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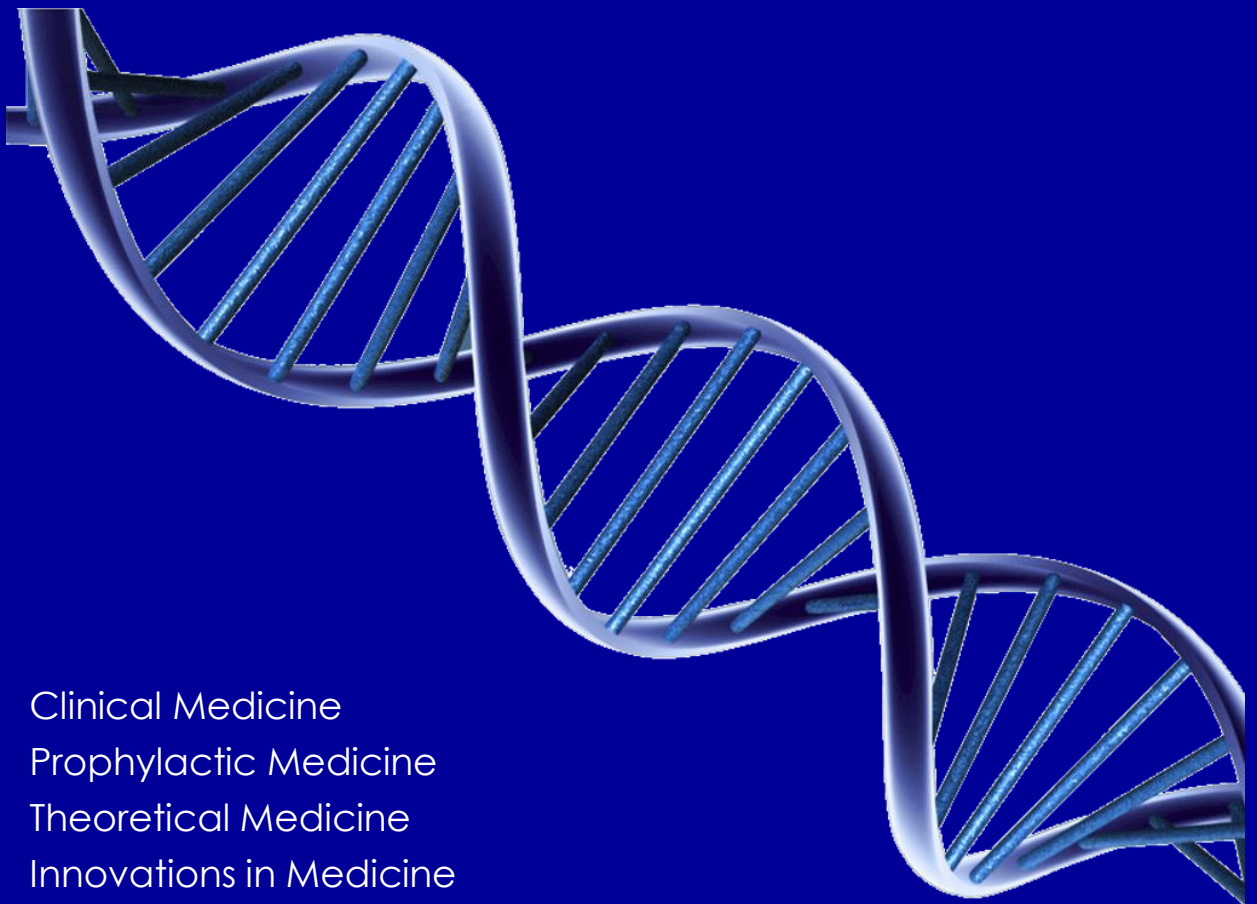
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CHARACTERISTICS OF IMMUNE SYSTEM OF THE SKIN (REVIEW)

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Being the largest organ of the body, skin protects the internal organs from various external insults, such as invading pathogens (bacteria, fungi, viruses, parasites, and mites), exogenous physical stresses, chemicals, and others. Besides, it has an essential role in regulating temperature, electrolytes, water, and others, and providing essential vitamins to the whole body, ie, Vitamin D. Unlike other mucosal epithelia, skin possesses a dry (due to lipids) and a formidable layer of epithelia, which prevent the ease of access of microorganism entry.^{1,2} Despite other routes of pathogen entry, the skin plays an important role in protecting from pathogens. Besides, skin cells also produce many chemicals, such as fatty acids and defensins (antibacterial peptides), to destroy the pathogens. As such, skin is composed of three different major layers, which harbor several types of cells, including immune cells, that perform various functions.³ Considering this high amount of immune niches in the skin, it is regarded as “skin immune system” or “tertiary lymphoid structures” or “tertiary lymphoid organs”^{4,5}. In addition, damaged or tender skin is the best route of entry for many microorganisms. Therefore, regulation of immune responses in the skin is at most important. The skin-associated lymphoid system is composed of tightly coordinated innate and adaptive arms of the immune system. Despite the innate immune system, humoral immunity (also called antibody-mediated immunity) in the adaptive immune system is also critical for regulating immune homeostasis in the skin. B-cells and their subtypes in the skin have been implicated in antibody-mediated protective immunity. However, the type of antibody production (either self-reactive or non-self-reactive) depends on the type of antigen (self or foreign) exposed, and may drive or suppress the inflammatory response. Therefore, B-cells are implicated in both homeostatic and pathogenic mechanisms in the skin. Although information about localized skin-resident B-cells is inadequate, their migration, via expressing cutaneous lymphocyte-associated antigen and chemokine receptors, to the skin during the inflammatory diseases is well established. Many autoimmune skin diseases are positively correlated with the infiltrating B-cell subsets. Moreover, the skin-homing B-cells respond to local antigens and produce antibodies, which is devoid of primary and secondary lymphoid organs. These antibodies play a crucial role in autoimmune diseases. Some B-cell-mediated autoimmune diseases are mostly by autoreactive B-cells that are possibly devoid of T-cell involvement. The precise source of the autoreactive B-cells in the skin is unknown and is debatable. It is assumed that autoreactive B-cells are generated from either bone marrow or secondary lymphoid organs. However, how these cells are produced by escaping the central or peripheral tolerance checkpoints is still an unanswered question. Once autoreactive B-cells differentiate into memory B-cells and plasma cells in the germinal centers, they become culprits for systemic secretion of autoantibodies.^{6,7} Once the plasma cells are generated, it's their innate nature to reach bone marrow and become a reservoir for a long time (even lifelong) of autoantibody secretion, upon antigen encounter. In skin-associated or cutaneous autoimmune diseases, the presence of autoantibodies is considered a unique diagnostic method. The skin resident autoreactive B-cells amplify or aggravate the



autoimmune disease via antibody secretion (IgM, IgG, and IgA), antigen-presentation, T-cell stimulation, pro- and anti-inflammatory cytokine secretion (IL-6, IL-10, and TGF- β), and growth factors secretion (platelet-derived growth factor, basic fibroblast growth factor) in the microenvironment. Skin-associated lymphoid tissue contains both innate and adaptive immune systems, which confer protection locally and systemically. 7. Disturbance in the above system leads to episodes of opportunistic infections and the development of tumors or other immunological diseases. The skin protects the host from most infectious agents by two mechanisms; antigen-nonspecific and antigen-specific. 8. If a physical barrier (stratum corneum or sebaceous gland secretions) is breached, the innate immune system comes into action. Like other parts of the body, the innate immune system is the first-line defence in the skin, and keratinocytes, monocytes, macrophages, Langerhans cells, dendritic cells, mast cells, and complement components are the innate components of the skin.9,10.

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CURCUMIN AND RESVERATROL TREATMENT OUTCOMES IN DERMATOLOGY

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Curcumin originates from turmeric or *Curcuma longa* and belongs to the family of Zingiberaceae or ginger that is usually used as spice for food flavouring. Turmeric is commonly-used in South Asia, India, and Indonesia and is often used as a dye or food color since it exists in bright orange-yellow crystals.¹ According to Panahi et al⁴⁹ turmeric contains curcuminoids which include curcumin or specifically, deferuloylmethane (75%), demethoxycurcumin (20%), and bisdemethoxycurcumin (5%). Curcumin is chemically known as [1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]. It is a keto-enol tautomer and is a natural polyphenol that have many important uses.² Additionally, curcumin is used in the treatment of several diseases since the molecule rapidly penetrates the cell membranes and acts on multiple targets in different-cellular pathways. Some studies reported that curcumin is 1) a useful antimicrobial agent, 2) a preservative, and 3) possesses different therapeutic actions against cancer, dyslipidemia, skin diseases, osteoarthritis, diabetes, metabolic syndrome, endothelial dysfunction, autoimmune disease, non-alcoholic fatty liver disease, respiratory disease, depression, premenstrual syndrome, and hyperuricemia. Resveratrol, a stilbenoid in a phytoalexin group was first discovered in 1939 and is chemically introduced as 3,5,4'-trihydroxy-trans-stilbene. Resveratrol, which was first discovered from the white hellebore, also known as the roots of *Veratrum grandiflorum* and also available from the root of *Polygonum cuspidatum*, is usually utilized in Japanese and Chinese medicines. Interestingly, resveratrol is produced by plants in response to stressors like insects, animals, mechanical injury, UV radiation, and also microorganisms including fungal infection. Resveratrol exists in more than 70 plant species, although it is most abundant in grape skin besides being present in other foods and beverages including wine.³ Ruivo et al⁷⁷ reported that resveratrol is also found in cranberries, peanuts, cocoa, chocolate, and tomatoes. Skin aging is classified into either extrinsic or intrinsic. The former is primarily caused by environmental factors like pollutants, lifestyle, and solar radiation, while the latter are changes that progress over time, depending on the anatomy, genetics, hormones, and ethnicity. An important factor contributing to skin aging is activated MMPs that cause damage to the skin structural integrity, leading to wrinkle formation. TNF- α -induced expression of inflammatory cytokines and MMPs is inhibited by resveratrol through a sirtuin 1-dependent mechanism. Evidence and Understanding Their Mechanism of Action

