <0.001) after 8 weeks of disease modeling, it was 3% lower than data obtained after the 4th week of disease modeling.
After the 8th week of hypertension in rats given serum with palozuran, Na + decreased by 13% (p <0.01), and only an increasing trend of 5% was observed from the data. healthy rats.
Administration of L-NAME to rats receiving palosuran showed a tendency of Na + to increase by 3.5% and decrease by 10% (p <0.05) compared to untreated animals.
After 12 weeks of disease modeling in hypertensive rats, treatment with palozuran showed a tendency for the Na + concentration to decrease by 7% compared to data for untreated rats. And it was increased by 21.7% (p <0.001) compared to the results obtained after 4 weeks of hypertension in the treated rats.
Administration of L-NAME to animals receiving palosuran showed a tendency to increase Na + by 2%. It also did not differ statistically from results in untreated rats and was significantly increased by 28.8% (p <0.001) compared to results in healthy animals in the group.

Graph 1

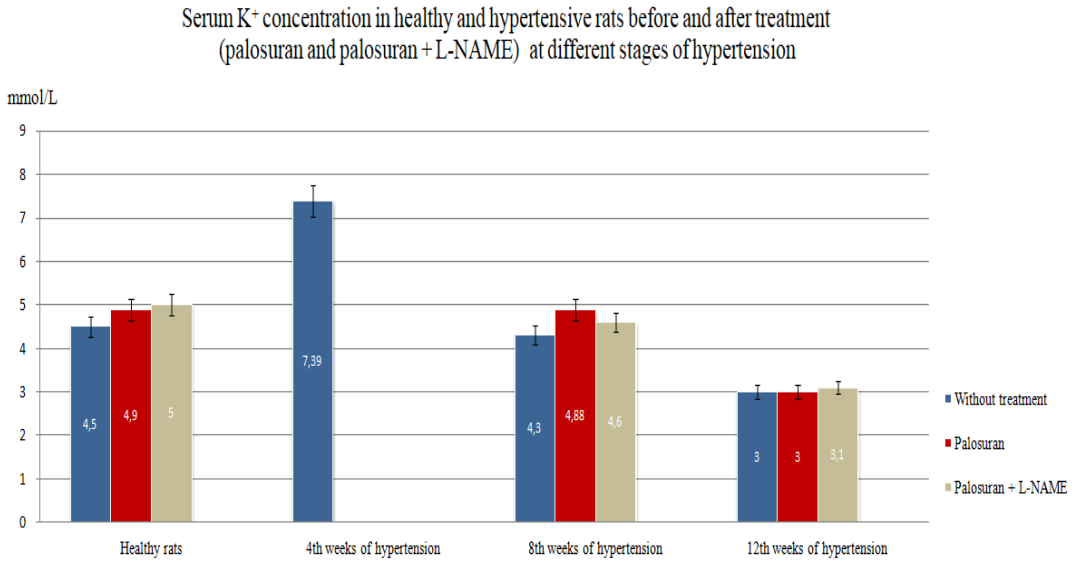


In healthy rats changes in serum K^+ concentration were not statistically significant neither in case of Palosuran, nor L-NAME administrations. In Palosuran treated group animals there was only a tendency of increase in serum K^+ concentration by 8,9% and in case of L-NAME injection – by 2% (p>0,05) compared to the initial values.

Graph 2



Graph 3



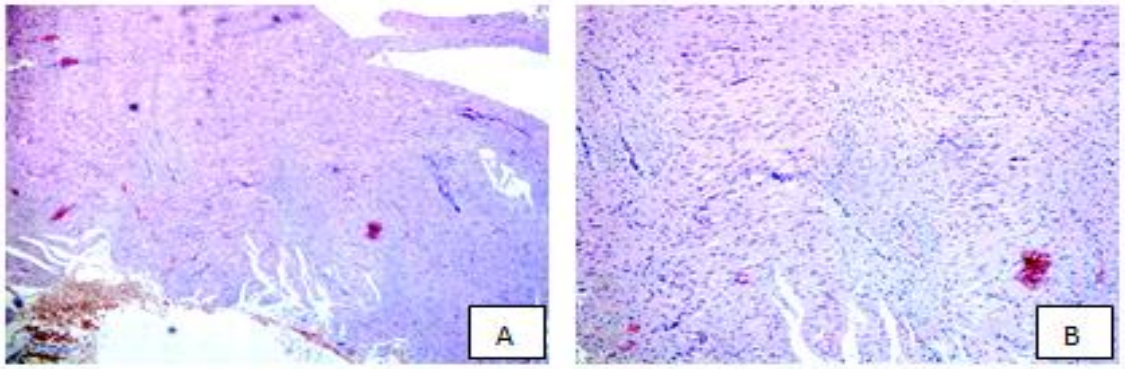
In hypertensive rats after 4 weeks of disease modeling decrease in serum K^+ by 9% was not statistically significant compared to the data of healthy rats. After 8 weeks of disease modeling decrease in serum K^+ by 5,5% was not statistically significant also and it was slightly increased compared to the data obtained by 4^{th} weeks of disease modeling.

In treated with Palosuran group animals after 8 weeks of disease modeling serum K^+ was increased by 13,5% ($p<0,05$). After administration of L-NAME serum K^+ concentration was changed unreliably by 6% ($p>0,05$).

Following administration of L-NAME, there was no statistically significant increase in MAP

compared to animals given palosuran, while MAP decreased compared to untreated hypertensive control rats, but this decrease was statistically significant only in the treatment group.
After the introduction of L-NAME as an inhibitor of NO synthase, a significant increase in blood pressure was expected compared to data from animals in the control group. However, experiments showed exactly the opposite reaction in rats treated with Palosuran, especially when treatment was started early. This may be explained by the fact that palosuran, which inhibits the effects of urotensin, may increase the production of NO, thereby suppressing the vasoconstrictor effects of L-NAME.

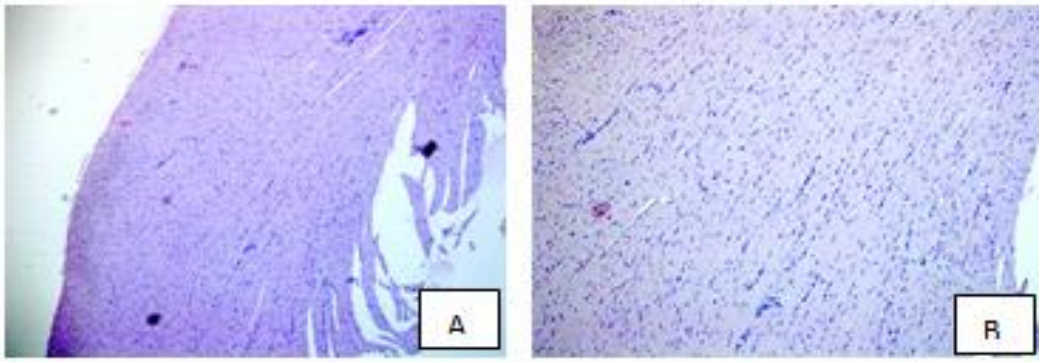
In tissue samples from the heart of a healthy rat, the wall thickness of the left ventricle was 1.0 mm, the wall thickness of the right ventricle 0.2 mm; Cardiomyocytes were in the normal range



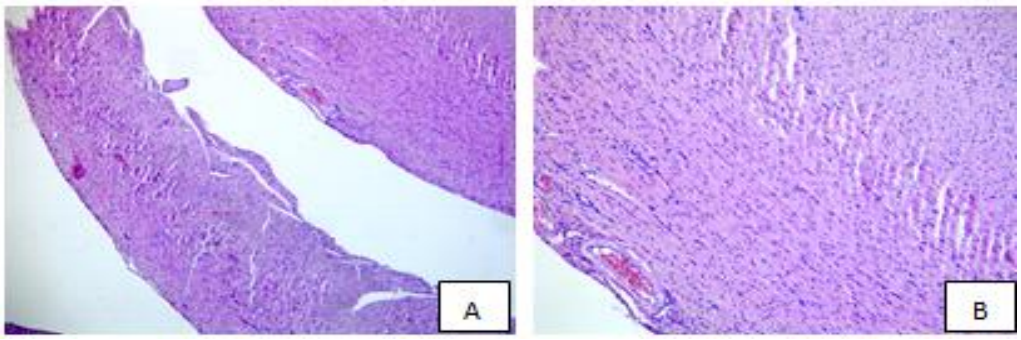
(Pic. 1)

Pic.1. Healthy rat myocardium. Painted H&E; A: Increase - 50X; B: Increase -100X

In 8 weeks after modeling renovascular hypertension, mild left ventricular hypertrophy was observed in myocardial tissue samples from untreated rats. The wall thickness of the left ventricle was 1.4 mm; The wall thickness of the right ventricle is 0.21 mm;

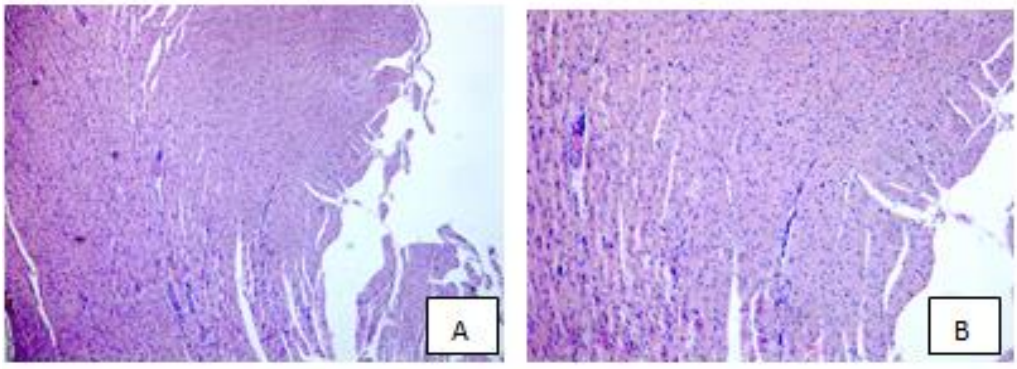


Pic. 2. The myocardium of an untreated hypertensive rat - after 8 weeks of hypertension.
Painted H&E; A: Увеличение - 50X; B: Увеличение -100X.
Left ventricular hypertrophy was observed in myocardial tissue samples from untreated rats 12 weeks after modeling renovascular hypertension. The wall thickness of the left ventricle was 2 mm, the wall thickness of the right ventricle was 0.22 mm.



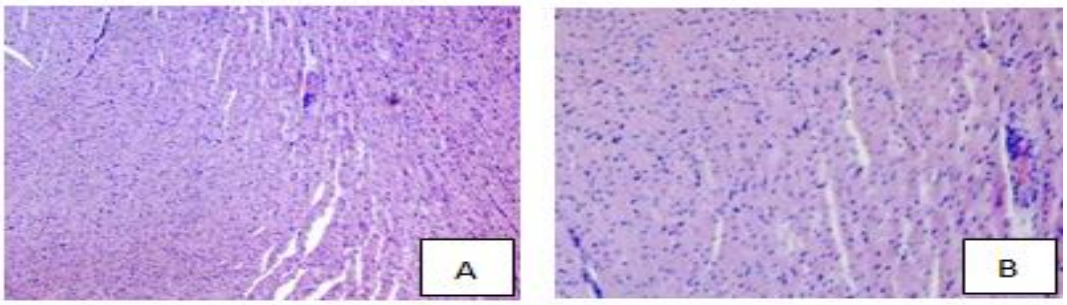
Pic. 3. Myocardium in an untreated hypertensive rat after 12 weeks of hypertension. Painted H&E; A: Increase - 50X; B: Increase -100X

In myocardial tissue samples from rats with hypertension, which received Palosuran intraperitoneally for 4 weeks, 8 weeks after modeling of hypertension, the left ventricular wall thickness was 1.07 mm; The wall thickness of the right ventricle is 0.19 mm; Cardiomyocytes within normal limits.



Pic N4. Myocardium of a hypertensive rat treated with Palosuran after 8 weeks of hypertension. Painted H&E; A: Increase - 50X; B: Increase -100X

Mild left ventricular hypertrophy was observed in myocardial tissue samples from hypertensive rats treated with Palosuran for 4 weeks at 12 weeks after modeling the disease. Left ventricular wall thickness - 1.12 mm; Right ventricle - 0,21 мм.



Pic.5. The myocardium of a hypertensive rat was treated with Palosuran 12 weeks after hypertension. Painted H&E; A: Increase - 50X; B: Increase -100X

An increase in serum Na + in renovascular hypertension develops due to renal artery ischemia and activation of the RAAS, which leads to an increase in sodium reabsorption. From the eighth week of hypertension onwards, a slight decrease in the serum Na + level could be explained by a compensatory renal reaction. In the first case of Goldblatt hypertension with a clamp and two kidneys, the ischemic kidney secretes renin, which leads to increased production of angiotensin II and, as a result, to an increase in blood pressure. If the blood pressure rises, the sodium excretion through the intact contralateral kidney increases (pressure natriuresis), so that there is no sodium retention.

The decrease in serum potassium levels observed in our experimental studies in advanced hypertension can be explained by the reciprocal relationship of sodium and potassium in the kidneys. The potassium level often changes with the sodium level. When sodium levels go up, potassium levels go down, and when sodium levels go down, potassium levels go up. The hormone aldosterone also affects potassium levels. In renal hypoxia and an activated RAAS system, the hormone aldosterone, which acts on the distal tubules, causes potassium to be excreted and sodium reabsorbed.

During our studies we could not find any significant differences in mean serum calcium levels between the groups of healthy, control and treated animals. It is possible that intracellular calcium levels are more important in systemic hypertension than serum calcium levels, which were not measured in our study. Numerous experimental studies show that the intracellular Ca2 + concentration in the vascular myocytes of hypertensive animals is abnormally increased [24] and that calcium uptake can influence blood pressure by increasing the intracellular calcium in muscle cells. Vessel volume by renin. - Angiotensin-Aldosterone System (RAAS).

Conclusion

Based on the results obtained, we can say that palosuran shows an antihypertensive effect in both healthy and hypertensive rats. With early treatment, no left ventricular hypertrophy was detected in the myocardium of the hypertensive rat compared to the myocardium of the untreated rat, while with late treatment the left ventricular hypertrophy was mild. Treatment with Palosuran Lab. Together with lowering the blood pressure in rats, it significantly reduces the stress on the myocardium and thus the complication to be expected. Based on the results of the experiments it could be concluded that palosuran shows a blood pressure lowering effect in the laboratory in the early stages of hypertension. Rats with renovascular hypertension caused significant changes in serum Na^+ and K^+ levels, with the exception of serum Ca^{++} concentration. Palosuran significantly reduced the concentration of Na + and K + in the blood serum of rats with hypertension. The Na^+ and K^+ concentrations were maintained within normal limits even after administration of L-NAME, with the exception of late initiation of treatment.

REFERENCES

1. Sidharta PN, Wagner FD, Bohnemeier H, Jungnik A, Halabi A, Krahenbuhl S, et al. Pharmacodynamics and pharmacokinetics of the urotensin II receptor antagonist palosuran in macroalbuminuric, diabetic patients. Clin Pharmacol Ther. 2006; 80: 246–256;
2. Clozel M, Hess P, Qiu C, Ding SS, Rey M. The urotensin-II receptor antagonist palosuran improves pancreatic and renal function in diabetic rats. J Pharmacol Exp Ther. 2006; 316: 1115–1121;

3. Kajaia A, Gabunia L, Ghambashidze K., et al. Urotensin-2Receptor Antagonist - Palosuran Decreases Blood Pressure And Plasma Renin Concentration In Laboratory Rats With Renovascular Hypertension. International Journal of Progressive Sciences and Technologies (IJPSAT) ISSN: 2509-0119. 2021, vol. 26, No. 1, pp. 16-24;
4. Goldblatt P. The Goldblatt experiment: a conceptual paradigm. In: Hypertension: Pathophysiology, Diagnosis and Management, edited by J. H. Laragh and B. M. Brenner. New York: Raven, 1995; pp. 23–35;
5. Burnier M., Kjeldsen S., Heagerty A., Williams B. Drug treatment of hypertension Oxford MedicineOnlinehttps://oxfordmedicine.com/view/10.1093/med/9780198784906.001.0001/med-9780198784906-chapter-569;
6. Podzolkov V., Tarzimanova A., Georgadze Z. Modern Principles of Treatment of Uncontrolled Hypertension. Rational Pharmacotherapy in Cardiology Home. 2019; 15(5): 736-741;
7. Suguro T, Watanabe T, Ban Y, et al. Increased human urotensin II levels are correlated with carotid atherosclerosis in essential hypertension. Am J Hypertens. 2007 Feb; 20(2):211-217;
8. Totsune K, Takahashi K, Arihara Z, et al. Elevated plasma levels of immunoreactive urotensin II and its increased urinary excretion in patients with Type 2 diabetes mellitus: association with progress of diabetic nephropathy. Peptides. 2004 Oct; 25(10):1809-1814;
9. Bousette N., Hu F., Ohlstein E. H., Dhanak D., Douglas S. A., Giaid A. Urotensin-II blockade with SB-611812 attenuates cardiac dysfunction in a rat model of coronary artery ligation. J. Mol. Cell. (2006). Cardiol. 41, 285– 29510.1016/j.yjmcc.2006.05.008;
10. Desai N, Sajjad J, Frishman WH. Urotensin II: a new pharmacologic target in the treatment of cardiovascular disease. Cardiol Rev. 2008 May-Jun; 16(3):142-153;
11. Suguro T, Watanabe T, Ban Y, et al. Increased human urotensin II levels are correlated with carotid atherosclerosis in essential hypertension. Am J Hypertens. 2007 Feb; 20(2):211-217;
12. Douglas SA, Ohlstein EH. Human urotensin-II, the most potent mammalian vasoconstrictor identified to date, as a therapeutic target for the management of cardiovascular disease., Trends Cardiovasc Med. 2000 Aug; 10(6):229-237;
13. Gardiner SM, March JE, Kemp PA, et al. Regional heterogeneity in the haemodynamic responses to urotensin II infusion in relation to UT receptor localisation.J Pharmacol. 2006 Mar; 147(6):612-621;
14. Lapp H, Boerrigter G, Costello-Boerrigter LC, et al. Elevated plasma human urotensin-II-like immunoreactivity in ischemic cardiomyopathy.Int J Cardiol. 2004 Mar; 94(1):93-97;
15. Bottrill FE, Douglas SA, Hiley CR, White R, Br. Human urotensin-II is an endothelium-dependent vasodilator in rat small arteries. J Pharmacol. 2000 Aug; 130(8):1865-1870;
16. Matsushita M, Shichiri M, Imai T, et al. Co-expression of urotensin II and its receptor (GPR14) in human cardiovascular and renal tissues. J Hypertens. 2001 Dec; 19(12):2185-2190;
17. Maguire JJ, Davenport AP. Is urotensin-II the new endothelin? Br J Pharmacol 137: 579–588, 2002;
18. Douglas S. A., Dhanak D., Johns D. G. From “gills to pills”: urotensin-II as a regulator of mammalian cardiorenal function. Trends Pharmacol. Sci. 2004; 25:76–8510.1016/j.tips.2003.12.005.