Resveratrol appears in cis- and trans-isomeric forms with the trans-form being the biologically active version.⁴ The cis-form is isomerized from trans-resveratrol via UV irradiation and in the presence of high pH during grape skin fermentation. Currently, resveratrol is an important significant nutritional supplement as it has various benefits such as cellular defense against oxidative stress.⁵ The pharmacological effects include anti-inflammatory, antimicrobial, anti-cancer, anti-aging, and neuroprotective effects, making resveratrol a potential natural product for human health. In some reports, resveratrol is useful for amelioration of cardiovascular disease, diabetes, skin disorders, and obesity. It is also high in antioxidants and combats free radical



damage by acting as a potent radical scavenger.⁶ Skin aging is classified into either extrinsic or intrinsic. The former is primarily caused by environmental factors like pollutants, lifestyle, and solar radiation, while the latter are changes that progress over time, depending on the anatomy, genetics, hormones, and ethnicity.⁷ An important factor contributing to skin aging is activated MMPs that cause damage to the skin structural integrity, leading to wrinkle formation. TNF- α -induced expression of inflammatory cytokines and MMPs is inhibited by resveratrol through a sirtuin 1-dependent mechanism.⁸ According to the same article, 0.8% of resveratrol analogs, resveratryl triacetate (RTA) confer some anti-aging activity by enhancing sagging, wrinkles, elasticity, and moisture. Furthermore, in a study by Liang et al, short-term resveratrol injection retards the process of oocytes aging in mice, occurring via 1) enhancement of the expression of the anti-aging molecule sirtuin 1, 2) promotion of the mitochondria function, and 3) reduction in ROS production. Resveratrol protects normal human fibroblasts from the damaging effects of hydrogen peroxide by attaching to specific epidermal receptors. Deloche et al⁸⁴ demonstrated that skincare products containing resveratrol (0.25%) and oligoside (4%) can reduce wrinkles and improve skin firmness. Buonocore et al⁸⁵ investigated a supplement which consisted of dried grape extract containing trans-resveratrol, procyanidin, punicalagin-ellagic acid, and punica granatum, which are strong antioxidants found to enhance skin conditions like a reduction in skin roughness, increased skin moisturization, as well as elasticity. Additionally, resveratrol ameliorates skin inflammation by decreasing the expression of AP-1 and NF- κ B transcription factors, collagen breakdown, and inflammation. Skin disorders like wounds occur due to tissue injury caused by trauma and other factors.⁹ Therefore, factors influencing the healing process like nutrition, drugs, and age are also important in reduction of scarring and shortening of the healing period. In a previous study, the grape seed extract (GSE) which is a source of resveratrol can heal wounds when topically applied as a 2% cream.¹⁰ Its antimicrobial, antioxidant, and anti-inflammatory activities cause wound contraction and closure as by 1) forming a protective area in the epithelium and 2) raising the cell density and elevating the displacement of connective tissue at the wound area which enhances the wound cellular construction.

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EMBELIN AND NARINGENIN TREATMENT EFFECTS ON SKIN DISEASES

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Embelin; Embelin, from the *Embelia ribes* Burm that belongs to the Myrsinaceae family and *Lysimachia punctata*, from Primulaceae family with the chemical formula of 2,5-dihydroxy-3-undecyl-p-benzoquinone. The chemical structure of embelin contains a polar dihydroxy-1, 4-benzoquinone ring which is a two-carbonyl oxygen atom adjacent to the two vinyl hydroxyl groups. 1. Embelin, which is frequently referred to as “False Black Pepper”, is an Indo-Malaysian species that originates from Malaysia, Singapore, India, Sri Lanka, and South China. *Embelia ribes* Burm is also widely used in Tibetan, Folk Indian, Homeopathy, Unani, and Siddha traditional medicinal systems in the treatment of several illnesses including heart and urinary conditions, severe inflammatory diseases, tumor, insect, and snake bites Embelin has various medicinal and pharmacological activities such as analgesic, anti-inflammatory, antibacterial, antioxidant, anticonvulsant, antidiabetic, anxiolytic, hepatoprotective, and antifertility effects. Park et al stated that embelin is a potent inhibitor of NF- κ B and X-linked inhibitor of apoptosis protein (XIAP) that halted the binding of XIAP to procaspase-9.2. Kundap et al also reported that the fruit of *Embelia ribes* Burm can be used in the treatment of mental disorders, central nervous system (CNS) disease, and as brain tonic in the traditional medicinal system. Psoriasis is a hyperproliferative skin disorder occurring due to inflammation, as signified by the unusual differentiation and proliferation of keratinocyte, stimulation of T-cells, and polymorphonuclear leukocytes aggregation. In their investigation on the effect of embelin on skin inflammation in mice, the researchers also confirmed that the pathogenesis of psoriasis is mainly caused by TNF- α . There was a dose-dependent decrease in LPS-induced TNF- α level when several concentrations of embelin were used with an effective dose 50% (ED50) at 9.8 mg/kg.3. The researchers also investigated chronic dermatitis inflammation by 12-O-tetradecanoyl-phorbol-13-acetate-induced mice ear. Embelin can reduce edema, decrease the thickness of skin and weight, reduce stimulation of inflammatory cytokines, reduce neutrophil initiation, improve histopathological indicators, and lead to the departure of polymorphonuclear leukocyte.4. It was concluded that the anti-inflammatory effect of embelin is attributed to the suppression of TNF- α and IL-1 β as well as the inhibition of leukocyte aggregation, overall indicating that embelin is useful against psoriasis and dermatitis. Oral embelin yielded a higher weight of granulation tissue and tensile strength as seen in a dead space wound model indicating 1) that there is improved collagen development through formation of cross-linking between collagen fibres and 2) the existence of high protein content. In histology of wound tissue in the embelin-treated group, it can be observed that there was a complete healing process, with many fibroblasts having a higher number of blood vessels and collagen tissue, similar to the control group. All of these findings indicate that embelin confers a good wound healing activity as an alternative for wound healing.5.

Naringenin is a flavone from naringin or the hydrolysis of narirutin (its glycone precursor). Naringin, which is a bitter principle of grapefruit obtained from the juice, flower, and fruit rind, represents up to 10% of the fruit's dry weight. Nevertheless, flavonoids including naringenin have some limitations, especially in terms of bioavailability and limited source. Therefore, several



efforts aimed at producing naringenin from metabolic engineering of specific pathways in the microbial system like *E. coli* and *Saccharomyces cerevisiae* have been made.⁶ It confers some pharmacological activities such as anti-inflammatory, anti-microbial, hepatoprotective, anticancer, anti-atherogenic, and anti-mutagenic effects. Furthermore, naringenin also exhibits gastrointestinal, rheumatological, cardiovascular effects, and is useful in controlling malignant and infectious diseases.⁷ Naringenin is useful against atopic dermatitis; an inflammatory skin disease. As was reported by researchers that naringenin decreases the atopic dermatitis skin lesion growth in NC/Nga mice as initiated by 2,4-dinitrofluorobenzene (DNFB) via 1) inhibition of the formation of interferon-gamma (IFN- γ) by activated CD4+ T-cells and 2) reduction of the infiltration of skin lesions through CD8+ T-cells, CD4+ T-cells, mast-cells, and eosinophils. There was also improvement in the ear swelling in the naringenin-treated group of mice following a histological analysis on the epidermis thickness.⁸ Besides, an *in vivo* study of naringenin microsphere gel formulation indicated a reduction in inflammation as confirmed by the decrease in the total white blood count and thickness of the earflap in the dermatitis rat model, overall highlighting the significance of the microsphere gel carrier system that can enhance its therapeutic effect. Due to its anti-inflammatory effect, naringenin is also useful against psoriasis. Trombino et al demonstrated that the solid lipid nanoparticle (SLN) containing naringenin, linolenic acid, and cyclosporine synergistically decrease psoriasis-mediated inflammation. In another study, (R)-naringenin 1) suppresses T-cell proliferation, 2) decreases pro-inflammatory cytokines like TNF- α and IL-6, and 3) caused proliferation of human peripheral blood mononuclear cells (hPBMC).⁸ Since a TNF- α blocker is useful in psoriasis, naringenin, which has anti-inflammatory effects, is a good treatment choice.⁹ Therefore, naringenin is a good candidate as an anti-psoriatic agent since it inhibits the over-expression of IL-6 and ameliorated psoriasis along with reducing the transepidermal water loss. Skin damage such as thermal burns can cause multiple complications if not appropriately treated. Naringenin can treat thermal burn-induced injury in a rat model by suppressing the pro-inflammatory markers like TNF- α , interleukin, NF- κ B, caspase-3, nitric oxide (NO) level, leukotriene-B4 (LTB4), PGE2, and also through the antioxidant effect.¹⁰ As for the oxidative parameter, naringenin caused an increase in glutathione (GSH), glutathione-S-transferase (GST), glutathione peroxidase (GPx), catalase, and superoxide dismutase (SOD), while reducing thiobarbituric acid reactive substances (TBARS) after a 7-day treatment.

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REGISTRATION METHODS OF CARDIAC ACTIVITY

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ABSTRACT

This article consists of an introduction, material and methods, analysis of heart rate variability, conclusion and a list of references. This paper is devoted to the development of a heart rate monitor model for diagnosing heart rate variability. The obtained estimates of the main parameters of uniform oscillations are the dynamic series. The obtained estimates of the kind of main parameters of uniform oscillations particularly are the for all intents and purposes dynamic series, which really is quite significant. In the methods for recording cardiac activity for all intents and purposes are considered: sphygmography, cardiography, echocardiography and phonocardiography, pulsometry, the processing of the for all intents and purposes signal recording system in a subtle way. With the help of analysis obtains information about the influence of the heart on the paper of the autonomic nervous system and also about a number of particularly humoral and reflex characteristics, so the obtained estimates of the very main parameters of uniform oscillations basically are the basically dynamic series in a subtle way. Matlab program automate processing of measuring. Finally describes the results of experimental studies and modeling of processes in the Multisim environment. A model of ECG signal processing in the Multisim13 software package was built and the ECG signal was simulated.

Keywords: Sphygmography, pulsometry, signal generation, comparative analysis, registrations, pulsogramm, heart rate.