19. Sondermeijer B., Komp A., Komesaroff P., Krum H. Effects of exogenous urotensin-II on vascular tone in skin microcirculation of patients with essential hypertension. Am.J. Hypertens. 2005; 22:1341–1344
20. Douglas SA, Ohlstein EH. Human urotensin-II, the most potent mammalian vasoconstrictor identified to date, as a therapeutic target for the management of cardiovascular disease. Trends Cardiovasc Med. 2000; 10: 229–237;
21. Cheung, Bernard MY; Leung, Raymond; Man, Yu Bun; Wong, Louisa YF. Plasma concentration of urotensin II is raised in hypertension. Journal of Hypertension: July 2004,v. 22 - Issue 7 pp. 1341-1344;
22. Douglas SA, Ashton DJ, Sauermelch CF, Coatney RW, Ohlstein DH, Ruffolo MR, et al. Human urotensin-II is a potent vasoactive peptide: pharmacological characterization in the rat, mouse, dog and primate. J Cardiovasc Pharmacol. 2000; 36: S163–S166;
23. Douglas SA, Sulpizio AC, Piercy V, Sarau HM, Ames RS, Aiyar NV, et al. Differential vasoconstrictor activity of human urotensin-II in vascular tissue isolated from the rat, mouse, dog, pig, marmoset and cynomolgus monkey. Br J Pharmacol. 2000; 131: 1262–1274;
24. Gardiner SM, March JE, Kemp PA, Davenport AP, Bennett T. Depressor and regionally-selective vasodilator effects of human and rat urotensin II in conscious rats. Br J Pharmacol. 2001; 132: 1625–1629;
25. Gardiner SM, March JE, Kemp PA et al. Regional heterogeneity in the haemodynamic responses to urotensin II in relation to UT receptor localization. Br J Pharmacol 2006; 147:612-621
26. Watanabe T, Kanome T, Miyazaki A, Katagiri T. Human urotensin II as a link between hypertension and coronary artery disease. Hypertens Res, 2006; 29: 375–387;
27. Zhu YC, Zhu YZ, Moore PK. The role of urotensin II in cardiovascular and renal physiology and diseases. Br J Pharmacol 2006; 148: 884–901;
28. Song W, Abdel-Razik AE, Lu W, Ao Z, Johns DG, et al. Urotensin II and renal function in the rat. Kidney Int 2006; 69: 1360– 1368;
29. Balment RJ, Song W, Ashton N. Urotensin II: ancient hormone with new functions in vertebrate body fluid regulation. Ann N Y Acad Sci 2005; 1040: 66–73;
30. Bond H., Winter M.J., Warne J.M. , et al. Plasma concentrations of arginine vasotocin and urotensin II are reduced following transfer of the euryhaline flounder (Platichthys flesus) from seawater to fresh water. Gen Comp Endocrinol, 125 (2002), pp. 113-120;
31. ouglas S.A., Dhanak D., Johns D.G. From ‘gills to pills’: urotensin-II as a regulator of mammalian cardiorenal function. Trends Pharmacol Sci, 25 (2004), pp. 76-85;
32. Carotenuto A., Grieco P., Rovero P., et al. Urotensin-II receptor antagonists. Curr Med Chem, 13 (2006), pp. 267-275;
33. Clozel M. , C. Binkert, M. Birker-Robaczewska, et al. Pharmacology of the urotensin-II receptor antagonist palosuran (ACT- 058362; 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulfate salt): first demonstration of a pathophysiological role of the urotensin system. J Pharmacol Exp Ther, 311 (2004), pp. 204-212;
34. Lim et al., 2004 Lim M., Honisett S., Sparkes C. D., Komesaroff P., Kompa A., Krum H. Differential effect of urotensin II on vascular tone in normal subjects and patients with chronic heart failure. Circulation. 2004; 109, 1212–1214;
35. American Journal of Hypertension. Am J Hypertens 2007;20: 211–217;

36. Lim M, Honisett S, Sparkes CD, et al. Differential effect of urotensin II on vascular tone in normal subjects and patients with chronic heart failure. Circulation. 2004 Mar 16; 109(10):1212-1216;
37. Clozel M, Hess P, Qiu C, Ding SS, Rey M J.The urotensin-II receptor antagonist palosuran improves pancreatic and renal function in diabetic rats. Pharmacol Exp Ther. 2006 Mar; 316(3):1115-1121;
38. Pehlivan Y, Turkbeyler IH, et al. Urotensin inhibition with palosuran could be a promising alternative in pulmonary arterial hypertension. Onat AM1, Hypertension. 2010; 55 (5):1206-9;
39. Sidharta PN, Wagner FD, Bohnemeier H, et al. Pharmacodynamics and pharmacokinetics of the urotensin II receptor antagonist palosuran in macroalbuminuric, diabetic patients. Clin Pharmacol Ther. 2006 Sep; 80(3):246-256;
40. Vogt L1, Chiurchiu C, Chadha-Boreham H. et al. Effect of the urotensin receptor antagonist palosuran in hypertensive patients.Trends Pharmacol Sci. 2004 Feb; 25(2):76-85;
41. Каджаия А.А, Габуния Л.И, Гамбашидзе К.Г, Пачкория К.З, Сулашвили Н.В, Гогиберидзе А.П; Effect of U-II-receptor antagonist – Palosuran on Arterial Pressure and Myocardium in Hypertensive Lab. Rats; ISBN 978-88-32012-34-7; DOI10.51582/interconf.19-20.07.2021; UDC 001.1; Index Copernicus International; SCIENTIFIC EDITION; InterConf-Scientific Publication Center; Scientific Collection InterConf, №67; Proceedings of the 4 th International Scientific and Practical Conference «Theory and Practice of Science: Key Aspects» (19- 20 of July, 2021); Rome, Italy-2021; Pp: 307-316.
42. L. Gabunia, D. Vadachkoria, Sh. Khetsuriani, N. Gamkrelidze, L. Rukhadze, N. Sulashvili; Mechanisms of Pharmacological Action of Ecstasy Substances, Consequences of Episodic and Chronic Use and Expected Complications; Caucasus Journal of Health Sciences and Public Health; E ISSN 2449-2450 ISSN 2449-2647 The University of Georgia Publishing House; www.caucasushealth.ge Official Journal of the University of Georgia and Iv.Javakhishvili Tbilisi State University with Support of the Arctic University of Tromsø/Norway; Volume 4, Supplement 6; July 20-24, 2020; Pp 66-69.
43. Vilaseca M, García-Calderó H, Lafoz E, Ruart M, López-Sanjurjo CI, Murphy MP, Deulofeu R, Bosch J, Hernández-Gea V, Gracia-Sancho J, García-Pagán JC. Mitochondria-targeted antioxidant mitoquinone deactivates human and rat hepatic stellate cells and reduces portal hypertension in cirrhotic rats. Liver Int 2017; 37(7): 1002–1012
44. Rockey DC, Fouassier L, Chung JJ, Carayon A, Vallee P, Rey C, Housset C. Cellular localization of endothelin-1 and increased production in liver injury in the rat: potential for autocrine and paracrine effects on stellate cells. Hepatology 1998; 27(2): 472–480
45. Iwakiri Y. Pathophysiology of portal hypertension. Clin Liver Dis 2014; 18(2): 281–291
46. Nishimura Y, Ito T, Hoe K, Saavedra JM. Chronic peripheral administration of the angiotensin II AT(1) receptor antagonist candesartan blocks brain AT(1) receptors. Brain Res 2000; 871(1): 29–38
47. Ames RS, Sarau HM, Chambers JK, Willette RN, Aiyar NV, Romanic AM, Louden CS, Foley JJ, Sauermelch CF, Coatney RW, Ao Z, Disa J, Holmes SD, Stadel JM, Martin JD, Liu WS, Glover GI, Wilson S, McNulty DE, Ellis CE, Elshourbagy NA, Shabon U, Trill JJ, Hay DW, Ohlstein EH, Bergsma DJ, Douglas SA. Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14. Nature 1999; 401(6750): 282–286

48. Ross B, McKendy K, Giaid A. Role of urotensin II in health and disease. Am J Physiol Regul Integr Comp Physiol 2010; 298(5): R1156–R1172
49. Thanassoulis G, Huyhn T, Giaid A. Urotensin II and cardiovascular diseases. Peptides 2004; 25(10): 1789–1794
50. Kemp W, Roberts S, Krum H. Increased circulating urotensin II in cirrhosis: potential implications in liver disease. Peptides 2008; 29 (5): 868–872
51. Liu D, Chen J, Wang J, Zhang Z, Ma X, Jia J, Wang Y. Increased expression of urotensin II and GPR14 in patients with cirrhosis and portal hypertension. Int J Mol Med 2010; 25(6): 845–851
52. Liu DG, Wang J, Zhang ZT, Wang Y. The urotension II antagonist SB-710411 arrests fibrosis in CCl4 cirrhotic rats. Mol Med Rep 2009; 2(6): 953–961
53. Clozel M, Binkert C, Birker-Robaczewska M, Boukhadra C, Ding SS, Fischli W, Hess P, Mathys B, Morrison K, Müller C, Müller C, Nayler O, Qiu C, Rey M, Scherz MW, Velker J, Weller T, Xi JF, Ziltener P. Pharmacology of the urotensin-II receptor antagonist palosuran (ACT-058362; 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)- ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulfate salt): first demonstration of a pathophysiological role of the urotensin system. J Pharmacol Exp Ther 2004; 311(1): 204–212
54. Mejias M, Coch L, Berzigotti A, Garcia-Pras E, Gallego J, Bosch J, Fernandez M. Antiangiogenic and antifibrogenic activity of pigment epithelium-derived factor (PEDF) in bile duct-ligated portal hypertensive rats. Gut. 2015; 64(4): 657–666
55. Clozel M, Hess P, Qiu C, Ding SS, Rey M. The urotensin-II receptor antagonist palosuran improves pancreatic and renal function in diabetic rats. J Pharmacol Exp Ther 2006; 316(3): 1115–1121
56. Hsu SJ, Lee FY, Wang SS, Hsin IF, Lin TY, Huang HC, Chang CC, Chuang CL, Ho HL, Lin HC, Lee SD. Caffeine ameliorates hemodynamic derangements and portosystemic collaterals in cirrhotic rats. Hepatology 2015; 61(5): 1672–1684
57. Delgado MG, Gracia-Sancho J, Marrone G, Rodríguez-Vilarrupla A, Deulofeu R, Abraldes JG, Bosch J, García-Pagán JC. Leptin receptor blockade reduces intrahepatic vascular resistance and portal pressure in an experimental model of rat liver cirrhosis. Am J Physiol Gastrointest Liver Physiol 2013; 305(7): G496–G502
58. Mitchell K., Navar L.. Intrarenal actions of angiotensin II in the pathogenesis of experimental hypertension. In: Hypertension: Pathophysiology, Diagnosis, and Management, edited by J. H. Laragh and B. M. Brenner. New York: Raven, 1995, pp.1437– 1450;
59. Ploth D. Angiotensin-dependent renal mechanisms in two-kidney one-clip renal vascular hypertension. Am. J. Physiol. 1983. 245 (Renal Fluid Electrolyte Physiol. 14): F131–F141;
60. Kim, M-H & Choi, M-K Seven dietary minerals (Ca, P, Mg, Fe, Zn, Cu, and Mn) and their relationship with blood pressure and blood lipids in healthy adults with self-selected diet. Biol Trace Elem Res. 2013, 153, 69–75;
61. Gijsbers, L, Dower, JI, Mensink, M et al. Effects of sodium and potassium supplementation on blood pressure and arterial stiffness: a fully controlled dietary intervention study. J Hum Hypertens. 2015, 29, 592–598;
62. Tostes R.C.A., Wilde D.W., Bendhack L.M., Webb R.C. Calcium handling by vascular myocytes in hypertension. Braz J Med Biol Res, March, 1997, v. 30(3) 315-323.
63. Clozel M, Binkert C, Birker-Robaczewska M, et al. Pharmacology of the urotensin-II receptor antagonist palosuran (ACT- 058362; 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-

ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulfate salt): first demonstration of a pathophysiological role of the urotensin system. J Pharmacol Exp Ther. 2004; 311: 204–212;
64. Clozel M, Hess P, Qiu C, Ding SS, Rey M. The urotensin-II receptor antagonist palosuran improves pancreatic and renal function in diabetic rats. J Pharmacol Exp Ther. 2006; 316: 1115–1121;
65. Ames RS, Sarau HM, Chambers JK, Willette RN, Aiyar NV, Romanic AM, et al. Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14. Nature. 1999; 40: 282–286;
66. Goldblatt P. The Goldblatt experiment: a conceptual paradigm. In: Hypertension: Pathophysiology, Diagnosis and Management, edited by J. H. Laragh and B. M. Brenner. New York: Raven, 1995; pp. 23–35;
67. Mitchell K., Navar L.. Intrarenal actions of angiotensin II in the pathogenesis of experimental hypertension. In: Hypertension: Pathophysiology, Diagnosis, and Management, edited by J. H. Laragh and B. M. Brenner. New York: Raven, 1995, pp.1437–1450;
68. Ploth D. Angiotensin-dependent renal mechanisms in two-kidney one-clip renal vascular hypertension. Am. J. Physiol. 245 (Renal Fluid Electrolyte Physiol. 14): F131–F141, 1983).
69. Ishihata A, Ogaki T, Aita T, Katano Y. Role of prostaglandins in urotensin II-induced vasodilatation in the coronary arteries of aged rats. Eur J Pharmacol 523: 119–126, 2005;
70. Lin L., Ding WH., Jiang W., Zhang YG., Qi YF., Yuan WJ., Tang CS. Urotensin-II activates L-arginine/nitric oxide pathway in isolated rat aortic adventitia. Peptides 25: 1977–1984, 2004;
71. Katano Y, Ishihata A, Aita T, Ogaki T, Horie T. Vasodilator effect of urotensin II, one of the most potent vasoconstricting factors, on rat coronary arteries. Eur J Pharmacol 402: 209–211, 2000;
72. Gibson A. Complex effects of Gillichthys urotensin II on rat aortic strips. Br J Pharmacol 91: 205–212, 1987;
73. Kimiko Ishiguro, Hiroyuki Sasamura, Yusuke Sakamaki, Hiroshi Itoh, Takao Saruta. Developmental Activity of the Renin- Angiotensin System during the “Critical Period” Modulates Later L-NAME–Induced Hypertension and Renal Injury. Hypertension Research. 2007, p.30–75;
74. Liffert Vogt, Carlos Chiurchiu, Harbajan Chadha-Boreham, et al. Effect of the Urotensin Receptor Antagonist Palosuran in Hypertensive Patients With Type 2 Diabetic Nephropathy. Hypertension. 2010;55:1206-1209;
75. Wendy J. Bottinor, Megan M. Shuey, Ali Manouchehri, et al. Renin-Angiotensin-Aldosterone System Modulates Blood Pressure Response During Vascular Endothelial Growth Factor Receptor Inhibition. JACC: CARDIOONCOLOGY, 2019;1(1); http://creativecommons.org/licenses/by-nc-nd/4.0/;
76. Marisa K. Ames, Clarke E. Atkins, Bertram Pitt. The renin-angiotensin-aldosterone system and its suppression. J Vet Intern Med. 2019;33(2):
77. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet. 2008;371:1513–1518;
78. Darlington AS, Dippel DW, Ribbers GM, van Balen R, Passchier J, Busschbach JJ. A prospective study on coping strategies and quality of life in patients after stroke, assessing prognostic relationships and estimates of cost-effectiveness. J Rehabil Med 2009; 41(4): 237–241