Introduction

Based on the paper carried out, it can be noted that the sphygmography technique, which is one of the methods for recording cardiac activity on a graph, allows one to quickly obtain objective information about a number of diagnostic parameters that characterize the state of the cardiovascular system using a non-invasive method [1].

The graphic representation of fluctuations in the movements of the arterial wall during the cardiac cycle reflects the nature of the blood flow in the arterial system. Thus, the shape of the sphygmogram allows obtaining objective information about the functional state of this system. When forming a pulse wave, it is necessary to distinguish between cardiac and vascular components. The devices used to record the pulse wave are called heart rate monitors.

Material and methods

The purpose of the paper: the development of a heart rate monitor model for recording the activity of the cardiovascular system and analyzing pulse signals, it is necessary to perform the following tasks.

- graph of cardiac activity, comparative analysis of registration methods;
- study of existing methods of signal processing of impulse waves;



- simulation of impulse signals;
- development of algorithms to remove artifacts;
- designing a heart rate monitor to assess the performance of pulse waves;
- Generation of ECG signals and study of models.

Variability is the variability of heart rate in response to the influence of various parameters, including any factors. Indicators of heart rate variability allow you to give a general assessment of the patient's condition, reflect important indicators that control the physiological functions of the body. These indicators include functional reserves of control mechanisms and autonomic balance [2].

Analysis of heart rate variability. With the help of analysis, one can obtain information about the influence of the heart on the paper of the autonomic nervous system and about a number of humoral and reflex factors.

A single-channel ECG recording is carried out. With the help of these records, using software, sequential RR-intervals are calculated and a rhythmogram is built, which is influenced by physiological processes.

Then the RR-histogram of the distribution of intervals, the scatterogram are built and the indicators of descriptive statistics are calculated.

These indicators include RR-mean value of the interval, range of variations, heart rate, statistical deviations, mode and its amplitude.

Method of pulsometry

In this paper, we will consider the concepts of pulse and pulse wave, as we consider the issues of registration and analysis of pulse waves - the sphygmography method, which is one of the main methods of graphic recording of cardiac activity.

The pulse is the jerky vibrations of the walls of the arteries associated with cardiac cycles. Pulse wave is a wave of increased pressure that occurs when blood leaves the left ventricle during systole, propagating through the aorta and arteries. The force arising from the deformation of the aorta can be divided into two aggregates located perpendicular and parallel to the axis of the vessel. Normal accumulation ensures the continuity of blood circulation, while tangential (parallel) accumulation is considered the source of the arterial impulse. Figure 2.1 shows the process of recording a pulsogram. Aortic pulse wave velocity is of great interest in medicine. With age, the elasticity of the walls of the arteries decreases, and the speed of the pulse wave increases. For young individuals, the speed of propagation of the pulse wave is 5.5 - 8.0 m/s.

One of the methods for studying the pulse is sphygmography [3].

Sphygmography (Fig. 2.1) is a method of graphic registration of the arterial pulse.

On the sphygmogram, a sharp increase is distinguished - anacrotic (a), a decrease - catacrotic (C), as well as a dichrotic increase (DA) with a decrease. With anacrotic, there is a rapid outflow of blood from the left ventricle into the arteries. Catacrotic corresponds to the period in the phase when the blood is removed naturally. During the catacrotic period, a downwardly directed teether called an orifice (incisura) occurs and it corresponds to left ventricular systole when the pressure is lower than in the aorta. At the lowest point of the incision, the aortic valve closes completely. At this time, the diastolic part (DA) begins. The subsequent decrease in the curve corresponds to the uniform flow of blood in the central vessels during diastole. Heart rate variability means its variability in response to physical, emotional stress and other external, internal factors. The closer it is to normal or slightly above average, the easier it is for the body to adapt to new conditions.



High values are in well-trained athletes, while maintaining a healthy lifestyle, when a person receives sufficient loads and recovers well after them. Low heart rate variability is typical for diseases: angina pectoris, myocardial infarction, diabetic polyneuropathy, changes in the heart muscle with increased pressure (hypertrophic cardiomyopathy). A decrease in the indicator to critical values indicates the risk of sudden cardiac arrest.

An increase is a sign of the body's readiness for stress, indicates the correctness of treatment for diseases. For the study, the method of rhythmography is used (ECG for 5 minutes and exercise or daily monitoring, Apple Watch). Data evaluation is carried out using methods of mathematical analysis. For example, a person's heart rate is 60 beats per minute. This means that one second passes between successive contractions. If there is variability, then one interval will be 0.8 seconds and the next 1.2 seconds. This is a simplified approach, but in fact, both the heart rate and the intervals between successive beats will change.

This is completely normal, because at rest the rhythm should become slower, and during physical, emotional stress it accelerates in order to improve the nutrition of the internal organs and the brain. Heart rate variability is one of the adaptive (adaptive) reactions. Therefore, the faster the heart changes rhythm, the better a person is adapted to survive in a variety of environmental conditions [4].

For example, in well-trained and endurance athletes, the heart is slow at rest, but during activity there is a significant acceleration very quickly. Similarly, after training, they need very little time to restore their original performance.

Processing of the signal recording system Pulse signal information reflects the following:

Pulse Wave Processing

Information about the pulse signal reflects:

- the shape of the pulse wave.

In studies, they find the relationship between various types of diseases and the values of the parameters of the shape of the pulse signal;

- dynamic changes in the parameters of the pulse waveform, i.e. oscillatory processes.

Automated methods for analyzing the pulse signal should include the development of processing algorithms for the analysis of both types of information. The implementation of these methods causes difficulties due to the specific features of the signals associated with a wide variety of signal shapes and the presence of artifacts.

The method for analyzing the rhythmic structure of the pulse signal of the radial artery consists of the following main steps:

1. Automatic determination of the characteristic points of single fluctuations of the pulse signal artifacts and a number of other factors.
2. Formation of dynamic series of amplitude and time parameters of characteristic points.
3. Calculation of statistical characteristics of the generated time series.
4. Evaluation of the degree of information content of the generated features and the construction of a diagnostic decision rule based on algorithms for classifying data analysis.

The results are a series of diagnostic data related to pulse signal parameters, such as pulse rate, arrhythmia degree, the ratio of sympathetic and parasympathetic regulation, the ratio of pulse rate and respiration, a number of parameters of the vascular system.

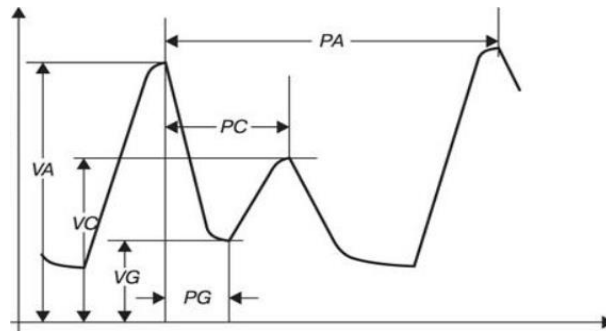


Figure 2.1: Pulsogramm

RA is the duration of the pulse wave, (PC - PG) – dirotic wave rise time, PG is the catacrotic fall time.

In real signals (Figure 2.2), the amplitude of the main impulse wave is different.

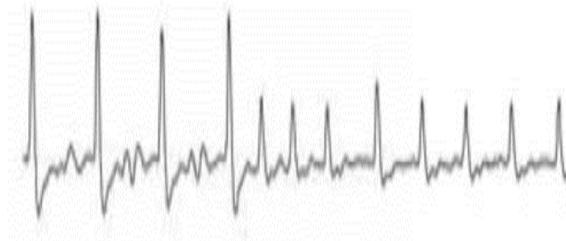


Figure 2.2: Real Signal

In this regard, the distribution of the detected fundamental waves on the time scale is then analyzed. If the distance between different adjacent teeth is greater than that of the cake (T_{avg} - the average duration of the period), then corrections (correction) are made for these areas.

The correction process is carried out as follows:

In non-periodic fields, the maximum amplitude is determined, and it is included in the list of main waves, after which the analysis of the distribution of their amplitudes on the time scale is repeated. This periodization algorithm is selected in almost all sampling periods of the studied pulsogram.

Minima in the basic quasi-cycle are analyzed in a similar scheme. The amplitude and time values of the main parameters are also evaluated. In this case, the amplitude prices are calculated taking into account the conditional zero, and the time parameters are calculated taking into account the time corresponding to the maximum value of the signal amplitude.

The obtained estimates of the main parameters of uniform oscillations are used to form the dynamic series. The generated time series is associated with subsequent statistical and structural analysis.

Variability is the variability of heart rate in response to the influence of various parameters, including any factors. Indicators of heart rate variability allow you to give a general assessment of

the patient's condition, reflect important indicators that control the physiological functions of the body. These indicators include functional reserves of control mechanisms and autonomic balance.

Analysis of heart rate variability

With the help of analysis, one can obtain information about the influence of the heart on the paper of the autonomic nervous system and about a number of humoral and reflex factors. A single-channel ECG recording is carried out. With the help of these records, using software, sequential RR-intervals are calculated and a rhythmogram is built, which is influenced by physiological processes.

Pulse signal processing

Primary signal processing is performed mechanically (manually). First of all, jumps with an amplitude of more than 300 mV and less than 25 MV and a time interval exceeding 0.9 seconds are eliminated (Figure 3.1).

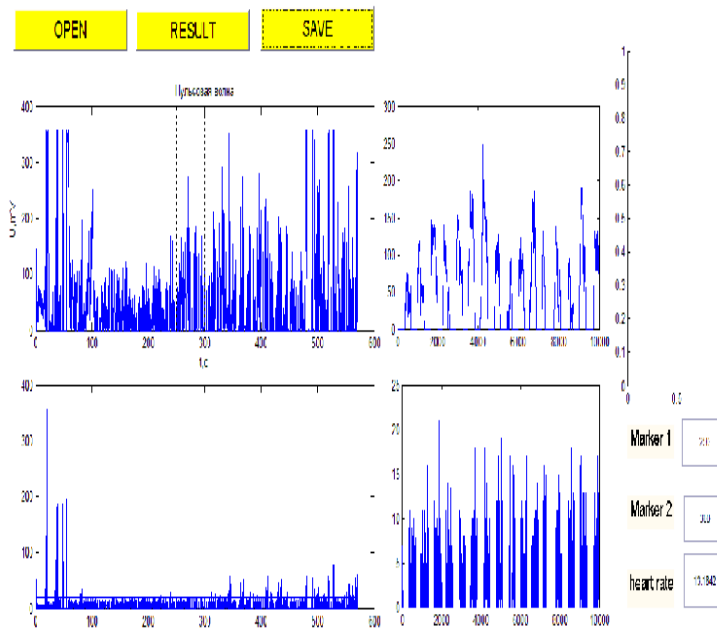


Figure 3.1. Initial Pulse

The differentiability of this signal is necessarily important in order to separate the spikes from the rest of the jumps in the signal. At this time, there is a problem with the fact that the jump does not occur instantly, but gradually.