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

THE SPECIFICITIES PARACHUTE MITRAL VALVE

Ketevan Lartsuliani[1], Lali Patsia[2], Nodar Sulashvili[3]
[1]MD, Doctor of Medicine, Doctor Cardiologist at Aversi Clinic, Tbilisi-Georgia;
[2]MD, PhD, Doctor of Medical Sciences, Doctor Cardiologist at Republican Hospital, Tbilisi-Georgia, Associate Professor of International School of Medicine at Alte University, Tbilisi, Georgia;
[3]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences, Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Invited Professor/Lecturer of Tbilisi State Medical University, Tbilisi, Georgia;
Email: n.sulashvili@ug.edu.ge

ABSTRACT

Parachute mitral valve (PMV) is a rare congenital valvular anomaly, occurring in 0.2% of patients with congenital heart disease. No racial or sex predilection is known. Asymptomatic patients may be discovered incidentally. Usually, the anomaly is detected in childhood, adult presentation is extremely rare. In PMV all the chordae tendineae of the mitral valve are attached to a single papillary muscle. PMV is commonly associated with mitral valve stenosis. The mechanism for the mitral valve stenosis is the reduced mobility of the leaflets due to the short and thick chordae. PMV may occur as an isolated lesion or in association with other congenital cardiac anomalies. The most common associated malformations are coarctation of the aorta, aortic valve stenosis, and subvalvular aortic stenosis. We describe the case of a 29-year-old asymptomatic woman who visited cardiologist for performing echocardiographic examination. A transthoracic echocardiography (TTE) revealed the presence of PMV with mild mitral stenosis, bicuspid aortic valve with mild aortic regurgitation. Asymptomatic patients with mild mitral stenosis require no significant therapy. They should undergo yearly follow-up care with physical examination, chest radiography, ECG and echocardiography. These patients may remain stable for decades before mitral stenosis progresses and the patient requires surgical intervention. Surgical intervention is indicated for the symptomatic and hemodynamically compromised patients. Two-thirds of PMV patients require surgical treatment of the mitral valve lesions. PMV is curable by mitral valve repair in most cases, and mitral valve replacement is indicated only for patients with severe mitral valve lesions. Mitral valve repair is preferred over mitral valve replacement for the mitral valve abnormalities. The patients often have a promising outcome. The clinical course of isolated PMV will depend on the presence and severity of mitral stenosis or regurgitation. Some patients remain asymptomatic with normal hemodynamics across the valve and no medical or surgical intervention is needed. Diuretic therapy and regular follow-up with repeat echocardiograms have been described. Mitral valve replacement or repair is indicated when the patient is symptomatic with hemodynamically significant stenosis or regurgitation of the valve. In conclusion, PMV is a rare congenital anomaly usually seen in infants and children, but may discover incidentally in adults. These patients may remain stable for a long time and do not need any treatment. The parachute mitral valve can be an isolated lesion or one of the combinations of Shawn syndrome. Patients with severe congenital mitral stenosis had PMV. The syndrome consists primarily of four defects: supravalvular mitral membrane, MVP, subaortic stenosis (membranous or muscular), and coarctation of the coarctation. A single papillary muscle and orientation of a severely affected PMA contributes to subaortic stenosis. Although the surgical

treatment of PMA is consistently reported, the morphologic features of PMA and the indications for surgical intervention are described in limited cases.
Keywords: Parachute mitral valve; Asymptomatic woman; Congenital valvular anomaly; Mitral stenosis; Echocardiography.

Introduction

Parachute mitral valve (PMV) is an extremely rare congenital valvular anomaly, occurring in 0.2% of patients with congenital heart disease. Asymptomatic patients may be discovered incidentally. Mitral valve stenosis due to the PMV can commonly be diagnosed at childhood whereas the less common it can progress even silently to the adulthood [1-4].

PMV results from an embryological disturbance during the normal delamination of the trabecular ridge between the fifth and nineteenth week of gestation. Parachute mitral valve can occur in association with other cardiac defects in approximately 95% of cases, including: aortic valve stenosis (32%), atrial septal defects (54%), and hypoplastic left heart (19%). Isolated PMV is rare accounting for less than 1% of all cases [5-8].

The association of multiple levels of left-sided inflow and outflow tract obstruction is termed the Shone complex: supraannular mitral ring, subaortic stenosis, and aortic coarctation.

Mitral stenosis can be associated with Lutembacher syndrome. This syndrome is defined as a combination of mitral stenosis and a left-to-right shunt at the atrial level. Typically, the left-to-right shunt is an atrial septal defect (ASD) of the ostium secundum variety. Both these defects, ASD and mitral stenosis, can be either congenital or acquired [9-12].

The normal mitral valve is a complex apparatus composed of an annulus and 2 leaflets that are attached by chordae tendineae to 2 papillary muscles. PMV is a congenital valvular anomaly in which all the chordae tendineae of the mitral valve are attached to a single papillary muscle. The chordae tendineae in PMV are often underdeveloped and hence short, thick, and adherent causing decreased mobility of the valve leaflets and reducing the size of mitral orifice. The unifocal attachment of the chordae results in a restricted valve opening and the potential for subvalvular obstruction and, less frequently, valvular regurgitation [13-16].

Echocardiography establishes the diagnosis in the majority of the patients with PMV (77.77%). The typical parachute deformity of the mitral valve is best demonstrated in parasternal short axis views of the left ventricle (LV): a single papillary muscle is confirmed at the mid- level of LV and the typical “parachute leaflets” are noted at the basal level short axis view [17-20].

first reported a mitral valve pathology consisting of the insertion of the tendons into a single papillary muscle to form a funnel valve and they identified this lesion as a parachute mitral valve (PMV). Subsequently, Bett and Stovin reported on a patient with MVP and a bicuspid aortic valve. In PMA, all of the chordae are usually shortened and thickened and attach to the posterior medial papillary muscle while the anterolateral papillary muscle is absent [21-24].

The parachute mitral valve can be an isolated lesion or one of the combinations of Shawn syndrome. Patients with severe congenital mitral stenosis had PMV. Aslam et al. have also reported on Shawn syndrome in congenital heart disease. Shawn syndrome consists primarily of four defects: supravalvular mitral membrane, MVP, subaortic stenosis (membranous or muscular), and coarctation of the coarctation. A single papillary muscle and orientation of a severely affected PMA contributes to subaortic stenosis. Although the surgical treatment of PMA is consistently reported, the morphologic features of PMA and the indications for surgical intervention are described in limited cases [25-29].

Mitral stenosis associated with PMA has often led to failed biventricular reconstruction in neonates with borderline small left ventricular size, which has increased the importance of left ventricular inflow status when choosing a single or biventricular treatment strategy. Balloon mitral valve repair reduced peak and mean mitral valve gradients by an average of 33% and 38%, respectively; however, 54.5% (6/11) of patients with a supravalvular mitral annulus developed significant mitral valve regurgitation after mitral valve balloon repair. Mitral valve repair was the preferred operation over MVR. In some patients, correction of the stenotic PMA was achieved by dissecting the papillary muscles and fenestration the leaflet. In children, MVR has several disadvantages, such as: High operative mortality, high rate of complete heart block and pacemaker implantation, lack of prosthetic valves suitable in size and growth potential for young children, difficulty with postoperative anticoagulant treatment and rapid wear of the valve bio prosthesis [30-35].

Mitral valve obstruction was the most serious problem of this lesion. The severity of mitral valve obstruction was found to be inversely correlated with long-term outcomes, and operative mortality in patients with Schon syndrome was found to ultimately negatively affect operative mortality. However, there is no significant association between progressive mitral stenosis and PMA type, dominant papillary muscle, sex, or surgical or interventional treatment [36-39].

Since MVPs are usually not isolated lesions and are characterized by a combination of pathological changes in the mitral valve leaflets, annulus, adhesions, sub valvular apparatus, and supravalvular mitral annulus, most patients require one or more surgeries and the frequency of reoperations is high [40-43].

Thus, approximately two-thirds of patients with a parachute mitral valve require surgical treatment for mitral valve damage. Parachute mitral valves are cured by mitral valve repair in most cases, and mitral valve replacement is only indicated in patients with severe mitral valve disease [45-49].

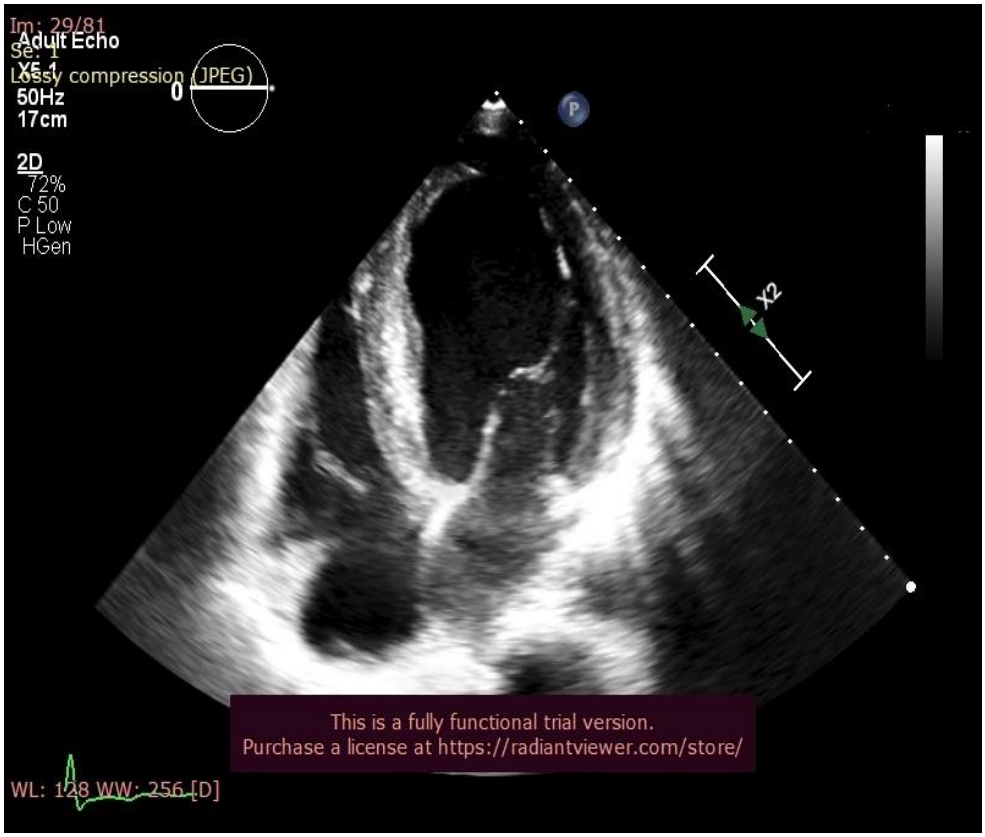
Parachute mitral valve disease is more common in males and is characterized by attachment of all tendon cords to one muscle group of the papillary muscles, resulting in obstruction of mitral valve inflow. The parachute mitral valve is said to have a distinctive "pear shape" in an apical four-chamber view. In adults, and because mitral valve opening is limited, it is strongly associated with mitral stenosis, mitral regurgitation is less common. This disease is reported as an isolated lesion in 55.5% of cases and with other left-sided obstructive heart lesions such as supravalvular mitral ring, sub valvular stenosis, aorta and aortic stenosis known as Shawn's disease in 44.4% of cases illness. Complex, as well as aortic valve stenosis, atrial septal defects and hypoplasia of the left heart. This occurs when the development of the anterolateral and posteromedial papillary muscles is interrupted between the fifth and nineteenth week of gestation, causing the embryonic progenitors of the papillary muscles to thicken into a single muscle. The results of treatment of patients with a parachute mitral valve depend on the spectrum of concomitant cardiac lesions, the degree of mitral valve obstruction remains stable; most do not require a valvotomy. Surgical treatment consists of either choroidal fenestration or papillary muscle dissection with or without a commissurotomy [50-54].

Isolated congenital anomalies of the tricuspid valve. Valves are relatively rare. In most cases these malformations coexist with other concomitant defects. The meaning of this condition and related. Symptoms depend on the functional consequences such as tricuspid regurgitation and/or stenosis. Presence of other associated injuries. Parachute deformity is one of the congenital one’s developmental defects. This happens when the agreements tendons arise from a single papillary muscle. This type of deformity can include one or both atrioventricular valves. First case with

parachute deformity from. The tricuspid valve was confirmed by autopsy and has been published in the literature [55-58].

Case report

We present a case of 29-year-old asymptomatic female with PMV who came to our attention for routine echocardiographic examination for evaluation of cardiac function. TTE showed a single papillary muscle centrally placed receiving chordae from both the anterior and posterior mitral valve leaflets. The short-axis view revealed the presence of a symmetric mitral valve orifice with all chordae attaching to a large anterolateral papillary muscle. The mitral valve orifice was mildly stenotic, no mitral valve regurgitation was shown. The examination revealed the presence of bicuspid aortic valve with mild to moderate aortic regurgitation, moderately dilated ascending aorta - 40mm. Left ventricular end-diastolic diameter was 45mm, end-diastolic volume 82ml, left ventricular ejection fraction 60%, and left atrial diameter 39 mm (anteroposterior diameter), left atrial volume index (LAVI)-29ml/m2. For further assessment, the patient was referred for a computed tomography (CT) because of bicuspid aortic valve. No sign of aortic coarctation was found. A decision was made to follow-up the patient closely for worsening of valvular function.



Video 1. Echocardiographic Finding.
Transthoracic echocardiogram, apical four chamber view showing single papillary muscle.

Discussion

The differential diagnosis for mitral stenosis includes parachute-like asymmetrical mitral valve, anomalous mitral arcade, double orifice mitral valve, hammock mitral valve and rheumatic mitral stenosis.

Most adult patients with PMV usually present with dyspnea and have hemodynamically significant lesions of variable severity across mitral valve. However, some cases may be incidentally diagnosed during echocardiography.

Asymptomatic patients with mild mitral stenosis require no significant therapy. They should undergo yearly follow-up care with physical examination, chest radiography, ECG and echocardiography. These patients may remain stable for decades before mitral stenosis progresses and the patient requires surgical intervention. Surgical intervention is indicated for the symptomatic and hemodynamically compromised patients. Two-thirds of PMV patients require surgical treatment of the mitral valve lesions. PMV is curable by mitral valve repair in most cases, and mitral valve replacement is indicated only for patients with severe mitral valve lesions. Mitral valve repair is preferred over mitral valve replacement for the mitral valve abnormalities. The patients often have a promising outcome.

Conclusions

The clinical course of isolated PMV will depend on the presence and severity of mitral stenosis or regurgitation. Some patients remain asymptomatic with normal hemodynamics across the valve and no medical or surgical intervention is needed. Diuretic therapy and regular follow-up with repeat echocardiograms have been described. Mitral valve replacement or repair is indicated when the patient is symptomatic with hemodynamically significant stenosis or regurgitation of the valve.

In conclusion, PMV is a rare congenital anomaly usually seen in infants and children, but may discover incidentally in adults. These patients may remain stable for a long time and do not need any treatment.

REFERENCES

1. Mark V. Schaverien; Robert M. Freedom; Brian W. McCrindle. Independent Factors Associated With Outcomes of Parachute Mitral Valve in 84 Patients. Circulation. 2004;109:2309–2313.
2. Anna Chow; Jen Lie Yau; Valeria Matto Morina; Shubhika Srivastava. Prevalence, Associations and Outcomes of Double Orifice and Parachute Mitral Valve. Circulation. Nov 2020;142:A14338.
3. Bo Remenyi1, Tom L Gentles. Congenital mitral valve lesions: Correlation between morphology and imaging. Ann Pediatr Cardiol. 2012 Jan-Jun; 5(1): 3–12.
4. Bradley S. et al. Parachute mitral valve: morphologic descriptors, associated lesions and outcomes after biventricular repair. The Journal of Thoracic and Cardiovascular Surgery. Volume 137. Issue 2. February 2009. 385-393.
5. Claire L. Montgomery Alexandra M. Murphy, Jijin Joseph. An Unusual Cause of Stroke in a Young Adult. Journal of Cardiothoracic and Vascular Anesthesia. 34(2020) 2269-2271.
6. Priyankar Sinha. Mitral valve repair for a parachute-like asymmetrical mitral valve during pregnancy. Journal of Cardiac Surgery. 2 October 2020. 333-335.
7. William F. Armstrong. Thomas Ryan. Feigenbaum's echocardiography. Seventh Edition.
8. Catherine Otto. The Practice of Clinical Echocardiography. Fifth Edition.