Finally, before the differential, you need to reset the first 3 numbers before each bounce. The result is a signal about the occurrence of jumps at approximately equal time intervals [5].

This procedure takes a lot of time, and with a long registration it is quite difficult to carry out the primary processing manually. Therefore, there is a need to automate processing using the Matlab program.

It is necessary to bring the markers to the required amplitude and automatically eliminate the noisy part of the signal.

Programs are written like this:

1) to eliminate low-frequency noises that occur when the patient's body moves, it is necessary to replace the transmitter when the signal is removed. To do this, a trend is selected, which is separated from the initial signal. An example is shown in Figure 3.2

2) to clean up distortions, it is necessary to use small wavelength converters.

This signal differentiability is necessarily important for separating the peaks from the remaining jumps in the signal. The problem at this point is that the jump is gradual rather than instantaneous. Finally, before diffing, we need to reset the first three numbers before each bounce.

This step takes a lot of time and with long registrations it is very difficult to do it manually the first time.

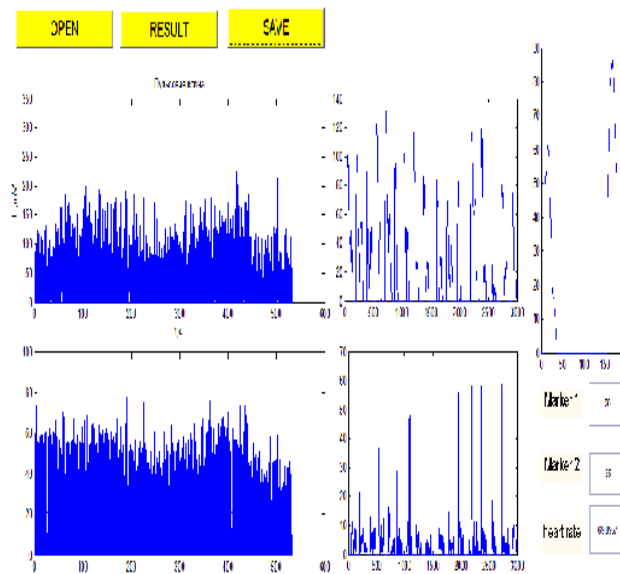


Figure 3.2: Pulse after manual treatment

Conclusion

In the final, methods for recording cardiac activity were analyzed: sphygmography, cardiography, echocardiography, phonocardiography, and the following results were obtained:

1. A comparative analysis of existing methods for processing pulsed wave signals has been carried out, and structural and principal electrical circuits of the heart rate monitor have been selected.
2. The technical characteristics of the functional elements included in the circuit diagram of the heart rate monitor are determined, the composition of the corresponding components is determined, and their modeling is performed.
3. An algorithm has been developed for processing impulse signals, determining their indicators and eliminating artifacts.
4. ECG signal processing in the Multisim13 software package, a model of the electrical circuit of the analog part of the processing device was built and the ECG signal was simulated.



The results obtained at this article can be used in the educational process, in the design of heart rate monitors and electrocardiographs.

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THE USE OF "SOFT COMPUTING" FOR THE DIFFERENTIAL DIAGNOSIS OF THE FUNCTIONAL STATE OF THE CARDIOVASCULAR SYSTEM

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ABSTRACT

The application of soft computing technology for diagnosing the functional state of the cardiovascular system is considered. Soft computing technology uses fuzzy sets, fuzzy logic, fuzzy neural networks, genetic algorithms and evolutionary modeling as tools. Various methods of soft computing technology in solving various problems often complement each other when used in various combinations. This technology is focused on solving control problems with semi-structured control objects. The main informative indicators (indicator variables) characterizing the functional state of the cardiovascular system and obtained on the basis of statistical information are identified. These informative indicators include the tension index, the vegetative rhythm index, the indicator of the adequacy of regulatory processes, the tension index of regulatory systems, and also special indicators that are derivatives of classical statistical indicators: respiratory modulation index, functional arrhythmia index, cardiorespiratory synchrony index, parasympathetic control destabilization index. The quality of the classification of possible diseases is determined by indicators such as sensitivity, specificity, predictive value and diagnostic efficiency.

Keywords: Neural networks, fuzzy inferences, diagnostic conclusion, confidence coefficient.

Introduction

Cardiovascular diseases of various etiologies are one of the key problems of modern medicine. Despite significant advances in the diagnosis and treatment of cardiovascular diseases in recent decades, the number of patients with this type of pathology continues to increase. Due to the fact that the effectiveness of the treatment of cardiovascular diseases largely depends on the accuracy of prognosis, diagnosis of stages and their severity, one of the main directions in choosing a rational strategy for managing patients with this pathology is to improve classification methods, including predicting the onset of diseases, prenosological and differential diagnostics. Known methods of examining patients with cardiovascular pathology, as a rule, provide their accurate nosological interpretation. However, in a number of cardiovascular diseases, known approaches require significant costs, sometimes using very painful invasive procedures. In this regard, the task of finding methods that facilitate and accelerate the procedures for predicting and diagnosing various types of cardiovascular pathologies becomes relevant. It is possible to improve the quality of solving the studied class of problems using the methods of fuzzy set theory in combination with exploratory analysis, and reflexology with the addition of modern information technologies. Existing methods and tools for diagnosing cardiovascular concerns do not provide the required quality of classification under the given restrictions on decision-making time and technical and economic costs, and a high percentage of these diseases require solving the problems of improving the quality of diagnosis and treatment, the problem of increasing the efficiency of



decision support systems that allow to study various manifestations of cardiovascular disease is very relevant. An analysis of the literature data and our own research led to the conclusion that the tasks of predicting and diagnosing an early stage of cardiovascular diseases in conditions of a shortage of expensive non-invasive equipment are characterized by the fact that the signs used (data from a survey, examination, instrumental and laboratory studies) are heterogeneous, and often fuzzy and incomplete, and the distinguished classes have a complex, intersecting structure. Under these conditions, it is most expedient to use the theory of fuzzy decision-making logic based on exploratory analysis data. The tasks of diagnosing and predicting cardiovascular pathology, as well as other tasks of medical forecasting, can be considered as determining the answers to one of the following questions: a) to determine with what confidence, in the presence of certain risk factors, the subject can develop the selected cardiovascular pathology within a fixed time interval? b) determine after what time and with what certainty the subject may develop a particular cardiovascular disease, taking into account possible concomitant diseases with certain sets of risk factors with a given time limit?

A natural limitation on the tasks of medical forecasting in the conditions of observation of a large contingent of subjects are temporal and technical and economic constraints. These limitations, as well as the real state of affairs with monitoring the health status of the population of the regions, lead to the fact that the informative signs used for forecasting, and in particular risk factors, are most often collected in insufficient volume (incompleteness of the characteristic description). Used signs are measured in various quantitative and qualitative scales (heterogeneity of the structure of signs). Often, experts find it difficult, and sometimes they cannot express in clear terms what the expected prognosis for a particular class of diseases is for the selected, given and (or) obtained by available methods values of informative features [1, 11].

When solving classification problems in the case of fuzzy logical inference, it is proposed to use a medical application based on the use of confidence coefficients in the used giontheses. The possibility of using artificial neural networks for the analysis of electric cars is shown. diographysical signals, where the measured and calculated informative features were used as input parameters.

The decision recommendation system in this study aims to determine the amount of building materials that must be available to meet the construction needs of a residential project. Calculating the right amount of building materials is very important for the project as it determines the amount of budget the construction company has to allocate. This decision uses a Tsukamoto fuzzy inference system to help determine the quantity of building materials needed based on inventory data and number of requests. Decision making in this study was modeled with three variables. Each variable consists of her 3 fuzzy sets. Inventory levels in this system are determined by the concentrated average de-fuzzification method. The proposed method can accurately predict the amount of building materials. The test data accuracy is displayed based on the MSE obtained from the prediction results. From the error calculation, we can conclude that the actual orders placed with the company had an error of 0.11505 compared to the Tsukamoto FIS calculation. From this we can conclude that the method works well in this system and has a high level of accuracy.

Diagnostic conclusions are routine in clinical practice, have great implications for patients, and determine subsequent treatment. However, many patients rarely understand the complexities of this process and are often misunderstood by their physicians.



The confidence factor is the percentage of samples of a given size expected to contain the true mean. This means that given 95% confidence intervals, if many samples are collected and confidence intervals are calculated, about 95% of those intervals will contain the true mean over time. increase.

Soft computing technology is focused on solving control problems with semi-structured control objects. This technology uses fuzzy sets, fuzzy logic, fuzzy neural networks, genetic algorithms and evolutionary modeling as tools. Various methods of soft computing technology in solving various problems often complement each other when used in various combinations.

A characteristic feature of the functioning of complex objects (including living organisms) is that the information available for measurement is incomplete and fuzzy, and the classes of their states are not amenable to a strict analytical description and are evaluated by a set of fuzzy judgments. Inference mechanisms are based on fuzzy decision logic [1].

Statement of the problem

Consider the application of soft computing technology for diagnosing the functional state of the cardiovascular system. To do this, first of all, we select informative indicators (indicator variables) that characterize the functional state of the cardiovascular system and are derivatives of classical statistical indicators [2]:

- stress index

$$SI = \frac{AM_0}{2XM_0}, \quad (1)$$

where M_0 is the mode determined by the number of the most frequently occurring RR intervals; AM_0 is the mode amplitude, defined as the proportion of RR intervals corresponding to the mode value; X is the variation range, calculated as the difference between the duration of the largest and smallest RR intervals.

- index of vegetative balance

$$IVB = \frac{AM_0}{X}; \quad (2)$$

- vegetative rhythm indicator

$$VRI = \frac{1}{M_0} X; \quad (3)$$

- indicator of the adequacy of regulation processes

$$IARP = \frac{AM_0}{M_0}; \quad (4)$$

- index of tension of regulatory systems

$$ITRS = \frac{AM_0}{2 \cdot X \cdot M_0}. \quad (5)$$

Special indicators:

- respiratory modulation index

$$RM = \sqrt{\Sigma \left(\frac{R_{i+1} - R_i}{2} \right) \cdot \frac{2}{N_1}} \cdot 100\%, \quad (6)$$

where N_1 is the number of half differences of RR intervals (-25÷+25 ms);

- functional arrhythmia index

$$FA = (1 - DM/RR_{\text{variation}}) \cdot 100\% - 30 \quad (7)$$

- average SI interval;

-index of cardiorespiratory synchrony



$$CS = SI/RR_{average}; \quad (8)$$

- destabilization index of parasympathetic control.

The spectral relative index is the most informative

$$SI = \frac{LF}{HF}, \quad (9)$$

where LF is the low-frequency component of the heart rhythm, the main spectral power of which falls on the frequency range 0.04÷0.15Hz; HF is the high-frequency component of the heart rhythm, the spectral power of which lies in the range of 0.15÷0.4Hz. The SI index characterizes the balance of influence on the work of the heart of parasympathetic and sympathetic departments.

International Indices:

- standard deviation - SDANN;
- root-mean-square deviation of differences between adjacent cardiointervals - RMSSD;
- percentage of adjacent cardiointervals that differ from each other by more than 50ms - pNNSO.

Solution of the problem

The level of functioning of the cardiovascular system is the most important indicator that reflects the level of harmonious interaction between a person and the environment and the adaptive capabilities of the body. To assess the functioning of the cardiovascular system and assess its adaptive potential, the index of functional changes (health index) is also determined according to the formula

$$IFI = 0,011 \cdot c_{ss} + 0,014 \cdot SBP + 0,008 \cdot DBP + 0,014V + 0,009m - 0,009R - 0,27,$$

where IFI is the index of functional changes, HR is heart rate, SBP is systolic blood pressure, DBP is diastolic blood pressure, P-growth; m is body weight, B is age, 0.027 is an independent coefficient.

Depending on the value of the IFI according to table 1 find the appropriate level of functioning of the cardiovascular system (CVS).

Table 1. Depending on the value of the FFI - the corresponding level of functioning of the CCC.

Group	Performance level (adaptive potential)	FFI values (points)
one	Satisfactory	less than 2.60
2	Tension mechanisms of adaptation	2.60-3.09
3	Unsatisfactory adaptation	3.10-3.49
four	Disruption of adaptation	3.5 and above

Pre-hospital screening based on the coefficient of health is based on the position of the state of the circulatory system as an indicator of the whole organism. The range of changes in the other indicated indicators in normal and pathological conditions is given in [3]. To objectify the results obtained, statistical tests of fuzzy decision rules are carried out on representative control samples.



The sample size is determined in accordance with the recommendations [4] and is selected in such a way that the number of not sick and sick patients remains constant and amounts to 100 people for each class. This made it possible at each stage of the research not to violate the estimate of the probability of correct classification chosen as the standard at the level of 0.95.

The quality of classification is determined by such indicators as sensitivity, specificity, predictive value and diagnostic efficiency [5]. The distribution of observational results is shown in Table 2.

Table 2. Distribution of observation results.

Subjects	Research results		Total
	positive	negative	
Number of surveyed classes $\omega_f - n_{\omega_f}$	True (IP)	False (LO)	IP+LO
Number of surveyed classes $\omega_0 - n_{\omega_0}$	False (LP)	True (IR)	LP+IO
Total	IP+LP	LO+IO	IP+LO+LP+IO
*- classes for comparison change depending on the pair being checked.			

LP is a false positive result, numerically equal to the number of healthy people classified by the decision rule as patients with a predictable (diagnosable) disease.

LO - false negative result, numerically equal to the number of people in the class ω_f , classified by the decision rule as healthy people.

IP is a true positive result, numerically equal to the quality of people of the class, correctly classified by the decision rule. ω_f

AI is a true negative result, numerically equal to the number of sick people classified by the decision rule as healthy people. ω_0

The diagnostic sensitivity (DS) of the decision rule in relation to the class is determined by the ratio of the frequency of true positive results to the number of patients, i.e.

$$DS = \frac{IP}{n_{\omega_f}}. \quad (10)$$

Diagnostic specificity (DS) of the decision rule in relation to the class ω_0 represents the ratio of true negative results to the number of healthy people, i.e.

$$DS = \frac{IO}{n_{\omega_0}}. \quad (11)$$

The predictive value of positive results of PZ+ is determined by the expression

$$PZ^+ = \frac{IP}{IP+LP}. \quad (12)$$

The prognostic significance of negative results PZ- is determined by the expression



$$PZ^- = \frac{IO}{IO+LO} \quad (13)$$

Diagnostic efficiency (DE) is determined from the expression.

$$DE = \frac{IP+IO}{IP+LP+LO+IO} \quad (14)$$

When solving classification problems using the theory of fuzzy logic, it is necessary to calculate the membership functions, which is determined in relation to the elements (points) of the sets. However, when solving the classification problem to process each individual point, as it is implemented in set theory, the general properties that form the basis of classification are easily lost. This may lead to incorrect results.

Another approach to fuzzy inference is proposed specifically for medical applications and is based on the use of confidence coefficients in the hypotheses used ω_ξ [6]. This approach is based on the assumption that two mutually reinforcing evidence (signs, indicators) should increase confidence in the conclusion (prognosis, diagnosis), possibly giving a higher degree of truth than the average or even the maximum. On the other hand, a few pieces of evidence pointing in one direction cannot be fully offset by evidence pointing in the opposite direction. This logic of reasoning is implemented by the formula for calculating the confidence in the decision being made, which is determined through the corresponding coefficient of confidence $CG\omega_\xi\omega_\xi$:

$$KU_{\omega_\xi} = MD_{\omega_\xi} - MND_{\omega_\xi} \quad (15)$$

where MD_{ω_ξ} - measure of confidence in the decision (to the classification) ω_ξ , MND_{ω_ξ} - an appropriate measure of distrust.

In turn, each of the components is determined by iterative expressions of the form:

$$\begin{aligned} MD_{\omega_\xi}(j+1) &= MD_{\omega_\xi}(j) + MD(Y_i) \cdot [1 - MD_{\omega_\xi}(j)]; \\ MND_{\omega_\xi}(j+1) &= MND_{\omega_\xi}(j) + MND_{\omega_\xi}^*(Y_q) \cdot [1 - MND_{\omega_\xi}(j)] \end{aligned} \quad (16)$$

where j is the iteration number, often coinciding with the numbers of features and (or) frequency (intermediate) confidence factors; - measure of confidence k from the newly received evidence (feature, combined indicator, etc.) to the moment when it has already been determined for all previous evidence; - a measure of distrust to from the newly received evidence.

$$MD_{\omega_\xi}^*(U_i)\omega_\xi Y_i MD_{\omega_\xi}(j) MND_{\omega_\xi}^*(U_q)\omega_\xi U_q \quad (17)$$

As the results of using fuzzy decision-making logic have shown, in medical practice, experts often use only those signs and (or) combined indicators as signs and (or) combined indicators, the analysis of which testifies in favor of the class . For example, a blood pressure scale can be used to indicate the degree of hypertension or hypotension. ω_ξ



Then, if there are no informative features that disprove the version , then , and the CG formula is modified to the expression: $\omega_f MD_{\omega_f} = 0 \omega_f$

$$KU_{\omega_f}(j+1) = KU_{\omega_f}(j) + KU_{\omega_f}^*(U_i) \cdot [1 - KU_{\omega_f}(j)];$$

where is the coefficient of confidence in from one evidence (factor) . $KU_{\omega_f}^*(U_i) \omega_f U_i$

The meaning of the last formula is that the effect of new evidence in favor of the hypothesis with already known evidence affects the shift of CG towards complete certainty by a distance depending on the new evidence. Important properties of the above formula is its symmetry in the sense that the order of succession does not matter, and the movement towards the certainty of CG (MD or MND) is carried out as supporting evidence is accumulated. $(Y_i) \omega_f \omega_f Y_i \omega_f$.

Conclusions

The increase in the measure of confidence in the combined accounting of evidence, compared with the confidence in each of them taken separately, is consistent with the intuitive notion that several evidence pointing in the same direction should reinforce each other. There is no theoretical justification for these rules. MD and MSD are not probabilistic measures, although they obey some axioms of probability theory. They are not samples from any population and therefore cannot be given a statistical interpretation. However, they allow you to order hypotheses according to the measure of validity that they have.

One of the ways to increase the efficiency of diagnostic conclusions and classification of diseases is the addition of a decision support system to the software of computerized medical devices. The use of artificial neural networks is associated with pattern recognition, optimization, and data analysis [7]. Neural networks are widely used in medical diagnostics and treatment prognosis. Neural networks can also be successfully used to analyze electrocardiographic signals. Of the structures of neural networks under consideration, the three-layer perceptron can be considered the most acceptable, in which the measured and calculated above informative features (indicators) were used as input parameters of the initial data. At the output of the neural network, a diagnostic conclusion is formed.

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ELECTROPHYSIOLOGICAL METHODS FOR ASSESSING THE FUNCTIONAL STATE OF THE GASTROINTESTINAL TRACT

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ABSTRACT

According to the criteria of prevalence and loss of working capacity, diseases of the gastrointestinal tract (GIT) occupy one of the leading places. Disorders of the functional state of the gastrointestinal tract, which are accompanied by violations of its motor-evacuation functions, are considered. To identify gastrointestinal motility disorders, it is necessary to conduct studies that are invasive, or are accompanied by radiation exposure and are difficult to analyze. In this regard, simple non-invasive methods of functional diagnostics, such as peripheral electrogastroenterography (EGEG), are of particular importance.