9. Roberto M. Lang. Steven A. Goldstein. Itzhak Kronzon. Bijoy K. Khandheria. Victor Mor-Avi. ASE's Comprehensive Echocardiography. Second Edition.
10. Abelson M. Parachute mitral valve and a large ventricular septal defect in an asymptomatic adult. Cardiovasc J S Afr. 2001;12:212–214. [PubMed] [Google Scholar]
11. Agnoletti G, Raisky O, Boudjemline Y, Ou P, Bonnet D, Sidi D, et al. Neonatal surgical aortic commissurotomy: predictors of outcome and long-term results. Ann Thorac Surg. 2006;82:1585–1592. [PubMed] [Google Scholar]
12. Akgüllü C, Erdoğan E. Adult patient with Shone"s syndrome and patent ductus arteriosus: a case report. Turk Kardiyol Dern Ars. 2012;40:350–353. [PubMed] [Google Scholar]
13. Almeida S, Cotrim C, Miranda R, Lopes L, Almeida AR, Loureiro MJ, et al. The role of echocardiography in assessing parachute mitral valve. Rev Port Cardiol. 2009;28:335–339. [PubMed] [Google Scholar]
14. Bobylev D, Meschenmoser L, Boethig D, Horke A. Surgical repair of Shone"s complex with anomalous origin of the left coronary artery arising from the right pulmonary artery. Interact Cardiovasc Thorac Surg. 2015;20:439–442. [PubMed] [Google Scholar]
15. Chandra S, Kharwar RB, Mundhekar A. Shone complex. J Cardiovasc Ultrasound. 2015;23:54–55. [PMC free article] [PubMed] [Google Scholar]
16. Cho S, Kim WH, Kwak JG, Lee JR, Kim YJ. Surgical results of mitral valve repair for congenital mitral valve stenosis in paediatric patients. Interact Cardiovasc Thorac Surg. 2017;25:877–882. [PubMed] [Google Scholar]
17. Delmo Walter EM, Hetzer R. Repair for congenital mitral valve stenosis. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2018:46–57.
18. Demirkol S, Baysan O, Celik T, Kurt IH, Kucuk U, Balta S. Incremental value of three-dimensional transesophageal echocardiography in a patient with parachute mitral valve. E24-5Echocardiography. 2012;29
19. Demirkol S, Arslan Z, Balta S, Küçük U. A parachute mitral valve accompanying persistent left superior vena cava: assessment by three-dimensional transthoracic echocardiography. E23-4Anadolu Kardiyol Derg. 2012;12
20. Dibardino DJ, Fraser CD Jr, Dickerson HA, Heinle JS, McKenzie ED, Kung G. Left ventricular inflow obstruction associated with persistent left superior vena cava and dilated coronary sinus. J Thorac Cardiovasc Surg. 2004;127:959–962.
21. Ekici B, Erkan AF, Sökmen Y, Tüfekçioğlu O. Shone"s complex with dextrocardia and situs inversus totalis: a case report. Turk Kardiyol Dern Ars. 2012;40:612–614.
22. Espinola-Zavaleta N, Chugh R, Ramírez GM. Parachute mitral valve with severe mitral regurgitation in an adult patient. E122-5Echocardiography. 2012;29
23. Fisher D, Dipietro A, Murdison KA, Lemieux CA. Full monosomy 21: echocardiographic findings in the third molecularly confirmed case. Pediatr Cardiol. 2013;34:733–735.
24. Gokhroo RK, Bisht DS, Padmanabhan D, Gupta S. Association of large muscular ventricular septal defect with parachute mitral valve: A rare case report. Indian J Cardiol. 2013;16:64–66.
25. Gori T, Salerno D, Donati G. "Parachute" accessory mitral leaflet and pulmonary valve stenosis in an asymptomatic 85-year-old man. Eur Heart J. 2008;29:223–223.
26. Grimaldi A, Vermi AC, Maisano F, Sacco F, Castiglioni A, Zangrillo A, et al. Echocardiographic patterns of incomplete Shone"s syndrome in adults. J Heart Valve Dis. 2011;20:552–556.

27. Henaine R, Nloga J, Wautot F, Yoshimura N, Rabilloud M, Obadia JF, et al. Long-term outcome after annular mechanical mitral valve replacement in children aged less than five years. Ann Thorac Surg. 2010;90:1570–1576.
28. Hosseinpour AR, Amanullah M, Ramnarine IR, Stümper O, Barron DJ, Brawn WJ. Combined atrial arterial switch operation (double switch) for hearts with Shone syndrome and pulmonary hypertension. J Thorac Cardiovasc Surg. 2006;131:471–473.
29. Isılak Z, Deveci OS, Yalcın M, Uz O, Dogan M, Uzun M. A unique case of parachute mitral valve in an adult: an abnormally long chorda tendinea. E245-6Echocardiography. 2012;29
30. Jain D, Martel M, Reyes-Múgica M, Parkash V. Heterotopic nephrogenic rests in the colon and multiple congenital anomalies: possibly related association. Pediatr Dev Pathol. 2002;5:587–591.
31. Jiang ZY, Pircova A, Sekarski N, Hack I, Laurini R, Janzer R, et al. Transposition of the great arteries, pulmonary atresia, and multiple ventricular septal defects associated with multiple cardiac rhabdomyomas in a case of tuberous sclerosis. Pediatr Cardiol. 2000;21:165–169.
32. Kim WH, Lee TY, Kim SC, Kim SJ, Lee YT. Unbalanced atrioventricular septal defect with parachute valve. Ann Thorac Surg. 2000;70:1711–1712. [PubMed] [Google Scholar]
33. Kurtul A, Duran M, Akkaya E, Ornek E. Parachute mitral and tricuspid valves together with ventricular septal defect. Turk Kardiyol Dern Ars. 2013;41:264–264.
34. López-Pardo F, Urbano-Moral JA, González-Calle A, Laviana-Martinez F, Esteve-Ruiz I, Lagos-Degrande O, et al. Three-Dimensional Transesophageal Echocardiography in the Anatomical Assessment of Isolated Parachute Mitral Valve in an Adult Patient. Echocardiography. 2015;32:1732–1735.
35. Lorenzo N, Claver E, Alió J, Aguilar R. Incomplete Shone"s complex in the sixth decade of life: echo and cardiac magnetic resonance imaging assessment. Eur Heart J. 2017;38:459–459.
36. Lu M, Tang H. 3166: Echocardiographic in the diagnosis of parachute mitral valve. P219Ultrasound Med Biol. 2006;32
37. Ma XJ, Huang GY, Liang XC, Liu XQ, Jia B. Atypical Shone"s complex diagnosed by echocardiography. Pediatr Cardiol. 2011;32:442–448.
38. Mądry W, Karolczak MA, Grabowski K. Supravalvar mitral ring with a parachute mitral valve and subcoarctation of the aorta in a child with hemodynamically significant VSD. A study of the morphology, echocardiographic diagnostics and surgical therapy. J Ultrason. 2017;17:206–211.
39. Marino BS, Kruge LE, Cho CJ, Tomlinson RS, Shera D, Weinberg PM, et al. Parachute mitral valve: morphologic descriptors, associated lesions, and outcomes after biventricular repair. J Thorac Cardiovasc Surg. 2009;137:385–393.
40. Meenakshi K, Chidambaram S, Dhandapani VE, Rameshwar R. A rare association of parachute mitral valve with double outlet right ventricle and severe pulmonary hypertension in an adult. J Assoc Physicians India. 2014;62:50–52.
41. Mohan JC, Shukla M, Mohan V, Sethi A. Parachute mitral valve and Pacman deformity of the ventricular septum in a middle-aged male. S126-S30Indian Heart J. 2016;68.
42. Mohan JC, Shukla M, Sethi A. Parachute deformity of both atrioventricular valves with congenitally corrected transposition in an adult. Indian Heart J. 2015;67:565–569.

43. Motoda H, Murata M, Iwanaga S, Matsushita K, Nakamizo H, Wakino S, et al. Parachute mitral valve incidentally diagnosed in an adult patient with hypertension. J Echocardiogr. 2010;8:28–29.
44. Myers PO, del Nido PJ, Bautista-Hernandez V, Marx GR, Emani SM, Pigula FA, et al. Biventricular repair for common atrioventricular canal defect with parachute left atrioventricular valve. Eur J Cardiothorac Surg. 2016;49:546–551.
45. Nikolic A, Joksimovic Z, Jovovic L. Exuberant accessory mitral valve tissue with possible true parachute mitral valve: a case report. J Med Case Rep. 2012;6:292–292.
46. Nkoke C, Lekoubou A, Yonta EW, Dzudie A, Kengne AP. Shone"s anomaly: a report of one case in sub-Saharan Africa. Cardiovasc Diagn Ther. 2014;4:495–498.
47. Park SJ, Kwak CH, Hwang JY. Long-term survival in double inlet left ventricle combined with pulmonary stenosis and parachute mitral valve: a rare case. Int Heart J. 2007;48:261–267.
48. Patsouras D, Korantzopoulos P, Kountouris E, Siogas K. Isolated parachute mitral valve as an incidental finding in an asymptomatic hypertensive adult. Clin Res Cardiol. 2007;96:38–41.
49. Popescu BA, Jurcut R, Serban M, Parascan L, Ginghina C. Shone"s syndrome diagnosed with echocardiography and confirmed at pathology. Eur J Echocardiogr. 2008;9:865–867.
50. Prunier F, Furber AP, Laporte J, Geslin P. Discovery of a parachute mitral valve complex (Shone"s anomaly) in an adult. Echocardiography. 2001;18:179–182.
51. Purvis J, Sharma D. Adult parachute mitral valve detected in pregnancy. Heart. 2011;97:1192–1192.
52. Purvis JA, Smyth S, Barr SH. Multi-modality imaging of an adult parachute mitral valve. J Am Soc Echocardiogr. 2011;24:351–351.
53. Rybicka J, Dobrowolski P, Kuśmierczyk M, Rózański J, Kowalski M, Hoffman P. Parachute mitral valve in a young adult with recurrent pulmonary oedema. Acta Cardiol. 2011;66:401–403.
54. Sadeghian H, Savand-Roomi Z. Parachute mitral valve. In: Sadeghian H, Savand-Roomi Z, editors. Echocardiographic Atlas of Adult Congenital Heart Disease. Cham: Springer; 2015. pp. 349–350.
55. Saroli T, Gelehrter S, Gomez-Fifer CA, van der Velde ME, Bove EL, Ensing GJ. Anomalies of left coronary artery origin affecting surgical repair of hypoplastic left heart syndrome and Shone complex. Echocardiography. 2008;25:727–731.
56. Saura D, Campos JV, Villegas M, Picó F, de la Morena G, Valdés-Chávarri M. Heart-hand syndrome. e7-9Int J Cardiol. 2008;129
57. Sethi R, Kharwar RB, Sharma A, Kumar V, Narain VS. Multimodality imaging of holmes heart with parachute mitral valve. E132-5Echocardiography. 2014;31
58. Sharma V, Burkhart HM, Schaff HV, Cetta F, Cabalka A, Dearani JA. Management of zone of apposition in parachute left atrioventricular valve in atrioventricular septal defect. Ann Thorac Surg. 2013;95:1665–1669.

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

EFFECT OF AGE RELATED CHANGES IN MEMBRANE PROTEINS ON THE STABILITY OF HUMAN RED BLOOD CELLS

Nino Pruidze[1], Ramaz Khetsuriani[2], Manana Arabuli[3], Maia Matoshvili[4], Davit Tophuria[5]
[1]MD. PhD. Assoc. Professor of Human Normal Anatomy Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[2]MD. PhD. Professor of Human Normal Anatomy Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[3]MD. PhD. Assoc. Professor of Human Normal Anatomy Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[4]MD. PhD. Assoc. Professor of Dermato-Venerology Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[5]MD. PhD. Assoc. Professor of Human Normal Anatomy Dep. of Tbilisi State Medical University, Tbilisi-Georgia

People of different ages are often at risk of developing diseases caused by blood circulation disorders. What is often the basis of age-related changes at the cellular level. In this regard, erythrocytes are particularly important due to their physical and chemical characteristics. It is necessary to know the effect of age-related changes in erythrocyte membrane proteins on cell stability, so that we can further discuss the risks of various diseases. For this, we studied the blood of 56 healthy volunteers of different sexes (Tbilisi, Georgia). Volunteers were divided into two groups: 1. Young people aged 17-35 years; 2. Elderly people aged 60-90. We divided the (heparinized) blood taken from each individual into 18 test tubes and stored them in different temperature conditions - 6 test tubes were placed at room temperature, 6 - in refrigerated conditions (+50), 6 - in preserved condition at (-170). On the last days (7th, 10th, 15th, 20th, 40th and 60th day), we opened a new test tube, performed a general blood analysis and observed erythrocytes. Red blood cell membrane proteins were taken from heparinized human blood and their mobility was studied by electrophoretic method. Electrophoretic mobility of red blood cell membrane proteins decreases with age in healthy volunteers, indicating a decrease in the total charge of proteins, depending on the content of electrically charged amino acids. As a result of the experiment, it was found that red blood cells in young volunteers are characterized by much lower stability compared to the elderly. An increase in the content of low molecular weight proteins, tropomyosin, glycophorin C, actin and band 4.9 protein was revealed in the composition of the membranes of peripheral blood erythrocytes of elderly people, which inhibits complement-induced cell lysis (MIRL), its stability under mechanical stress (tropomyosin, glycophorin C, actin and 4.9 band protein) contribute. Erythrocytes in young volunteers have a much lower stability than in elderly people. The much higher stability of erythrocytes in young volunteers is probably due to the high content of membrane inhibitor of reactive lysis protein (MIRL) in the membranes of erythrocytes of elderly people.
Keywords: tropomyosin, glycophorin C, actin, 4.9 band protein.

REFERENCES

1. Bhateria M, Rachumallu R, Singh R, Bhatta RS. Erythrocytes-based synthetic delivery systems: transition from conventional to novel engineering strategies [published online June 9, 2014]. Expert Opin Drug Deliv. doi:10.1517/17425247.2014.927436
2. .Bosman GJ, Lasonder E, Groenen-Dopp YA, Willekens FL, Werre JM, Novotny VM: Comparative proteomics of erythrocyte aging in vivo and in vitro. J Proteomics 2010, 73: 396-402. 10.1016/j.jprot.2015.07.010
3. Hess JR: Red cell changes during storage. Transfus Apher Sci 2015, 43: 51-59. 10.1016/j.transci.2015.05.009

4. Hamasaki N, Yamamoto M: Red blood cell function and blood storage. Vox Sang 2000, 79: 191-197. 10.1046/j.1423-0410.2000.7940191.x
5. Narla M. Red blood cell membrane dynamics and organization. http://www.uptodate.com. Updated 2013. Accessed July 13, 2016.
6. Petropoulos IK, Margetis PI, Antonelou MH, Koliopoulos JX, Gartaganis SP, Margaritis LH, Papassideri IS.Graefes Arch Clin Exp Ophthalmol. 2017 Aug;245(8):1179-88. doi: 10.1007/s00417-006-0500-6.PMID: 17219119.

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

CELL THERAPY FOR CUTANEOUS DISEASES

Maia Matoshvili[1], Davit Tophuria[2], Marina Tsimakuridze[3], Nata Durglishvili[4]
[1]MD. PhD. Assoc. Professor of Dermato-Venerology Dep Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[2]MD. PhD.Assoc. Professor of Human Normal Anatomy Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[3]MD. PhD. Assoc. Professor of Nutrition, Aging Medicine, Environmental and Occupational Health Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[4]MD. PhD. Assoc. Professor of Human Anatomy, University of Georgia Tbilisi-Georgia
E-mail:m.matoshvili@tsmu.edu

Introduction

The harnessing the regenerative capacity of keratinocytes and fibroblasts from human skin has created new opportunities to develop cell-based therapies for patients. Cultured cells and bioengineered skin products are being used to treat patients with inherited and acquired skin disorders associated with defective skin, and further clinical trials of new products are in progress. The capacity of extensive skin wounds and chronic erosions. Ulceration of the skin caused by common pathologies such as venous hypertension, arterial impairment, diabetes mellitus, or neuropathies creates an enormous clinical and health economic burden. Therapeutic interventions to restore an intact epithelium and recover skin function have therefore been an important long-term focus of both traditional and translational medicine, and one in which a number of key advances and clinical benefits have occurred in recent years.

Methodology

The Cellular therapy to repair or restore a defective epithelium of the skin and possibly deeper skin layers represents an attractive area of translational research that could have significant health benefits for many people. The development and application of cell therapy in dermatology, with a special focus on inherited skin disorders in which chronic ulceration has a major impact on quality of life. Nowdays the main emphasis of the text is on recent clinical studies as well as new and emerging strategies that can exploit and harness the regenerative potential of human cells to restore skin tissue, although an overview of the extracutaneous sources of cells such as bone marrow is also being investigated for its plasticity in regenerating skin, and new strategies, such as the derivation of inducible pluripotent stem cells, also hold great promise for future cell therapies in dermatology. This article reviews some of the preclinical and clinical studies and future directions relating to cell therapy in dermatology, particularly for inherited skin diseases associated with fragile skin and poor wound healing.

One of the key functions of skin is to provide a mechanical barrier against the external environment. In several inherited and acquired dermatological disorders, however, this resilience is broken. Loss of a functional epidermis can have profound biological and clinical consequences including loss of water and electrolytes, cutaneous and systemic infections, as well as impaired thermoregulation. Epidermal failure can occur from burns, trauma, and adverse drug reactions. Several inherited diseases associated with inherent mechanical weaknesses in epidermal or dermal structural proteins can all be associated with clinical applications of cell therapy across a range of skin diseases. With regard to the focus of this review, it is hoped that cell therapy lessons learned from studies on rare skin diseases will also be relevant to improving future healthcare of patients with more common disorders associated with defective skin.