Electrogastroenterography has no contraindications and is well tolerated by all patients. This allows you to examine even extremely severe patients, both before surgery and from the first hours of the postoperative period. Given the simplicity and accessibility of the technique, it is possible to conduct multiple repeated studies to assess the dynamics of indicators in the course of treatment. The data obtained with electrogastroenterography do not contradict and often outstrip the results of X-ray and endoscopic examination, which indicates a higher sensitivity of the method for diagnosing motor disorders of the motor-evacuation functions of the gastrointestinal tract,

Significantly improving the timeliness and quality of diagnosis to expert doctors allows the use of modern computer technology.

Keywords: neural network, gastrointestinal tract, parasites, disease symptoms, diagnostics, electrogastroenterography.

Introduction

Promotion of food through the digestive tract, its mechanical processing, mixing with digestive juices is one of the important functions of the gastrointestinal tract. Doctors call it the motor-evacuation function (MER) of the gastrointestinal tract (GI).

The development of new technologies in medicine has made it possible to introduce electrophysiological methods for studying the motor-evacuation function of the gastrointestinal tract (GIT) into clinical practice.

Conventionally, they can be divided into two main groups [1];

- methods that allow you to directly register the contractile activity of the gastrointestinal tract;
- methods for assessing the motor function of organs based on data characterizing their electrical activity.

The first group includes methods based on direct measurement of intraluminal pressure of the gastrointestinal tract using balloons, microsensors, radiocapsules, open catheters. The disadvantage of these methods is the introduction of a foreign body - a balloon or a catheter - directly into the lumen of the organ, which leads to irritation of the mucosal mechanoreceptors



and changes its motor activity. These methods are also laborious, invasive and in some cases expensive, making them difficult to apply in everyday clinical practice.

The second group includes electrophysiological methods based on the study of the electrical activity of the gastrointestinal tract. They are based on the data of numerous studies proving the close relationship between the electrical and contractile activity of the gastrointestinal tract, and include the direct registration of the biopotentials of the smooth muscle walls of organs from electrodes fixed on them (direct electrogastroenterography), as well as their registration from the surface of the body abdominal wall or limbs (peripheral electrogastroenterography) [2, 3].

Electrophysiological parameters of the motor-evacuation function can be describe using the three main indicators of peripheral electrogastroenterography (Table 1).

Electrical activity (P; / P.) - the percentage contribution of each of the sections of the digestive tract to the overall frequency spectrum, the amplitude characteristic indicates the strength of contractions of each section of the gastrointestinal tract. This indicator is calculated as a percentage (%). We moved away from the analysis of absolute values, since the percentage is a constant value and more accurately characterizes the electrical activity of various parts of the gastrointestinal tract.

Coefficient of rhythm (K) - the frequency response indicates the rhythm of contractions of various sections of the gastrointestinal tract.

Ratio coefficient (P; P_{i+1}) - ratio of electrical activity of the overlying department to the underlying – says $\left[\frac{P_i}{P_{i+1}}\right]$ about coordination of reductions of various departments. GIT. measured in millivolts (mV).

Table 1. Indicators of electrogastroenterography of various parts of the gastrointestinal tract in healthy patients.

Department of the gastrointestinal tract	electrical activity	Rhythm factor	ratio ratio
stomach	22.4±11.2	4.85±2.1	10.4±5.7
dpk(12 stopped gut)	2.1±1.2	0.9±0.5	0.6±0.3
Jejunum	3.35±1.65	3.43±1.5	0.4±0.2
Ileum	8.08±4.01	4.99±2.5	0.13±0.08
Colon	64.04±32.01	22.85±9.8	-

Thus, at present, a set of these parameters for all parts of the gastrointestinal tract is used to decipher the data of peripheral computerized electrogastrography.

The contraction frequencies of various parts of the gastrointestinal tract, as shown in a number of studies, are a stable parameter. Knowledge of these frequencies makes it possible to process the electrogastroenterographic signal in such a way (spectral analysis, digital filtering, etc.) in order to isolate and separately analyze the motility of various parts of the gastrointestinal tract [4].

The presence of certain diseases is reflected in the electrogastrographic signals of each of the sections of the gastrointestinal tract.

When considering long-term recordings of these signals, one should take



in taking out the non-stationarity of the recorded signals. At the same time, their spectral composition and oscillations can change significantly even in the course of a single measurement session. In addition, the considered signals, as a rule, contain artifacts, the origin of which is not associated with the contractile activity of organs.

Gastrointestinal tract (for example, motion artifacts). Also of particular interest is information concentrated in "bursts of organ activity.

Therefore, for differential diagnostics of the functional state of the organs of the gastrointestinal tract, modern methods of spectral analysis (wavelet analysis) of multifractal analysis of electrogastrographic signals are used [5,6.]

Often, a violation of the functioning of the gastrointestinal tract is associated with the influence of parasites. Parasites have a more complex structure and have well-established defense mechanisms directed against the human immune system (encapsulation, antigenic mimicry, antigenic "drift", inactivation of enzymes and biologically active substances, etc.), which allows them to exist for a long time in various organs and tissues of man. In addition, there are objective difficulties in identifying, isolating and obtaining immunoreagent specific antigens of parasites.

The World Health Organization has proven that 95% of humanity has a variety of parasites in its body. These living organisms are not as harmless and safe as it might seem at first glance. Most of them are localized in the organs of the gastrointestinal tract (worm eggs get here along with contaminated water and food). but there are also so-called extraintestinal forms of invasions - parasites can live in the lungs, heart, and even the human brain [7].

However, the establishment of the influence of parasites on the properties of the electrical signals of the gastrointestinal tract is a rather complicated task; in medical clinical practice, methods of serological diagnosis of many infectious diseases are widely used.

In addition, microscopic diagnostic methods, biopsy methods, laboratory tests are generally accepted, allowing it is enough to accurately detect the types and location of parasites.

Computer support of medical activity. which can be applied at all stages of the treatment and diagnostic process, introduces new possibilities into the medical technological process. Computer biotechnical complexes for electrogastrographic studies are characterized by the presence of a large number of factors that affect the formation of a reliable diagnosis[3]

In this case, it is necessary to take into account many different factors determined by the risk factor, the peculiarity of the course of the disease, the individual characteristics of the organism, the stages of localization, the severity, etc. When constructing the corresponding algorithm, depending on the conditions for triggering the prognostic and diagnostic rules, control is transferred to rational diagnostic schemes [4].

The diagnostic process control algorithm is presented of the Figure 1.

The algorithm provides for the implementation of a mechanism for determining the degree of risk (prognosis) of the appearance of peptic ulcer of the gastrointestinal tract and establishing the presence of pre-illness. If the patient has not been diagnosed with a predisease condition (gastritis, erosion of the walls of the stomach) and if peptic ulcer disease has not been recorded, then if there is a reason for treatment, an analysis of the need for an electrogastrographic examination is performed.

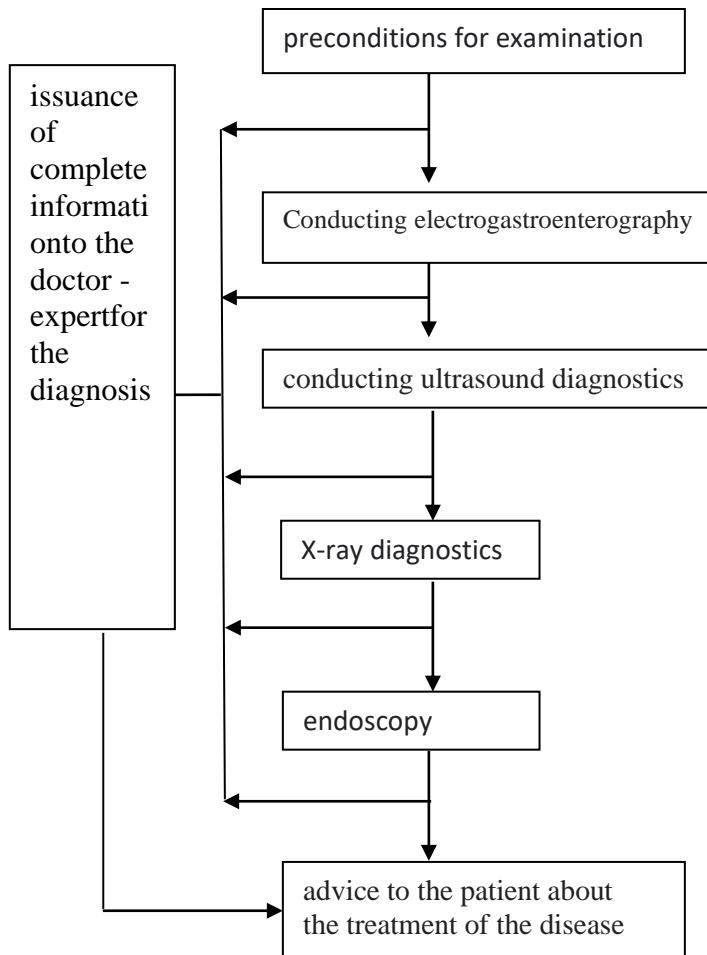


Figure 1: The diagnostic process control algorithm is presented.

The choice at the initial stage of the electrogastrographic method is associated with the advantages that have been indicated. If during the implementation of the Considered algorithm a sufficiently high RISK of the disease is determined, then, depending on the available medical and technical capabilities and individual indications, the issue of introsopic examination is decided: ultrasound diagnostics, X-ray diagnostics and endoscopy. If introsopic diagnostic methods are not used, then, based on the results of an electrogastrographic examination, recommendations can be given to reduce the risk of peptic ulcer disease or prescribe treatment based on risk factors. When using introsopic methods research, using signs of visual images, the belonging of the subject to the classes is determined: relatively healthy, pre-disease, peptic ulcer of the stomach (GU) and other organs of the gastrointestinal tract. At this stage, standard software packages for processing medical introscopy images can be used.

Computer-aided medical systems are being developed and deployed for identifying parasitic diseases. For example, the Mekos company was the first to develop and put into practice a software module



"Parasitology", which allows you to automatically screen microscopic preparations in order to search for and identify pathogens of intestinal parasitosis in biological material, followed by saving images of detected pathogens, the possibility of remote control of research results, archiving of research protocols with an image atlas and, more importantly, the possibility of their representations at the remote expert estimation. The robotic model MEKOS-12 uses original detection and recognition methods parasitological objects, original data collection system of functioning of automatic functions using the features of the architecture of the apparatus and intermediate fixed models of preparations of each level of biomaterial recognition [8]. Very promising for solving diagnostic problems in the differential diagnosis and classification of parasitic diseases of the gastrointestinal tract is the use of artificial neural networks and the fuzzy inference apparatus.

Conclusions

Currently, to diagnose diseases of the digestive system, expert doctors conduct examinations according to a certain scheme, which consists of a mandatory diagnostic minimum and a set of additional examinations.

1. Mandatory Diagnostic Minimum

Mandatory diagnostic minimum means that if a patient does not meet the criteria listed below, then he/she cannot receive treatment.

- a) A minimum of two symptoms should be present.
- b) Symptoms should last at least three months.
- c) Symptoms should be severe enough to interfere with daily activities.
- d) Symptoms should be accompanied by abnormal laboratory findings.
- e) Patients who do not have any of these conditions may still receive treatment if they have a history of chronic disease or if their condition worsens.

2. Additional Examinations

Additional examinations are performed to determine whether the patient's condition is caused by a specific disease. These examinations are optional and depend on the doctor's discretion.

a) Blood tests

Blood tests are conducted to check the levels of various substances in the blood.

b) Stool test

Stool tests are conducted to identify bacteria, parasites, viruses, and fungi.

c) X-ray examination.

This diagnostic minimum usually includes several or even all of the following types of examinations: questioning, palpation of the abdominal organs, complete blood and urine analysis, biochemical blood test, fecal occult blood test, ECG, ultrasound, X-ray examination of the stomach, gastroscopy with biopsy, determination of acidity gastric juice. All information on these examinations is placed in the medical history, which is further a source of information about the course of the disease and the history of its development (etiology).

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PECULIARITIES OF THE QUALITY OF LIFE OF PATIENTS WITH SCHIZOPHRENIA WITH CONCOMITANT DIABETES MELLITUS.

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ABSTRACT

In this article studied the features of the quality of life of patients with schizophrenia with concomitant diabetes mellitus. Conducting this study on the assessment of the quality of life of patients in the compared groups, we came to the conclusion that concomitant diabetes mellitus significantly reduces the quality of life of patients with schizophrenia. The revealed stronger relationship between the subjective assessment of one's QoL and the severity of positive and negative psychopathological symptoms in patients with concomitant somatic pathology suggests that the use of questionnaires to assess the quality of life in this category of patients for the development of individual rehabilitation programs is highly informative.

Keywords: quality of life of patients with schizophrenia, diabetes mellitus, positive and negative psychopathological symptoms, individual rehabilitation programs.

The relevance of the study

In recent years, in many studies, along with the "objective" quantitative and qualitative characteristics of the social functioning of patients, more and more importance is attached to their subjective experiences of their well-being, which has received the definition of "quality of life" [4, 8, 11, 12]. The involvement of this concept is a reflection of the principle of partnership, which involves taking into account the opinion and judgment of the patient about their well-being, the quality of care received and life in general, and also reflects the desire of modern medicine to ensure a decent life for the patient [3, 5, 18, 19]. Being a complex concept, the quality of life includes subjective and objective indicators of certain evaluation parameters, reflecting various aspects of social, physical and mental functioning [1, 15, 16, 17].

Quality of life indicators play a leading role in understanding many of the phenomena associated with schizophrenia spectrum disorders: dissociation between clinical prerequisites for adaptation and the actual level of adaptation, stigmatization and compliance processes. The study of quality of life indicators allows a deeper understanding of the patient's inner world, his response to treatment and becomes an additional criterion when choosing the tactics of psychopharmacology and psychosocial therapeutic measures [4, 9]. Currently, most researchers believe that a fruitful understanding of the quality of life is possible only through the synthesis of its objective and subjective aspects [14, 15, 16].

Purpose of the study

The study of the main indicators of the quality of life of patients with schizophrenia with concomitant diabetes mellitus.

Material and study methods



The object of the study were 111 patients who underwent inpatient treatment in the departments of the Republican Psychiatric Hospital of the Ministry of Health of the Republic of Azerbaijan and psychosomatic department of the Clinical Psychiatric Hospital No. 3 in Baku. In accordance with the selection criteria, the main study group included 72 patients with schizophrenia and schizophrenia spectrum disorders with concomitant diabetes mellitus. The comparison group consisted of 39 patients with similar psychiatric diagnoses without concomitant diabetes mellitus. The quality of life (QoL) of the patients of the main group was assessed twice - during the relief of psychotic symptoms and before discharge, by self-completion of the "SF-36 Health Status Survey" by patients. The Mentally Ill Social Functioning and Quality of Life Questionnaire is a structured interview and includes 36 items grouped into eight scales: physical functioning, role-playing, bodily pain, general health, vitality, social functioning, emotional state, and mental health. In addition to the objective criterion, each section also has a subjective assessment, i. reflects the satisfaction of the patient with the corresponding sphere of life. Each area of QoL was assessed in points, which makes it possible to identify the most problematic aspects of life well-being in each patient, assess the dynamics of the state and the effectiveness of treatment, and compare QoL indicators in different groups of patients. The questionnaire was filled in by respondents on their own and was a subjective measure of well-being and satisfaction with their living conditions.

The obtained results and their discussion

Our comparative analysis of two groups of patients with schizophrenia showed a lower level of quality of life in all spheres in the group of patients with concomitant diabetes mellitus. The results are presented in table 1.

Table 1. Comparison of indicators of the quality of life of patients with schizophrenia in depending on the presence of concomitant somatic pathology.

Quality of life spheres	Me ₁ , main gr., points	Me ₂ , compar. gr., points	P
General quality of life and health status	13	15	0,001
1. Physical sphere	13,3	16	0,000
2. Psychic sphere	13,5	14,4	0,006
3. Level of independence	13,6	16,6	0,000
4. Social relations	12,7	15,2	0,001
5. Environment	13,4	15,2	0,000
6. Spiritual sphere	15,5	16	0,081
Total value	82,1	92,7	0,000

Me₁- the value of the median in the main group

Me₂ - the value of the median in the comparison group

p - error probability

Most patients of the main group (with combined diabetes mellitus) rated their quality of life in various spheres as average (11-13 points) and good (14-17 points). Average scores were given for



overall quality of life and health, physical performance, social relationships, and environment. Patients with schizophrenia from the comparison group (without concomitant somatic pathology) rated their quality of life mainly as good in all spheres.

Statistically significant differences in QoL values ($p < 0.005$) were observed in all spheres, except for the spiritual. "General quality of life and state of health": median value in the main group (Me_1) 13 points, in the comparison group (Me_2) - 15 points ($p < 0.001$), "Physical sphere": $Me_1 = 13.3$ points, $Me_2 = 16$ points ($p < 0.001$), "Mental sphere": $Me_1 = 13.5$ points, $Me_2 = 14.4$ points ($p < 0.006$), "Level of independence": $Me_1 = 13.6$ points, $Me_2 = 16.6$ points ($p < 0.000$), "Social Relations": $Me_1 = 12.7$ points, $Me_2 = 16.2$ points ($p < 0.001$), "Environment": $Me_1 = 13.4$ points, $Me_2 = 15.2$ points ($p < 0.001$), "Total value": $Me_1 = 82.1$ points, $Me_2 = 92.7$ points ($p < 0.001$). In the spiritual sphere of QoL, the median values were also higher in the comparison group, but the differences did not reach the level of statistical significance ($p < 0.08$).

The physical sphere of quality of life consists of three sub-spheres: physical pain and discomfort; vital activity, energy and fatigue; sleep and rest. The results of comparing the quality of life indicators of patients with schizophrenia by subspheres of the physical sphere, depending on the presence of concomitant somatic pathology, are presented in Table 2.

Table 2. Comparison of indicators of the quality of life of patients with schizophrenia by subspheres of the physical sphere of QoL.

Subspheres of the physical sphere of quality of life	Me_1 , main gr., points	Me_2 , compar. gr., points	P
1. Physical pain and discomfort	14	15	0,009
2. Vitality, energy, fatigue	11	15	0,050
3. Sleep and rest	15	17	0,004

As can be seen from the table, the lowest indicators of QoL in the main group were observed in the subsphere "Vitality, energy, fatigue" ($Me_1 = 11$). The highest scores were obtained in the comparison group in the subsphere "Sleep and rest" ($Me_2 = 17$). For all three subspheres of QoL, statistically significant differences were found between the two groups of patients.

The psychological sphere of QoL consists of 5 subspheres: positive emotions; thinking, learning, memory and concentration (cognitive functions); self-esteem; body image and appearance; negative emotions. The results of comparing the quality of life indicators of patients with schizophrenia by subspheres of the psychological sphere, depending on the presence of concomitant somatic pathology, are presented in Table 3.

Table 3. Comparison of indicators of the quality of life of patients with schizophrenia by subspheres of the psychological sphere of QoL.

Subspheres of the psychological sphere of quality of life	Me ₁ , main gr., points	Me ₂ , compar. gr., points	P
1. Positive emotions	13	14	0,114
2. Cognitive functions	14	15	0,053
3. Self-esteem	14	14,5	0,181
4. Body image and appearance	15	15,5	0,168
5. Negative emotions	14	15	0,011

As can be seen from Table 3, the QOL indicators of the psychological sphere have statistically significant differences between the main group and the comparison group in only one sub-sphere "Negative emotions". The indicators of other sub-spheres are only approaching statistically significant ones.

In addition, one of the indicators of the quality of life of the examined patients is the levels of anxiety and depression, which are reflected in the diagrams below.