Conclusion

Having the capacity and technical ability to culture and expand human keratinocytes and fibroblasts has led to the widespread use of skin grafts to treat chronic wounds and ulcers in both inherited and acquired diseases. Although further refinements in bioengineering and construction of skin grafts are likely to lead to additional clinical benefits for patients, the concept and application of cell therapy for skin diseases recently has expanded to encompass other aspects of regenerative medicine. For inherited skin diseases, the potential to harness and exploit the potential of natural phenomena such as revertant mosaicism (revertant cell therapy), or the plasticity of BM cells to regenerate skin, provide exciting new opportunities to further develop cell therapy in dermatology. Moreover, emerging technologies such as the creation of iPSCs offer an even broader horizon to help deliver clinical benefits from regenerative medicine in dermatology.

Keywords: iPSCs, Cellular therapy, weaknesses in epidermal or dermal structural proteins.

REFERENCES

1. Arakawa M, Shiozuka M, Nakayama Y, Hara T, Hamada M, Kondo S, Ikeda D, Takahashi Y, Sawa R, Nonomura Y, et al. 2014. Negamycin restores dystrophin expression in skeletal and cardiac muscles of mdx mice. J Biochem 134: 751–758.
2. De Luca M, Albanese E, Bondanza S, Megna M, Ugozzoli L, Molina F, Cancedda R, Santi PL, Bormioli M, Stella M, et al. 2015. Multicentre experience in the treatment of burns with autologous and allogenic cultured epithelium, fresh or preserved in a frozen state. Burns
3. Goto M, Sawamura D, Ito K, Abe M, Nishie W, Sakai K, Shibaki A, Akiyama M, Shimizu H 2006. Fibroblasts show more potential as target cells than keratinocytes in COL7A1 gene therapy of dystrophic epidermolysis bullosa. J Invest Dermatol 2016
4. Hefton JM, Madden MR, Finkelstein JL, Shires GT 2016. Grafting of burn patients with allografts of cultured epidermal cells. Lancet 21:
5. Ishii G, Sangai T, Sugiyama K, Ito T, Hasebe T, Endoh Y, Magae J, Ochiai A 2015. In vivo characterization of bone marrow-derived fibroblasts recruited into fibrotic lesions. Stem Cells 37: 699–70
6. Kern JS, Loeckermann S, Fritsch A, Hausser I, Roth W, Magin TM, Mack C, Muller ML, Paul O, Ruther P, et al. 2017. Mechanisms of fibroblast cell therapy for dystrophic epidermolysis bullosa: High stability of collagen VII favors long-term skin integrity. Mol Ther 17: 1625–1632
7. Pasmooij AM, Jonkman MF, Uitto J 2018. Revertant mosaicism in heritable skin diseases: Mechanisms of natural gene therapy. Discov Med 14: 178–185
8. Sasaki M, Abe R, Fujita Y, Ando S, Inokuma D, Shimizu H 2019. Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type. J Immunol 196:
9. Tolar J, Mehta PA, Walters MC 2020. Hematopoietic cell transplantation for nonmalignant disorders. Biol Blood Marrow Transplant 89: S170–S179
10. Watson D, Keller GS, Lacombe V, Fodor PB, Rawnsley J, Lask GP 2021. Autologous fibroblasts for treatment of facial rhytids and dermal depressions. A pilot study. Arch Facial Plast Surg 1: 115–120

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

HEMATOPOIETIC STEM CELLS

Maia Matoshvili[1], Davit Tophuria[2], Nino Adamia[3], Marina Tsimakuridze[4]
[1]MD. PhD. Assoc. Professor of Dermato-Venerology Dep Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[2]MD. PhD.Assoc. Professor of Human Normal Anatomy Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[3]MD. PhD. Dr. of Pediatrics Dep. of Tbilisi State Medical University, Tbilisi-Georgia
[4]MD. PhD. Assoc.. Professor of Nutrition, Aging Medicine, Environmental and Occupational Health Dep. of Tbilisi State Medical University, Tbilisi-Georgia

Introduction

Stem/progenitor cells of the epidermis are recognized to play the most essential role in the tissue regeneration of skin. In this article we will discuss basic stem cell characteristics and various stem cell subtypes resided in the skin. We provided some main literatures to elucidate how stem/progenitor cells collaborate in the process of skin repair with the evidence from animal model studies and in vitro experiments. Also introduced several examples of skin cell products on the pharmaceutic market and the ongoing clinical trials aiming for unmet medical difficulties of skin Located at the follicle dermal papillae, might divide into erythroid and myeloid lineages, shared similar cell markers as counterparts in other organs or tissues. Among all these distinct skin stem cell subgroups, epidermal stem cells are the most deeply correlated to tissue repair and skin regeneration. Scientific reports supported that stem cells of epidermis are rare, infrequently dividing, and generate short-lived, rapidly dividing cells that carry out the regeneration of the epidermis. The same infrequently dividing stem cells of epidermis are assumed to be the major epidermal cell population responsible for repairing skin injury. Most epidermal stem cells reside in the basal layer of epidermis, some might also be found in the bulge region of the hair follicle and the base of the sebaceous glands [1], [2]. Throughout its whole life cycle, epidermal stem cells are circulated between two different cell phases. Under the slow cell phase, epidermal stem cells are quiescent. While entering transit amplifying cell phase, they are quickly divided and the number of skin cells is amplified for the replenishment of skin tissue. Finally, they undergo numerous cell divisions before becoming terminally differentiated to accomplish skin regeneration.

Methodology

Toward skin injury, both epidermal stem cells and follicular stem cells contribute to the re-epithelialization of wounds [7], [4], [6]. In the full-thickness wound, epidermal stem cells and progenitor cells from the hair follicle initially migrate toward the wound site. Epidermal stem cells have been reported to be reactivated in response to skin injury and contribute to skin regeneration on the cellular level [5]. Further clinical evidence also suggested that epidermal stem cells and follicular stem cells participate in the re-epithelialization of wounds by evaluating the potential healing capacity of autologous scalp follicle grafts transplanted into chronic leg ulcerations [3]. Epithelialization, neovascularization, and dermal reorganization were also enhanced within these wound areas. One interesting finding to note is that hair follicular progenitor cells were largely replaced by epidermal progeny following repair in a long-term follow-up [9]. This accidental finding might indicate that nevertheless epidermal stem cells and hair follicular stem cells collaborate in the early phase of skin healing, however, the hair follicular stem cells might not be essential for the long-term maintenance after skin repair.

Conclusions

The essential role of paracrine molecules in skin repair can also be illustrated by the following study. Scientists also discovered that the distressed hair follicle secretes the cytokine Ccl2; therefore M1 macrophages will be attracted to the distressed follicle. Subsequently, M1 macrophages will secrete Tnf-α to activate regeneration of both distressed and healthy follicles. Only high density of distressed follicles can recruit effective numbers of M1 macrophages to the follicles for skin regeneration [9]. To our understanding, several mesenchymal stem cells or progenitor cells have the capacity to release immunomodulation factors, and this might be the reason that different engrafted cell types have different efficacy upon skin repair [10]. Although the precise molecular mechanism of skin repair is still not clear, those studies already depicted an outline how epidermal stem cells participating in tissue regeneration and provided future strategies for skin cell products development.

Keywords: cytokine Ccl2, M1 macrophages.

REFERENCES

1. M. Ramalho-Santos, H. Willenbring On the origin of the term “stem cell” Cell Stem Cell, 1 (2015), pp. 35-37.
2. D.L. Clarke, C.B. Johansson, J. Wilbertz, B. Veress, E. Nilsson, H. Karlstrom, et al. Generalized potential of adult neural stem cells Science, 288, 2016.
3. V. Jaks, N. Barker, M. Kasper, J.H. van Es, H.J. Snippert, H. Clevers, et al. Lgr5 marks cycling, yet long-lived, hair follicle stem cells Nat Genet33, no. 2, pp. 542–556, 2017
4. E.K. Nishimura, S.A. Jordan, H. Oshima, H. Yoshida, M. Osawa, M. Moriyama, et al. Dominant role of the niche in melanocyte stem-cell fate determination Nature, 416 (2018), pp. 854-860.
5. M. Ito, G. Cotsarelis Is the hair follicle necessary for normal wound healing? J Invest Dermatol, 128, pp. 1059-1061, 2018.
6. H. Green, O. Kehinde, J. Thomas Growth of cultured human epidermal cells into multiple epithelia suitable for grafting Proc Natl Acad Sci U S A, 76 2019.
7. N.S. Greaves, S.A. Iqbal, M. Baguneid, A. Bayat The role of skin substitutes in the management of chronic cutaneous wounds Wound Repair Regen, 2020.
8. A.V. Rawlings Ethnic skin types: are there differences in skin structure and function? Int J Cosmet Sci, 28 (2020), pp. 79-93 2020.
9. D.C. Wan, V.W. Wong, M.T. Longaker, G.P. Yang, F.C. Wei Moisturizing different racial skin types 2021.
10. A. Nair, S. Jacob, B. Al-Dhubiab, M. Attimarad, S. Harsha Basic considerations in the dermatokinetics of topical formulations Braz J Pharm Sci, 49 (2021), pp. 423-434.

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

REVIEW OF DRUGS ISSUES OF CELL PRODUCTS DURING SKIN REPAIR

Maia Matoshvili[1], Davit Tophuria[2], Manana Arabuli[3], Natia Kvizhinadze[4]
[1]MD. PhD. Asoc. Professor of Dermato venereology Dep. Tbilisi State Medical University, Tbilisi-Georgia
[2]MD. PhD. Assoc. Professor of Human Normal Anatomy Dep; Tbilisi State Medical University, Tbilisi-Georgia
[3]MD. PhD. Assoc. Professor Human Normal Anatomy Dep. Tbilisi State Medical University, Tbilisi-Georgia
[4]MD. PhD. Assoc. Professor of Social and clinical pharmacy Dep. Tbilisi State Medical University, Tbilisi-Georgia

Among of all the cell products are facing similar reviewing challenges as below: 1. How to ensure stem/progenitor cells to differentiate into desired cell phenotypes? Are there potential karyotype changes during long-term cell culture?[1] 2. What are the best biomarkers to identify the cellular purity before cell products finalized? 3. What are the possible impacts of adjuvants and/or biomaterials for building suitable cellular microenvironment? Will these adjuvants and/or biomaterials induce unpredicted immunological responses?[2] 4. What types of grafting are planned for the patients? How to choose the appropriate method for delivering these grafting to patients? 5. How long will these cells persist to survive in patients' bodies? Are there any none- or minimal-invasive methods for tracing cells in vivo? 6. How to assess the benefit/risk of proposed cell products when comparing to standard treatments? What will be the clinical evaluation methods (end points) to investigate the functionality of the grafts? Among remarkable advances of cellular biology, some challenges now might be easier to overcome[3]; still some remained to be solved for better qualification control. On the other hand, for dermatological topical products, several controversial concerns have been raised in recent years. Since skin stem/progenitor cell products are belonged to the same pharmaceutic category, we first have to go through these disputatious reviewing issues on dermatological topical products[4]. Several new mechanisms underlying the development of dermatosis have recently been found; therefore, advances in the development of topical dermatological medication have been rapid. In the new era, some issues are still easily ignored, such as ethnic difference. For convenience, we refer to differences in race as ‘white’ or ‘black’ according to the most apparent appearance. However, melanin is only one component of skin. In fact, the compositions of this organ are more complicated. For the development of new drugs, some companies classify patients according to the Fitzpatrick skin phototype, claiming that types I and II represent Caucasians, whereas types III and IV represent Asians. This concept might be controversial. Thus, there are approximately 100% Caucasians volunteers in many pivotal studies initiated from European and American regions[5]. The relative lack of efficacy and safety data for Asians is a concern in the development of new drugs. The Fitzpatrick skin phototype was first described by Thomas B. Fitzpatrick in 1975 based on a person's natural color and responses to sun exposure in terms of degree of burning and tanning. It has most commonly been used to analyze sun sensitivity in studies related to the cause of skin cancer, exposure to ultraviolet radiation, tanning and protective behaviors. Skin phototype typing is also widely used for estimating UV, PUVA and laser treatment doses [6]. Thus, people who have the same Fitzpatrick skin phototype may have similar responses to light exposure. However, the Fitzpatrick skin phototype is unable to indicate similar responses to all drugs with various mechanisms and extrapolate ethnicity. Second, misinterpretation of Fitzpatrick skin phototype is sometimes noted. The Fitzpatrick skin phototype classification includes six different skin types that range from very fair (skin type I) to very dark (skin type VI). The two main factors that influence skin type are genetic disposition and reaction to sun exposure and tanning habits. Skin phototype is genetically determined and is one of the many aspects of overall appearance. It also comprises eye and hair color. The Fitzpatrick scale is a numerical

classification scheme for determining skin color based on a questionnaire related to an individual's genetic constitution, reaction to sun exposure and tanning habits. Response to each question is measured on a scale of 0–4. The responses to all the questions are totaled to obtain a final score corresponding to the Fitzpatrick skin type [7]. The score is not decided based on current skin color alone. Human skin color can be changed by several factors, including sun exposure, post-inflammatory hyperpigmentation, etc. The core determinate of the scores is the natural color of the skin, eyes and hair, and the Fitzpatrick skin phototype is almost genetically determined. Therefore, it is a useful tool to evaluate photoaging and risk of skin cancer, minimal erythema dose for UV phototherapy and cosmetic dermatology. However, if we observe skin color only, the Fitzpatrick skin types become changeable. Final, pigmentation is the most obvious morphology but not the only difference between different racial groups. Four chromophores are responsible for the varying colors found in human skin: hemoglobin, oxyhemoglobin, melanin and carotenoids. Skin hues are the result of a combination of all pigments. Melanin is the most apparent contributor to skin color. Melanin is synthesized in melanocytes and packaged into melanosomes that are found dispersed throughout the epidermis. Variations in melanosome distribution, together with the quantity and type of melanin present, are responsible for differences in skin pigmentation. Differences in racial skin pigmentation may be due to differences in the production of melanin. This indicates that there may be structural differences in the melanogenic enzymes. Besides, intracellular pH may also influence melanogenesis and differ between different ethnic skin cells [8]. These findings indicate that the amount of melanin is determined using multiple factors. There remain some differences in skin composition between ethnic groups, e.g. the stratum corneum structure. Investigations on transepidermal water loss in patients of different races have unfortunately reported conflicting results. However, when collectively interpreting all available data, most studies indicate differences between African American, Caucasian and Asian skin. These reports may demonstrate that Asian skin has the poorest barrier function upon mechanical challenge. These data emphasize racial differences in skin barrier function as measured by transepidermal water loss. The findings have important implications for the ability of different skin types to endure and recover from exogenous insults, absorb topical therapeutic agents and maintain moisture under various physiological conditions [9].

Topical dermatological formulations aim to deliver therapeutically effective concentration of drugs to the skin layers, which are also the target site. The barrier function of skin is mostly mediated by the stratum corneum. The stratum corneum consists of 15–20 layers of acutely flattened, metabolically inactive, polygonal cells. The process of drug or chemical absorption into the skin is influenced by several factors. These include molecular size, lipophilicity, pH of formulation, penetrant concentration, temperature and formulation compositions among others [10]. Although differences in morphology and physiology do not fully determine differences in efficacy and safety, variability between ethnic groups warrants further study.

Skin contains all the major enzymes found in the liver and other tissues capable of catalyzing a number of metabolic reactions. Metabolism of topically applied compounds results in altered pharmacological and toxicological effects. There are a number of chemical groups that are particularly susceptible to skin metabolism, including alcohols, acids, primary amines and esters, among others. Thus, the skin has unique and complicated dermatokinetics similar to pharmacokinetics in plasma. Assessment of the dermatokinetics of topical dermatological formulations is of utmost importance in assessing the safety and efficacy of dermatological products. Numerous approaches are reportedly being used to determine the real-time measurement of molecules in the skin layers. Regulatory agencies, such as the U.S. FDA, are still exploring different

techniques for characterizing drug dermatopharmacokinetics. Certain dermatological products applied to the skin surface may penetrate into deeper tissue layers and reach the systemic circulation [10]. The issue of efficacy must also be considered. As to the stem cell therapy on skin, although initially most clinical trials were mainly designed as autologous engraftment, nowadays already some of them aimed for allogeneic indications. Similar to the topical formulations applied in the dermatological fields, reviewing policies should be more dedicated on potential safety concerns, especially on ethnic bridging issues as mentioned above. Based upon the differences in morphology and physiology between different races, the possible variation in efficacy and/or safety of allogeneic skin cell products should not be ignored. Moreover, allogeneic skin cell/tissue engraftment might be in high demand under specific occasions with mechanic explosions or accidents. In 2015, there were massive burn victims in the Formosa Fun Coast Water Park event in Taiwan, and we are deeply appreciated to introduce the advanced technique of autologous transplantation of human keratinocyte cultivation (JACE®) by J-TEC (Japan Tissue Engineering Co., Ltd., now had been merged by Fuji). This technology was originally developed by Professor Howard Green of Harvard Medical School in the 1970s, and later been transferred to J-TEC by Professor Minoru Ueda of Nagoya University. By isolating keratinocytes from a 1-cm2 skin sample from the patient and culturing them on the fibroblast feeder, a sheet of cultured epidermis measuring around 1000 cm2 can be produced in around two weeks. In the event mentioned above, total five patients were benefited by JACE®, however, facing massive amount of burn patients, both autologous and allogenic skin products will be considered to facilitate skin repair under highly demanding circumstances. Therefore, both regulatory bodies and pharmaceutic companies should work together to set the standard bridging criterion for skin stem cell products, especially those of allogenic indications. The best solution will be always to enroll adequate numbers of non-Caucasian subjects into future clinical trials. For developing ideal medications, we definitely have to verify the characteristics of proposed skin stem cell products and clarify the differences in efficacy and safety across different races, hence to actually promote public health.

Keywords: facing massive, stem cell therapy.

REFERENCES

1. F.M. Watt, C. Lo Celso, V. Silva-Vargas Epidermal stem cells: an update Curr Opin Genet Dev, 16 (2015), pp. 520-527
2. R.A. Clark, K. Ghosh, M.G. Tonnesen Tissue engineering for cutaneous wounds J Invest Dermatol, 127 (2015), pp. 101-117
3. A.V. Rawlings Ethnic skin types: are there differences in skin structure and function? Int J Cosmet Sci, 28 (2016), pp. 59-73
4. D.C. Wan, V.W. Wong, M.T. Longaker, G.P. Yang, F.C. Wei Moisturizing different racial skin typesJ Clin Aesthet Dermatol, 7 (2017), pp. 52-67
5. A. Nair, S. Jacob, B. Al-Dhubiab, M. Attimarad, S. Harsha Basic considerations in the dermatokinetics of topical formulations Braz J Pharm Sci, 49 (2017), pp. 416-425
6. A.J. Wagers, I.L. Weissman Plasticity of adult stem cells Cell, 116 (2017), pp. 539-548
7. B.S. Atiyeh, M. Costagliola Cultured epithelial autograft (CEA) in burn treatment: three decades later Burns, 33 (2018), pp. 205-214
8. N.S. Greaves, S.A. Iqbal, M. Baguneid, A. Bayat The role of skin substitutes in the management of chronic cutaneous wounds Wound Repair Regen, 41 (2019), pp. 194-210

9. H. Green, O. Kehinde, J. Thomas Growth of cultured human epidermal cells into multiple epithelia suitable for grafting Proc Natl Acad Sci U S A, 76 (2019), pp. 5665-5668
10. J. Itskovitz-Eldor, S.S. Shapiro, M.A. Waknitz, J.J. Swiergiel, V.S. Marshall, et al. Embryonic stem cell lines derived from human blastocysts Science, 282 (2020), pp. 1125-1137

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

THE ROLE OF MESENCHYMAL SECRETOME ON THE SKIN DURING WOUND HEALING

Maia Matoshvili[1], Davit Tophuria[2], Maia Tsimakuridze[3], Nino Adamia[4], Irakli Amiranashvili[5]
[1]MD. PhD. Asoc. Professor of Dermato-venereology Dep. Tbilisi State Medical University, Tbilisi-Georgia
[2]MD. PhD. Assoc. Professor of Human Normal Anatomy Dep; Tbilisi State Medical University, Tbilisi-Georgia
[3]MD. PhD. Assist. Professor of Nutrition, Aging Medicine, Environmental and Occupational Health Dep. Tbilisi State Medical University, Tbilisi-Georgia
[4]MD. PhD. Dr. of Pediatric Dep. Tbilisi State Medical University, Tbilisi-Georgia
[5]MD. PhD. Asoc. Professor of Human Normal Anatomy Dep. Tbilisi State Medical University, Tbilisi-Georgia
Email:

Introduction: Secretome is known to have a variety of benefits in the treatment of various diseases. The main factor that play a role is the secreted protein, which can help repair and regenerate damaged tissue. Secretome of MSCs plays an important role as a therapeutic agent in dealing with various skin problems. Wound healing is a natural process of the body that repairs and regenerates damaged tissues and consists of three main phases—inflammation, proliferation, and remodeling that occur in overlap. Wound healing is stilla challenge in clinical management therapy problems, especially in chronic conditions.[1] The use of secretome as an alternative therapy in dealing with skin injuries has been widely reported, including accelerating wound closure.[2] Various studies to assess the benefits of secretome to wound healing have been done, both in vitro and in vivo. In vitro testing is generally done by looking at the migration and proliferation capabilities of cells. Use based on cell models has been tested using components of different types of skin cells, such as human immortalized keratinocytes (HaCaTs), human dermal fibroblasts (HDFs), human foreskin fibroblasts (HFFs),human dermal microvascular endothelial cells (HDMECs), and human umbilical vein endothelial cells (HUVECs). Cell migration capability can be determined using the assay migration method and/or starch assay. This test was conducted by comparing the speed of wound closure between control and treatment groups. To confirm the effects of cell migration, it can also be done by identifying the expression levels of MMP2 and MMP9, both of which are involved in the migration processes of cells.2 The proliferation ability of cells can be curated using the assay proliferation method, WST-1 assay and MTT assay. This test aims to see if there is an increase in viability of the cells after secretome administration. Another supporting method can also be done by looking at the ability of angiogenesis using the angiogenesis assay.[3] Secretome from a variety of different sources (such as bone marrow, adipose tissue, neonatal tissue, skin tissue and peripheral blood) have been shown to improve the migration ability of various dermal cells, such as fibroblasts, endothelial cells and keratinocytes, and the epidermis was able to stimulate the proliferation of these cells in vitro. Research by Miranda et al also stated that secretome from umbilical cord tissue-derived (UCX®) was able to increase HDF and HaCaT cell migration based on scratch test results.[4] Sera et al also noted that there was an increase in expression of ki67 markers involved in cell proliferation by treatment using secretome with MTTassay method.2 The use of secretome was also able tomodulate tube formation based on in vitro angiogenesis tests along with the migration and proliferation HUVECs. The speed of healing of wounds could be attributed to the trophic effects of MSCs, which affect dermal fibroblasts and keratinocytes.[5] Interestingly, Topouzi et al used secretome from the dermal papilla fibroblast follicles for wound healing therapy and showed that the wound healing increased by 1.8 times faster thancontrol.[6] In vivo experimental animal models can be used in the form of mice, rats, and pigs.[7] This method has been tested on animal

models with various conditions, such as chronic wounds,58 burns,38 diabetic foot ulcers, skin ulcers, and radiation wounds, which require special handlers. The results showed that wound treatment with secretome was able to accelerate wound healing by increasing the effect of cell migration and proliferation and triggering angiogenesis, re-epithelialization, neovascularization and deposition of collagen that play a role in the wound healing process.[8] According to Bari et al, secretome components in ADSC such as decorin (Dcn) and tenascin (Tnc) play an important role in epidermal growth factor receptor (EGFR) regulation.5 Various studies have been conducted to support data related to the benefits of secretome in vivo. Hackers et al studied the effects of secretome from peripheral blood mononuclear cells (SecPBMCs) and PBMC apoptosis (Apo-SecPBMC) on models of pigs with burns, showing an increase in the number of CD31+, which is especially greater in treatment with Apo-SecPBMCs, as well as a decrease in the number of mast cells in the wound area.[9] Using the same secretome source, Mildner et al found that there was a significant increase in the number of CD31+ cells that play a role in the angiogenesis process in the SecPBMCs group.19 Similarly, Wagner et al revealed that the use of secretome from PBMCs is a promising therapy in improving wound healing that has been tested on Leprdb/db mice.20 Secretome of adipose stromal stem cell (ASCs) in hypoxia showed a greater reduction in wound area compared to that in normoxia. The use of SecPBMCs has been further thoroughly related to toxicity testing using animal models of mice (assessing systemic toxicity) and mini pigs (local toxicity studies). The results showed that the minimum dose and the maximum dose considered for the treatment of diabetic foot ulcers (DFUs) were 0.42 U/kg and 3.3 U/kg, respectively. The results showed that the administration of secretome was able to accelerate the wound healing process compared to control. Secretome with a dose of 30 μg/mL of bone marrow (BMSC-CM) resulted in a maximum wound closure of 90% on the fifth day after treatment.2 While the secretome of the multipotent adult progenitor cell (MAPC-CM) used a dose of 100 μL of 20× the concentration of conditioned medium to test wound healing in trial animals receiving intradermal injections. In clinical testing, phase 1 included secretome from PBMCs (Apo-SecPBMCs) for chronic wound treatment. This study was conducted to assess the safety of dosages used for topical applications, supernatant of 12.5×106 low dose PBMCs and equivalents of 25×106 PBMCs resuspended in NuGel Hydrogel high doses. Their results showed the use of Apo-SecPBMCs with low and high doses is safe and well-tolerated by the skin and has an effect on the reduction of the wound area.

Keywords: blood mononuclear cells, human immortalized keratinocytes.

REFERENCES

1. Niada S, Giannasi C, Magagnotti C, Andolfo A, Brini AT. Proteomic analysis of extracellular vesicles and conditioned medium from human adipose-derived stem/stromal cells and dermal fibroblasts. J Proteomics. 2015 ;232:104076.
2. Wei W, Riley NM, Yang AC, et al. Cell type-selective secretome profiling in vivo. Nat Chem Biol. 2016;17(3):326–334. doi:10.1038/ s41589-020-00768-y
3. Ahangar P, Mills SJ, Smith LE, et al. Human multipotent adult progenitor cell-conditioned medium improves wound healing through modulating inflammation and angiogenesis in mice. Stem Cell Res Ther. 2016;11(1):1–16. doi:10.1186/s13287-020-018
4. Saheli M, Bayat M, Ganji R, et al. Human mesenchymal stem cells-conditioned medium improves diabetic wound healing mainly through modulating fibroblast behaviors. Arch Dermatol Res. 2016;312(5):325–336. doi:10.1007/-019

5. Mildner M, Hacker S, Haider T, et al. Secretome of peripheral blood mononuclear cells enhances wound healing. PLoS One. 2017;8(3): e60103. doi:10.1371/journal.pone.0063
6. Wagner T, Traxler D, Simader E, et al. Different pro-angiogenic potential of γ-irradiated PBMC-derived secretome and its subfractions. Sci Rep. 2018;8(1):1–15. doi:10.1038/s41598-018-36928-6
7. Hacker S, Mittermayr R, Nickl S, et al. Paracrine factors from irradiated peripheral blood mononuclear cells improve skin regeneration and angiogenesis in a porcine burn model. Sci Rep. 2018;6 (1):1–13. doi:10.1035srep25158
8. Guo S, Wang T, Zhang S, et al. Adipose-derived stem cell-conditioned medium protects fibroblasts at different senescent degrees from UVB irradiation damages. Mol Cell Biochem. 2019;463(1):67–78. doi:10.1007/s11010-019-
9. Sohn SJ, Yu JM, Lee EY, et al. Anti-aging properties of conditioned media of epidermal progenitor cells derived from mesenchymal stem Dermatol Ther (Heidelb). 2020;8(2):229–244. doi:10.1006
10. Amirthalingam M, Bhat S, Dighe P, Seetharam R. HumanMesenchymal-Stromal-Cells-Derived-Conditioned-Medium-BasedFormulation-for-Advanced-Skin-Care. Int J Mol. 2020;2:7

THE ROLE OF MESENCHYMAL SECRETOME ON THE SKIN DURING PHOTOPROTECTION, HAIR GROWTH AND PSORIASIS

Maia Matoshvili[1], Davit Tophuria[2], Marina Tsimakuridze[3], Maia Kharabadze[4], Sopho Kandelaki[5], Irakli Amiranashvili[6]

[1]MD. PhD. Asoc. Professor of Dermato-venereology Dep. Tbilisi State Medical University, Tbilisi-Georgia
[2]MD. PhD. Assoc. Professor of Human Normal Anatomy Dep; Tbilisi State Medical University, Tbilisi-Georgia
[3]MD. PhD. Asoc. Professor of Nutrition, Aging Medicine, Environmental and Occupational Health Dep. Tbilisi State Medical University, Tbilisi-Georgia
[4]MD. PhD. Asist. Profesoor of Human Normal Anatomy Dep. Tbilisi State Medical University, Tbilisi-Georgia
[5]MD. PhD. Asoc. Professor of Human Normal Anatomy Dep. Tbilisi State Medical University, Tbilisi-Georgia
[6]MD. PhD. Asoc. Professor of Human Normal Anatomy Dep. Tbilisi State Medical University, Tbilisi-Georgia

Introduction: Ultraviolet (UV) radiation can cause some skin problems, especially photoaging. Photoaging is skin aging caused by excessive UV exposure, which causes morphological and physiological changes of the skin such as the appearance of wrinkles and reduced skin elasticity.[1] Research into the secretome as a therapy to prevent the influence of photoaging has been reported. Several in vitro models of skin cells, HDFs and HaCaTs, both of which are cells that function against defenses due to UVB radiation, were used.[2] UV radiation can cause inhibition of the cell proliferation rate and reductions of collagen I, collagen III and elastin due to downregulation of expression of mRNA. UV radiation can also cause increased levels of MMP1 and MMP9, resulting in inhibited synthesis of procollagens and triggering activation of various signaling pathways, namely mitogen activated protein kinase (MAPK), protein activator 1 (AP-1) and nuclear factor kappa B (NF-κB), which contributes to cell damage due to ROS formation and can trigger the apoptosis of skin cells, so as to inhibit skin regeneration and be able to inflict DNA damage in keratinocytes.[3] Various studies have been conducted to investigate the effects of secretome as an agent in the fight against photoaging. In vitro testing was done by various methods. Methods that were used looked at cell proliferation. The secretome of ADSCs had the effect of providing photoprotection. This is related to the content of biological factors that play a role in particular platelet-derived growth factor AA (PDGF-AA), which can promote deposition and remodeling of the extracellular matrix. This effect is alsoassociated with the content of TGF-β1 in the secretome, which can stimulate mRNA expression and increase collagen production. This mechanism is also related to the upregulated expression of wnt3a and catenin in the Wnt/βcatenin signaling pathway, which is associated with increased expression of TGF-β2 (which is important for the synthesis of procollagen type I).[4] Other tests performed on the test animals, which were generally nude mice, pertained to UVB exposure. The results revealed a reduction in wrinkles and skin distress by improving skin hydration after macroscopic use of secretome and increased collagen synthesis based on Masson trichrome analysis. In some studies, it has been reported that secretome can be used as an active ingredient in cosmetics, reminding us of its benefits in regenerating the skin. Generally, research utilizes secretome as a skin care therapy to prevent various aging factors, including photoaging. Amirthalingam et al formulated secretome as an antiaging cosmetic product in the form of semi-solid serum preparations, with the following doses used 0.25%, 0.5% and 1%. Similar research by Kim et al utilized secretome as raw material in the manufacture of cosmetics applied using an air brush, with secretome concentration as high as 5%. The results showed a reduction in test parameters, such as wrinkles, and increased skin moisture.[5] Similarly, Kim et al also used secretome as a raw material cosmetic material in the form of cream preparations. The secretome

concentration used was 1%, which was contoured in 3D culture. The use of secretome can increase collagen synthesis greater than control and reduced aging by improving skin elasticity. Hair Growth- Alopecia is a term used to state thecondition of baldness or hair loss due to abnormalities in the scalp that can be caused by various factors.[6] This condition causes the active phase of hair growth (anagen stage) to be inhibited, while the rest phase (telogen stage) becomes faster in the hair growth cycle. So, a lot of research focuses onunderstanding the cycle of hair growth. The effect of secretome therapy on hair growth has been reported in various studies. In vitro testing is generally conducted to determine the proliferation ability of hair cells. Used human papilla cells of human follicles (HFDPCs), outer root sheath cells (ORCs) and human epithelial keratinocytes (HEKs),[7] which are types of cells located in hair follicles that can stimulate hair growth and regeneration through reciprocal communication processes with epithelial cells. Zhang et al investigated the paracrine factors that may be involved in hair follicle regeneration using secretome from dermal papilla cells (DPCs). The results showed that the use of the secretome of DPCs in passage 3 secreted a large amount of CXCL12, MMP3 and biglycan, which played a role in the activation of the Wnt/β-catenin signaling line, as well as LTBP1.[7] Activation of this pathway is known to trigger the proliferation of hair follicle cells. The use of secretome is able to trigger the proliferation of HFDPCs and ORCs, to accelerate the telogen phase to anagen and ex vivo can induce proliferation of the hair matrix. In the application using animal models in the form of mice C3H/HeN, secretome was able to induce hair follicle growth. Pu et al also reported that secretome was able to trigger proliferation and increase hair follicle growth in mice ischemia/reperfusion- (I/R-) models. Psoriasis- Psoriasis is a chronic inflammatory condition of the skin that causes increased levels of expression of interleukin (IL-17). In psoriasis, Langerhans cells represent a disorderin the migration of epidermis cells that serve as an immuneresponse associated with T cell responses, particularlyTh17-mediated. This condition also causes abnormalitiesin cytokine production that can cause epidermis hyperplasia as well as abnormal keratinocyte apoptosis (KCs).[8] Psoriasis is characterized by the appearance of patches or rashes with thick white scales on the skin and nails. Studies on secretome in the treatment of psoriasis have been conducted. Psoriasis modeling can be uses using imiquimod with Wistar rats models. Imiquimod causes inflammation characterized by the presence of coarse lamela and excoriation. The use of secretome is able to reduce the effects of inflammation caused by the use of imiquimod (IMQ) better than control. Zhang et al stated that exosomes (secretome) is able to decrease psoriasis score in IMQ rats model through inhibiting of maturation and activation of dendritic cells (DC) and IL-17 in HaCaTs.[9] Seetharaman et al reported that the secretome of adipose tissue, which is administered topically, showed a significant decrease in the amount of erythematous plaque and silver scales on the scalp of the sufferer after administration of the secretome for 2 weeks and disappeared after one month of administration.[10]

Conclusion: Secretome, a bioactive factor secreted by MSCs, has a variety of benefits on the skin as a therapeutic agent for various regenerative diseases. Research on the use of secretome for skin applications and formulation development are still very limited. Several studies reported that the process to obtain secretome from MSCs was through isolation from various adult tissues and cultured in a medium of growth. The culture process can affect the level of expression of the resulting factors. Applications of the secretome for skin include wound healing, photoprotection, promotion of hair growth, psoriasis treatment, and other application as antimicrobial. Considering the various constituents of secretome, it has a lot of potential in various diseases needing the development of and more indepth studies in order to be maximally used.

Keywords: dendritic cells (DC) and IL-17 in HaCaTs.

REFERENCES

1. Liu R, Wang F, Wang Q, Zhao X, Zhang K. Mesenchymal stem cells from skin lesions of psoriasis patients promote proliferation and inhibit apoptosis of HaCaT cells. Genet Mol Res. 2015;14:17758–17767
2. Eaton L, Mellody K, Pilkington S, Dearman R, Kimber I, Griffiths C. Impaired Langerhans cell migration in psoriasis is due to an altered keratinocyte phenotype induced by interleukin-17. Br J Dermatol. 2015;178(6):1364–1372
3. Myung PS, Takeo M, Ito M, Atit RP. Epithelial Wnt ligand secretion is required for adult hair follicle growth and regeneration. J Investigative Dermatol. 2016;133(1):31–52.
4. Jeong Y-M, Sung YK, Kim W-K, et al. Ultraviolet B preconditioning enhances the hair growth-promoting effects of adipose-derived stem cells via generation of reactive oxygen species. Stem Cells Dev.2016;22(1):158–179.
5. Brunchukov V, Astrelina T, Usupzhanova D, et al. Evaluation of the Effectiveness of Mesenchymal Stem Cells of the Placenta and Their Conditioned Medium in Local Radiation Injuries. Cells. 2017;9 (12):2556.
6. Hu Q, Luni C, Elvassore N. Microfluidics for secretome analysis under enhanced endogenous signaling. Biochem Biophys Res Commun. 2018;497(2):480–484.
7. Li M, Luan F, Zhao Y, et al. Mesenchymal stem cell-conditionedm medium accelerates wound healing with fewer scars. Int Wound J.2018;14(1):64–77.
8. Evans EA, Sayers SR, Kodji X, et al. Psoriatic skin inflammation induces a pre-diabetic phenotype via the endocrine actions of skin secretome. Mol Metab. 2019;41:101035
9. Park J, Jun EK, Son D, et al. Overexpression of Nanog in amniotic fluid–derived mesenchymal stem cells accelerates dermal papilla cell activity and promotes hair follicle regeneration. Exp Mol Med. 2019;51(7):1–17.
10. Abreu CM, Cerqueira MT, Pirraco RP, Gasperini L, Reis RL, Marques AP. Rescuing key native traits in cultured dermal papilla cells for human hair regeneration. J Adv Res. 2020.

MODERN APPROACH TO THE CLINICAL VIEW, PATHOGENESIS AND TREATMENT METHODS OF ENDOMETRIOSIS

Samadli Ulviyya, Asadova Shafaq, Vahabova Sharifa, Gurbanova Rena, Abbasova Feride
Departments of I obstetrics and gynecology and oncology of AMU.

Objective: Endometriosis is a progressive estrogendependent widely spread disease especially among women suffering of chronic pelvic pain (40-80%) and infertility (25-80%). Pathogenesis is multifactored, but ectopic dissemination of endometrial tissue with forming of endometrioid implants is doubtless. The role of stem cells in its pathogenesis is proved. The choice of therapeutic approaches is wide, however the unique approach has not been worked out yet. The management is determined with the aim of therapy (treatment of pelvic pain or infertility).

Results: Laparoscopic surgery and excision of en dometriomas are associated with decreasing pelvic pain. Therefore there is a number of patients for those surgery is the primary approach in endometriosis treatment. Bowel endometriosis is conjugated with severe pelvic pain and high risk of complicated surgery. Pharmacological agents (Gonadotrophin-Releasing Hormone analogs, progestagens, oral contraceptive pills, androgens, non-steroid anti-inflammatory drugs, etc.) are commonly applied ongoing for endometriosis of various location. They control pelvic pain syndrome effectively, but every of them has its advantages and disadvantages.

Conclusion: Elagolix treatment may become the basis of new strategy, which core is partial estrogen depression, therefore further research is required. Angiogenesis inhibition also represents a new line in endometriosis management. Sorafenib effects on stem cells proliferation, invasion and HIF-1 activation help to suppose new possibilities for its application. Anti-angiogenic drugs may show good result separate or being combined with hormone therapy and provide high efficacy of complex pharmacological approach.

The relevance of the problem

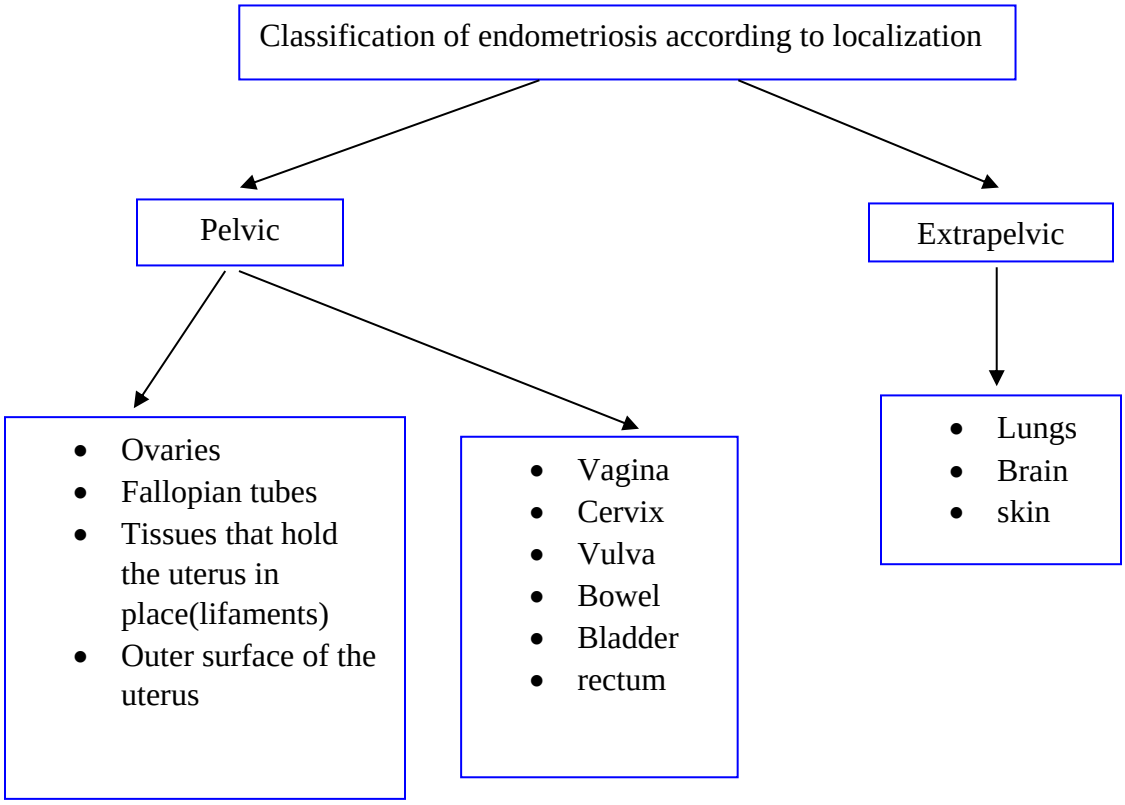
Endometriosis is an estrogen-dependent chronic progressive disease that is widespread in women with pelvic pain (40-80%) and infertility (25-80%). Although the pathogenesis of the disease is multifactorial, the spread of the endometrium to ectopic areas and the subsequent formation of endometrioid heterotopies are undeniable. The role of stem-shaped cells in this process has also been proven. Despite the wide range of treatment methods for endometriosis, a unified approach to them is not defined by specialists, and the choice of treatment method is determined individually by the goal (treatment of pelvic pain or infertility). Endometriosis remains an actual scientific and clinical problem, and its main controversial issues are: is endometriosis a disease; mechanisms of its formation and classification; genetic and immunological aspects; internal and external endometriosis and adenomyosis; diagnostic criteria, etc.

Terminology and classification

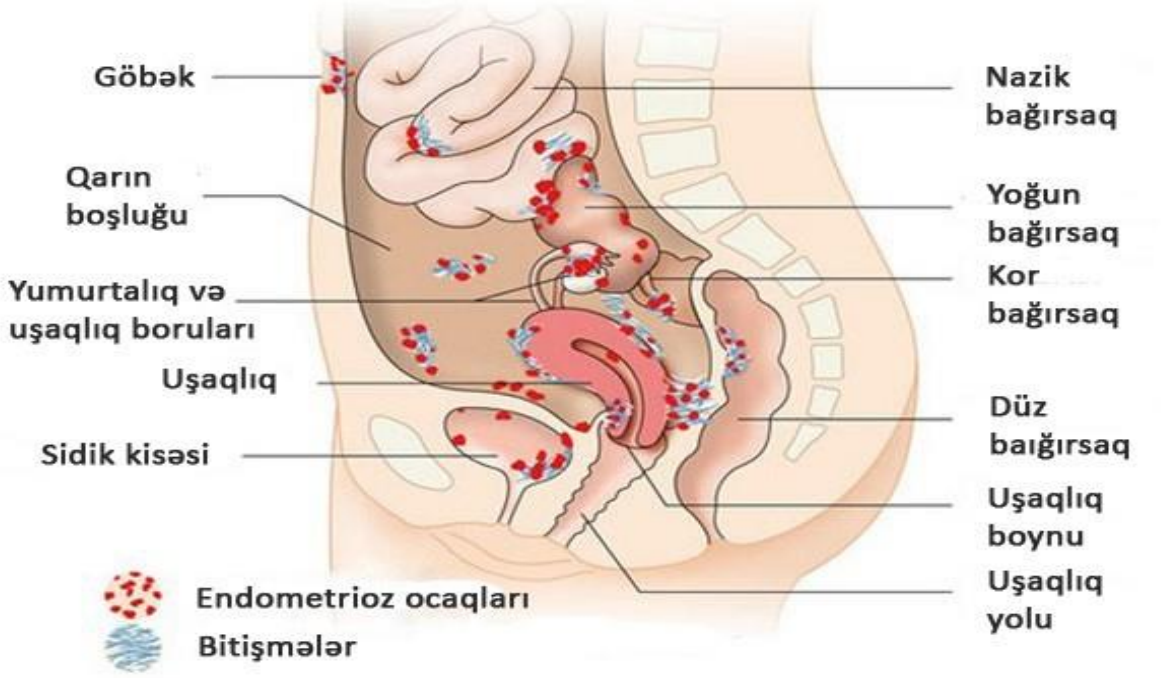
Endometriosis is a pathology characterized by the fact that endometrial tissue, normally found only in the inner lining of the uterus, is found in other membranes of this organ and other genital and extragenital organs outside the uterus. In most cases it is found in women of reproductive age (20 to 40 years old), but it rarely occurs in postmenopausal women as well. Although it manifests itself in

very frequent cases with pelvic pain and infertility, sometimes it can also be asymptomatic. It is usually found in the genitals and pelvic organs, but it can also appear in other areas. Since the endometrioid tissue contains receptors for hormones, the changes in the normal endometrium occur in that tissue and are manifested by bleeding once a month. There are several classifications of endometriosis. The most widespread classification is the one proposed by the American Veterinary Society (R-AFS) in 1979 and revised in 1985 and 1986. It is based on the calculation of the number of heterotopias expressed in points [I stage (minimal changes) - 1-5 points; II stage (moderate changes) – 6-15 points; III stage (acute changes) – 16-40 points; Stage IV (gross changes) – more than 40 points]. At the same time, clinical practice uses the classification of endometriosis based on its location. From this point of view, endometriosis is divided into two groups - genital and extragenital. Genital endometriosis can be located in the myometrium (adenomyosis), peritoneum, ovaries, cervix, uterus, and perineum. Extremal endometriosis, on the other hand, is not topographically related to the organs and tissues of the reproductive system, and mainly includes the organs of the abdominal cavity (appendix, rectum, small and large intestine), lungs and pleural cavity, skin (post-operative scars, extremities, lymphatic nodes).

Diagram 1



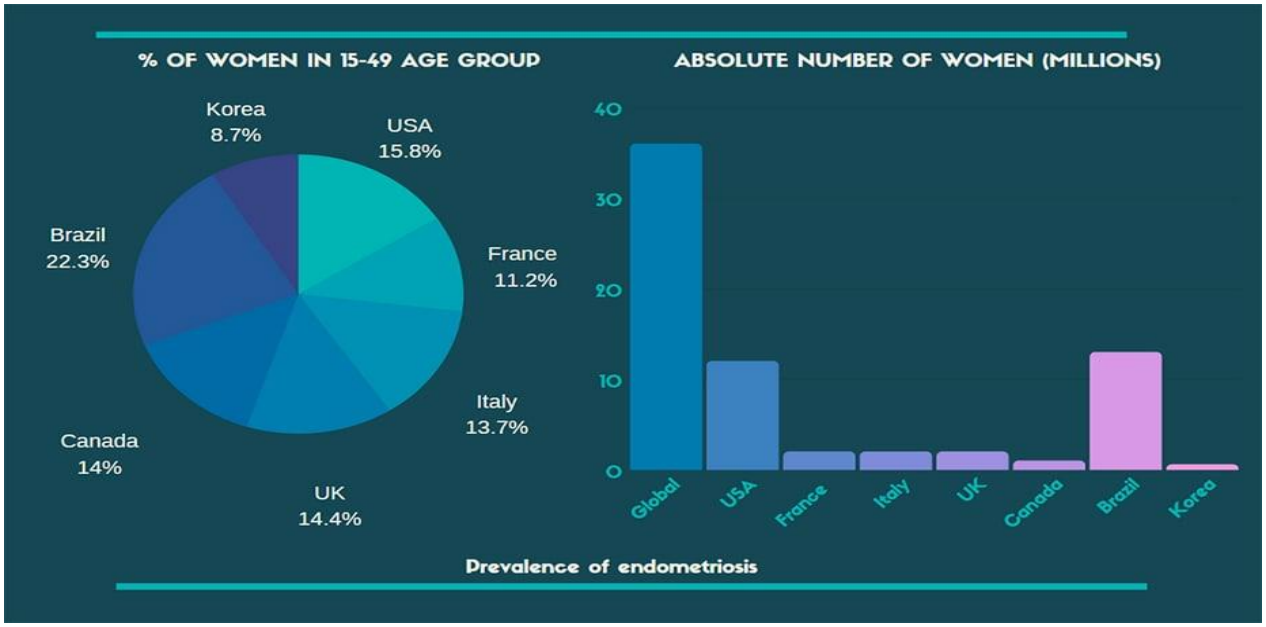
Picture 1



Epidemiology

Endometriosis ranks 3rd in prevalence after genital inflammatory diseases and uterine fibroids. It is observed in 7-50% of women. It occurs in 2-10% of women who apply for the first time, and in 30% of women who have undergone gynecological surgery. 20-50% of women suffering from infertility also have foci of endometriosis.

Picture 2. Prevalence of endometriosis in different countries



Pathogenetic factors
Hormonal disorders; immune system dysfunction and impaired biological response of endometrial cells to sex hormones; constitutional hereditary genetic predisposition; deficiency of the antioxidant system of the body; long-term tension of protective-adaptive reactions; prolonged use of intrauterine contraceptives; stressful situations.

Hormonal – the secretion and effect of progesterone is disturbed in patients. An elevated level of estrogens is noted, which stimulates the increased reproduction of endometrial cells. Most often, in such women, an increase in prolactin secretion and a violation of the function of the adrenal gland are observed.

Immunological – an imbalance in the growth and death of cells is characteristic. Intensified secretion of endothelial growth factor leads to the development of vessels and the spread of endometriosis foci. At the same time, the activity of killer cells decreases, apoptosis (genetically programmed death of cells) slows down. They investigated the inability of the immune system to cope with the cycle cell of retrograde mens fluid. If the immune system copes with endometriosis, then endometriosis is related to allergic and autoimmune pathologies. And the causality of this theory has not been fully investigated.

Retrograde theory (implantation theory) – it is the most widely accepted theory. It was first proposed by John Sampson. According to the theory, during menstruation, a part of the endometroid cells flows into the fallopian tubes, into the abdominal cavity, attaches to the peritoneal surface and develops there, but it appeared in women without mensis, in pre-pubescent girls (the theory did not justify itself), and endometriosis was also found in the lungs and brain, and this distanced us from this theory.
In addition, it is noted that endometroid cells differ from normal endometrial cells in their biochemistry, hormonal response and immunology. It is assumed that endometroid cells are a subset of endometrial cells.

Theory of endometrial formation – according to the theory, endometrial cells pass into the uterine wall during abortions, intrauterine diagnostic procedures, operations, that is, during manipulations accompanied by a violation of the integrity of the intrauterine mucous membrane. Moving to the muscle layer, endometrial cells begin to increase and multiply and create an endometriosis focus. This theory explains the appearance of foci of endometriosis in organs located far away by the proliferation of endometrial cells through blood vessels during operations on the uterus.

Other theories
Stem-like cells; environment; müllerionosis (embryonic); coelomic metaplasia; autoimmune; oxidative stress theories. Although the exact cause of endometriosis is unknown, many theories have been presented to better understand and explain its development. These concepts do not necessarily exclude each other. The pathophysiology of endometriosis is most likely multifactorial and involves an interaction between several factors.

Symptoms of endometriosis

The course of endometriosis can be different: at the beginning the disease passes symptom-free and can be detected only as a result of preventive examinations. However, there are also acute symptoms of endometriosis. One of them is **pelvic pain** and is identified in about 16-24% of patients. The nature of the pain (mild, severe, spastic, stabbing pain), localization (lower back, rectum, lower abdomen), the degree of pain does not depend on the degree and stage of proliferation of endometrioid tissue, the pain is associated with menstruation. It usually occurs 1 week before menstruation, during menstruation and 1 week after menstruation. If there is inflammation and adhesions, the pain is permanent and unrelated to menstruation, it becomes chronic. Pelvic pain has a significant negative impact on women's mental health and quality of life; especially in women suffering from pelvic pain, a high level of anxiety and depression, loss of working capacity, and restrictions on social activities are identified.

Dysmenorrhea — painful menstruation — it is found in 40-60% of patients. Most often it intensifies in the first 3 days of menstruation and is often due to bleeding into the cavity of the cyst and, as a result, its increased pressure; irritation of the peritoneum; and endometriosis bleeding from foci; are associated with compression of the blood vessels.

Dyspareunia (painful intercourse) – ain during defecation and urination. Discomfort and pain during sexual intercourse, which occurs when endometriosis is localized in the uterus, rectovaginal partition, oma-in the area of the uterine ligaments, and uterus-rectum cavity.

Menorrhagia — heavy and continuous menstruation — it is found in 2-16% of patients. It is often accompanied by adenomyosis and related diseases: uterine fibroids, ovarian polycystosis.

Infertility – it occurs in 25-40% of women with endometriosis. Gynecologists still do not know exactly what the mechanism of infertility in endometriosis is. It is assumed that inflammation and adhesions cause infertility. The main reason of infertility is the presence of adhesions in the pelvic organs, thereby the violation of normal anatomy.

Table 1. Main symptoms of localization of endometriosis.

Localization	Symptoms
Genital organs	Dysmenorrhea Pelvic pain Infertility Lumber-sacral pains Menstrual irregularity
Gastro-intestinal tract	Tenesmes and rectal bleeding Diarrhea, constipation
Urinary system	Hematuria (related to menstruation) Urethra obstruction
Scar area, umbilicus	Bleeding and pain associated with menstruation
Lung	Menstrual hemoptysis

Endometriosis and pregnancy

Endometriosis reduces the chances of pregnancy termination, so pregnant women with endometriosis should be constantly monitored. The probability of pregnancy after the first 6-14 months of endometriosis treatment is 15-56%. Main risks;; ectopic pregnancy; placental abruption - 1.5-6 times more common than other women; miscarriages; premature birth; preeclampsia according to recent evidence. In pregnant women with endometriosis, the prognosis is alleviated, the reason: an increase in progesterone level reduces the growth of endometric tissue; absence of menstruation; due to low levels of estrogen during lactation.

Diagnosis

To diagnose the disease, a gynecological examination is carried out. By means of colposcopy examination, the location and shape of the damage with endometriosis are clarified. The most valuable of radiological methods is spiral computed tomography. Because, by means of it, it is possible to accurately determine the nature of endometriosis, its localization, interaction with neighboring organs, as well as to clarify the state of the small pelvis cavity. One of the most informative research methods is magnetic resonance, which provides accurate visualization of small pelvic organs and their structure thanks to the high resolution of magnetic resonance imaging. Using this method, ovarian endometriosis is determined with an accuracy of 96%. One of the most accessible and widespread methods for diagnosing endometriosis is the ultrasound examination method. The method helps to clarify the location, dynamics, etc. of the focus under the influence of therapy.

Currently, one of the most accurate methods of diagnosing the disease is laparoscopy (puncture of the abdominal wall with the introduction of a special device - a laparoscope). For example, this method provides the diagnosis of ovarian endometriosis with an accuracy of 96%. Laparoscopy also assesses the degree of endometriosis; lesions may appear dark blue, powdery black, red, white, yellow, brown, or non-pigmented; detects the size of lesions; names endometriosis areas by various names, such as implants, lesions, or nodules. Larger lesions may appear inside the ovaries as endometriomas or "chocolate cysts", "chocolate", because they contain a thick brown liquid, mainly old blood.

The identification of various tumor markers in the blood serum is becoming increasingly important. Currently, most of the existing ones are the determination of CA-125, REA and SA 19-9 markers, as well as the RO-test (universal diagnostic test of tumor growth), carried out by the method of immunoenzyme analysis. It was determined that the concentrations of oncomarkers CA 125, CA 19-9 and REA in the blood serum of healthy people were on average 8.3, 13.3 degrees and 1.3 mg/ml, respectively. During endometriosis, these indicators are on average 27.2, 29.5 degrees and 4.3 mg/ml, respectively.

Treatment

In recent years, the treatment of endometriosis has been the most discussed aspect of the problem. The provision that is indisputable to this day — it is impossible to eliminate the anatomical substrate of endometriosis by means of any effect, except for surgical operation, at the same time, other procedures reduce the severity of disease symptoms in a limited number of patients and restore the functions of various parts of the reproductive system. The main goal of treatment — hormonal treatment aimed at preventing the growth of endometrioid cells and slowing down the progression of the process; treatment of infertility; surgical operation aimed at eliminating the hearth.

The most common variants of surgical intervention during pathology: destruction of foci in the cervix and uterus with laser, cold or electric current; removal of the uterus with or without increments; ablation (endoscopic resection) of endometriosis foci; laparoscopic removal of foci in the ovaries and peritoneum. Most often, hormonal treatment is prescribed before and after surgery. Hormonal therapy is also prescribed at times when there are contraindications to surgery. The goal of treatment is inhibition of ovulation, lowering of estrogen level, stopping of menstrual bleeding. All this leads to the atrophy of the endometrium and the reduction of the size of endometrioid foci.

However, surgical treatment is not always appropriate or acceptable to the patient. Alternatively, it can be considered a method of treating minimal and moderate endometriosis (without diagnostic testing), or rather, symptoms that are likely to be the cause of this disease. This therapy can be accepted only after a thorough examination of the patient, provided that there are no possible causes of other (non-gynecological) symptoms, with the exception of volumetric formations in the abdominal cavity, and only by a doctor who has extensive experience in the treatment of endometriosis.

The most commonly used drugs for the treatment of endometriosis are: progestagens; estrogen-gestagenic preparations; agonists of gonadotropin-releasing hormone; antigestagens.

Symptomatic treatment of endometriosis includes the following group of drugs: non-steroidal anti-inflammatory agents: spasmolytic drugs; iron preparations for the correction of anemia.

A socially significant complication of endometriosis is infertility. For its treatment, in vitro fertilization is widely used (IVF). IVF is effective during endometriosis only in 10-20% of cases. It is most commonly indicated in women over 35 years of age, for severe disseminated forms of the disease, in severe lesions of the fallopian tubes.

Prevention

avoid excessive physical stress during childhood and youth; taking combined oral contraceptives; reducing abortions and other intrauterine manipulations; avoiding contact between healthy and damaged tissues during surgical treatment of endometriosis.

Prognosis

Endometriosis tends to recur. During the last year's 5 years of treatment, this disease occurs in 40% of women, and in the next 5 years-in 75%. When menopause begins, the probability of recurrence of the disease decreases. In the case of radical removal of the organ damaged by the disease, the process does not progress.

Conclusion

Thus, for endometriosis, paradoxical aspects of etiopathogenesis and their clinical contrasts, the cause of which has not yet been found, are characteristic. In fact, in the benign nature of the disease, local invasion, an aggressive course with wide spread of foci is possible; minimal endometriosis is often accompanied by severe pelvic pain, large endometrioid cysts are asymptomatic; the cyclic effect of hormones causes the development of endometriosis, while continuous use stops the development of the disease. Such enigmas stimulates further deepening and expansion of fundamental and clinical research in all areas of the problem of endometriosis.

REFERENCES

1. http://www.mif-ua.com/archive/article/5993
2. http://www.medlinks.ru/article.php?sid=23139
3. http://mednik.com.ua/node/2258
   Konovalenko, A. A. Actual problems of diagnosis and treatment of endometriosis / A. A. Konovalenko. - Text: direct // Young scientist. - 2016. - No. 25 (129). - FROM.
4. 153-156. — URL: https://moluch.ru/archive/129/35861/

The Eighth International Scientific – Practical Virtual Conference in
Modern Medicine and Health: Prognosis, Achievement and Challenges

THE SCIENTIFIC TALKS OF INVOCATIONS OF SPECIFICITIES OF PHARMACIST PROFESSIONAL AND HIGHER MEDICAL-PHARMACEUTICAL EDUCATIONAL CHALLENGES OUTLOOKS AND ACHIEVEMENTS IN GEORGIA

Nodar Sulashvili[1], Nana Gorgaslidze[2], Luiza Gabunia[3], Marina Giorgobiani[4], Irine Zarnadze[5], Shalva (Davit) Zarnadze[6]

[1]MD, PhD, Doctor of Theoretical Medicine in Pharmaceutical and Pharmacological Sciences; Professor of Alte University, International School of Medicine, Division of Pharmacology, Tbilisi, Georgia; Invited Professor of Tbilisi State Medical University, Tbilisi, Georgia;

[2]MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Tbilisi State Medical University, Head of The Department of Social and Clinical Pharmacy, Tbilisi, Georgia.

[3]MD, PhD, Doctor of Medical Sciences, Professor, Director of the Scientific Research-Skills Center at Tbilisi State Medical University, Professor of the Department of Medical Pharmacology at Tbilisi State Medical University, Tbilisi, Georgia.

[4]MD, PhD, Doctor of Medical Sciences, Professor of Tbilisi State Medical University, Department of Hygiene and Medical Ecology, Tbilisi, Georgia.

[5]MD, PhD, Doctor of Medical Sciences, Professor of Tbilisi State Medical University, Department of Public Health, Health Care Management, Policy and Economy, Tbilisi, Georgia.

[6]MD, PhD, Doctor of Medical Sciences, Professor of Tbilisi State Medical University, Head of the Department of Nutrition, Aging Medicine, Environmental and Occupational Health, Tbilisi, Georgia.

Email:

ABSTRACT

The main objective of the study was to analyze the challenges of specificities of pharmacist occupation and higher medical-pharmaceutical educational outlook in Georgia. The study was a quantitative investigation and analysis of the challenges of specificities of pharmacist occupation and higher medical-pharmaceutical educational outlook in Georgia, by using questionnaires. Were conducted a survey study. The in-depth interview method of the respondents was used in the study. The 7 types of approved questionnaires were used (Respondents were randomly selected): Questionnaire for chief pharmacists: 410 chief pharmacists participated in the study. Questionnaire for patients: 1506 patients (customers of drug-stores) participated in the study. Questionnaire for the employed pharmacy faculty-student: 222 employed pharmacy faculty students participated in the study. Questionnaire for health-care specialists: 307 public health specialists participated in the study. Questionnaire for pharmacist specialist, 810 pharmacist specialists participated in the study. Were used methods of systematic, sociological (surveying, questioning), comparative, mathematical-statistical, graphical analysis. The data were processed and analyzed with the SPSS program. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. We defined $p< 0.05$ as significant for all analyses. According to the study results, the level of basic training of pharmacists should be in compliance with the contemporary requirements. The pharmacist should have deep knowledge in pharmacology, in pharmacotherapy, in toxicology, in pharmaceutical care, in clinical pharmacy, in pharmacokinetics, in pharmacodynamics, in basic of medicine and in other pre-clinical and clinical directions. Such knowledge can be obtained only in the higher pharmaceutical education institutions. Therefore, pharmacist working in pharmacy must have only higher pharmaceutical education. It is necessary to provide a deep cooperation between pharmacists and physicians on the issues of pharmacotherapy and healthcare to ensure the patients' health state effective improvement, and also to provide the best

feedback regulation and revision in the healthcare specialists' team work. Pharmacists also should be responsible for registration of the drugs' side effect, as well as be attentive in case of improperness and professional defects of drugs they provide. The results of our study have been shown and substantiated, that the pharmacists, as well as doctors and stomatologists, who are obliged to take part in the mandatory certification by the Government, in order to improve the responsibility on their own professional specialization for motivate and improve their vocational knowledge and skills with the help of continuous education.

It would be promoted, that pharmacist to become more responsible, accountable and liable on for enhance their professional knowledge, skills and competencies. All the above mentioned first time we conducted a comprehensive and deep study of the scientific research for specificities of the role, achievements, innovations, professional and enhancement prospects of pharmacists in health care sector globally. It should be noted that in developed countries and in many developing countries pharmaceutical specialty is regulated profession alike the family medicine. In western countries pharmacist as a family doctor need higher pharmaceutical education, diploma and continuous pharmaceutical education, pharmaceutical license and periodic accreditation. Only pharmacists with higher pharmaceutical education have the right to work as pharmacists' position in the pharmacies. On the pharmacists' certification programs should be only involved pharmacists who have graduated pharmaceutical faculties from state recognized and accredited universities. To increase the pharmacist's professional qualification, professionalism, professional knowledge and competency the higher pharmaceutical education universities programs should more emphasize the mentioned subjects. It is too important, that a pharmacist should realize and understand that qualification upgrading study courses, professional trainings and professional workshops are of great necessity for further professional advancement. Thus, the Government should develop continuous pharmaceutical education programs accessible to all pharmacists. The qualification upgrading study courses, professional education or training courses should be available for all pharmacists. Pharmacist's education process should not be stopped. Developing a continuous pharmaceutical education system will enhance the professionalism of the pharmaceutical personnel. Experiential education should encourage perfection of critical opinion and the problem resolving processes along with the medicine discovery.

Keywords: Pharmacist, occupation, higher medical, pharmaceutical, educational, outlook, Georgia.

TABLE OF CONTENTS

Organizer of the conference:

MTÜ. The International Research Education & Training Center. (Estonia, Tallinn).

LTD The Southern Caucasus International Academy of Modern Sciences. (UK, London).

LTD. Aspendos-Academy. International Academy of Medical and Social Sciences. (UK, London).

Tugay Pharmacy Company (Azerbaijan, Baku)

Invited organizations:

Azerbaijan Medical University (Azerbaijan)

Tbilisi State Medical University (Georgia).

NGO Education Support & Investment Fund (Georgia, Tbilisi)

WKMU Marat Ospanov (Kazakhstan, Aktobe)

Astana Medical University (Kazakhstan, Astana)

Alte University (Georgia, Tbilisi)

David Aghmashenebeli University (Georgia, Tbilisi)

©Publisher: NGO International Center for Research, Education and Training.
MTÜ Rahvusvaheline Teadus-, Haridus- ja Koolituskeskus.
Management Board Member: Seyfulla Isayev.
©Publisher: NGO Azerbaijan International Diaspora Center in Georgia.
Deputy of director: Aytan Huseynova.
©Editorial office: Narva mnt 5, 10117 Tallinn, Estonia.
©Typography: NGO International Research, Education & Training Center. The Baltic Scientific Journals.
Registered address: Narva mnt 5, 10117 Tallinn, Estonia.
Telephones: +994 55 241 70 12; +994518648894; +994 70 375 70 12;
Website: http://sc-media.org/
E-mail: gulustanbssjar@gmaill.com, sc.mediagroup2017@gmail.com
E-ISBN:
DOI suffix: 10.36962/MHPAS08

This book consist with 222 pages





THE EIGHTH INTERNATIONAL SCIENTIFIC – PRACTICAL VIRTUAL CONFERENCE IN MODERN MEDICINE AND HEALTH: PROGNOSIS, ACHIEVEMENT AND CHALLENGES

CONFERENCE PROCEEDINGS

AZERBAİJAN-ESTONIA-KAZAKHSTAN-TURKEY

ESTONIA, TALLINN OCTOBER 21-22, 2022