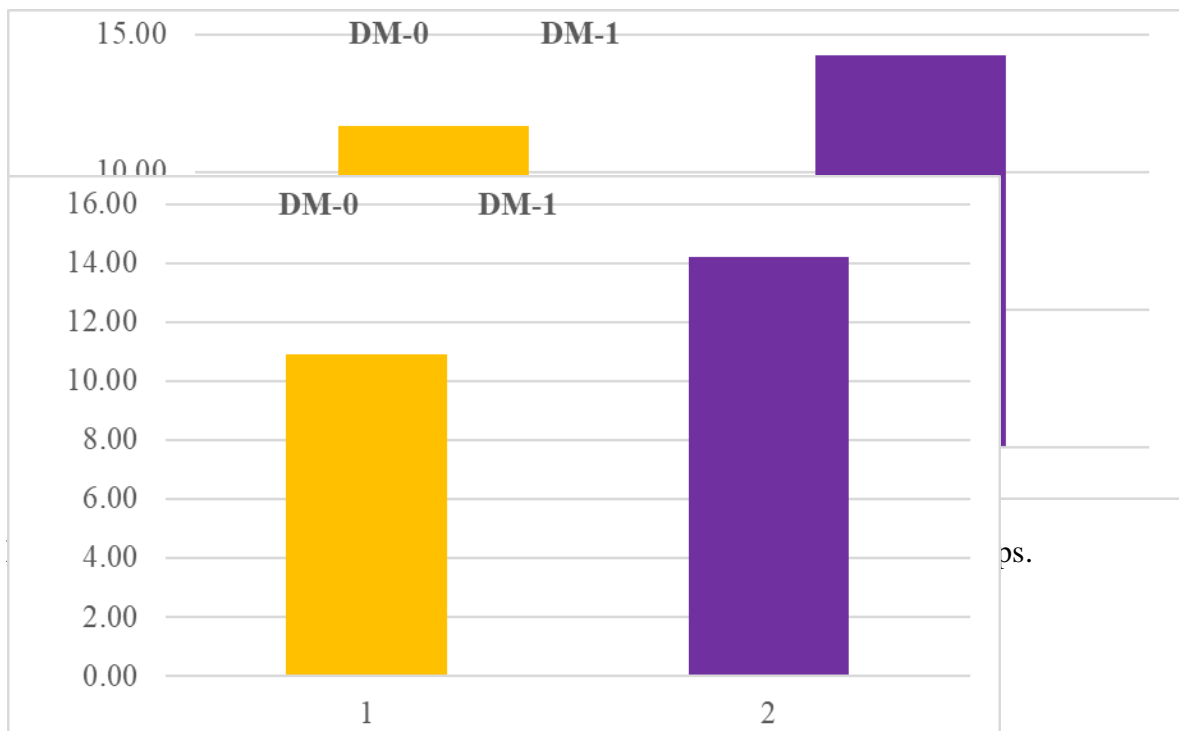


Diagram 2. The level of depression in patients of the main and comparison groups

As can be seen from the indicators of the diagrams, the level of anxiety and depression in patients with schizophrenia with diabetes mellitus significantly exceeded these indicators in patients of the comparison group.



The sphere of QoL “Level of independence” consists of 4 subspheres: mobility; ability to carry out daily activities; dependence on drugs and treatment; ability to work. The results of comparing the quality of life indicators of patients with schizophrenia by subspheres of the "Level of independence" sphere, depending on the presence of concomitant somatic pathology, are presented in Table 4.

Table 4. Comparison of indicators of the quality of life of patients with schizophrenia by subspheres of the sphere of QoL "Level of independence"

Sub-spheres of the sphere of quality of life "Level of independence"	Me ₁ , main gr.,points	Me ₂ ,compar. gr., points	P
1. Mobility	15	18	0,002
2. Ability to perform daily activities	14,5	16	0,021
3. Dependence on drugs and treatment	14	16	0,006
4. Ability to work	16	17	0,078

As can be seen from the table, the QoL indicators of the "Level of Independence" have statistically significant differences between the main group and the comparison group in three out of 4 sub-spheres. Particularly significant differences can be noted in the sub-spheres "Mobility" and "Dependence on drugs and treatment."

The sphere of QoL “Social relations” consists of three sub-spheres: personal relations; practical social support; sexual activity. The results of comparing the quality of life indicators of patients with schizophrenia by subspheres of the “Social Relations” sphere, depending on the presence of concomitant somatic pathology, are presented in Table 5.

Table 5. Comparison of indicators of the quality of life of patients with schizophrenia by subspheres of the sphere of QoL "Social relations"

Subspheres of the sphere of quality of life "Social relations"	Me ₁ , main gr.,points	Me ₂ ,compar. gr., points	P
1. Personal relationships	14	16	0,015
2. Practical social support	15	16	0,202
3. Sexual activity	10	13,5	0,000

As can be seen from the table, the indicators of QoL in the "Social Relations" sphere have statistically significant differences between the main group and the comparison group in only two of the 3 sub-spheres. Particular attention is drawn to the sub-sphere "Sexual activity", the indicators of which in the main group are minimal and correspond to a poor quality of life.

The sphere of QoL "Environment" consists of 8 sub-spheres: physical safety and security; home environment; financial resources; medical and social assistance (accessibility, quality); opportunities to acquire new information and skills; opportunities for recreation and entertainment and their use; the environment around (pollution, noise, climate, attractiveness); transport. The results of comparing the quality of life indicators of patients with schizophrenia by subspheres of

the “Environment” sphere, depending on the presence of concomitant somatic pathology, are presented in Table 6.

Table 6. Comparison of indicators of the quality of life of patients with schizophrenia by subspheres of the sphere of QoL "Environment".

Sub-spheres of the sphere of quality of life "Environment"	Me ₁ , main gr., points	Me ₂ , compar. gr., points	P
1. Physical security	13	15	0,002
2. House	15	16	0,028
3. Finance	11,5	14	0,000
4. Medical and social assistance	13,5	15	0,009
5. New information, skills	15	16	0,072
6. Recreation and entertainment	14	15	0,174
7. Environment around	14	15	0,024
8. Transport	14	15	0,017

As can be seen from Table 6, the QoL indicators in the "Environment" sphere have statistically significant differences between the main group and the comparison group in 6 out of 8 sub-spheres.

Thanks to a clear scoring system, structure and multidimensionality, the WHO QOL-100 questionnaire allows you to assess both the general profile of QOL and consider its components in detail. It should be noted that the indicators of the quality of life of patients according to the WHO QOL-100 questionnaire largely coincide with the data of other researchers who have studied this problem [3, 4, 6, 8].

Clinical manifestations of schizophrenia, the severity of psychopathological symptoms, of course, affect the quality of life of patients. According to most researchers, the quality of life of patients with schizophrenia largely depends on the biologically determined clinical manifestations of the disease [10]. Researchers are looking for clinical manifestations that have the greatest impact on the quality of life of patients [13]. Of particular importance in assessing the quality of life is the predominance of positive or negative symptoms in the clinical picture [7].

Correlation analysis in the study groups revealed the relationship between the severity of psychopathological symptoms and indicators of the main areas of quality of life of patients. Statistically significant positive correlations in the total sample of patients were traced between positive symptoms and the following spheres of QoL: physical sphere- Spearman's criterion (R)=0.244, $p<0.002$; psychological sphere - $R=0.22$, $p<0.004$; level of independence - $R=0.244$, $p<0.002$; environment - $R=0.17$, $p<0.021$; spiritual sphere - $R=0.20$, $p<0.010$; total value - $R=0.23$, $p<0.002$. A statistically significant negative correlation between negative symptoms and QoL was found in the following spheres: physical sphere- $R= -0.174$, $p<0.026$; psychological sphere - $R= -0.177$, $p<0.024$; total value - $R= -0.162$, $p<0.032$. Thus, regardless of the presence of concomitant diabetes mellitus, there is a direct correlation between positive symptoms and higher QoL, while negative symptoms correlate with lower quality of life.

In the main group of patients (with concomitant diabetes mellitus), a positive correlation between positive symptoms and quality of life indicators was more pronounced than in the comparison



group, and reached the level of statistical significance in the following spheres: physical sphere – Spearman's criterion(R) = 0.366, $p < 0.001$; psychological sphere - $R = 0.335$, $p < 0.002$; level of independence - $R = 0.306$, $p < 0.005$; total value - $R = 0.248$, $p < 0.018$. The negative correlation between negative symptoms and QoL indicators was also more pronounced in the main group (according to the total value of QoL $p < 0.011$) than in the comparison group (according to the total value of QoL $p < 0.035$). Thus, in the group of patients with concomitant diabetes mellitus, there is a more pronounced correlation between psychopathological symptoms and the level of quality of life.

Thus, in patients of both groups, there is a direct correlation between positive psychopathological symptoms and higher QoL (according to the total value of QoL, $p < 0.002$). In the main group of patients (with concomitant diabetes mellitus), a positive correlation between positive symptoms and quality of life indicators is more pronounced than in the comparison group. Negative symptomatology in patients of both groups correlates with lower quality of life indicators (according to the total value of QoL, $p < 0.032$). The negative correlation between negative symptoms and QoL indicators was also more pronounced in the main group (according to the total value of QoL $p < 0.011$) than in the comparison group (according to the total value of QoL $p < 0.035$).

Summing up the assessment of the quality of life of patients in the compared groups, we came to the conclusion that concomitant diabetes mellitus significantly reduces the quality of life of patients with schizophrenia. The revealed stronger relationship between the subjective assessment of one's QoL and the severity of positive and negative psychopathological symptoms in patients with concomitant somatic pathology suggests that the use of questionnaires to assess the quality of life in this category of patients for the development of individual rehabilitation programs is highly informative.

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PRINCIPLES OF TREATMENT AND REHABILITATION OF PATIENTS WITH SCHIZOPHRENIA WITH CONCOMITANT DIABETES MELLITUS

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ABSTRACT

In the course of the differentiated treatment and rehabilitation measures carried out, in the majority of patients with schizophrenia with concomitant diabetes mellitus, after a course of inpatient treatment, psychotic symptoms were completely or partially reduced, relative criticism of their condition was formed, and the subjective assessment of their quality of life improved significantly. The revealed differences in the frequency of rehospitalizations between the first (with a higher level of QoL at admission) and the second (with a lower level of QoL at admission) subgroups of patients indicate better curability of patients with an initially higher quality of life and the advisability of a differentiated (taking into account QoL) treatment and rehabilitation approach to patients. It is assumed that the further use of the proposed treatment and rehabilitation programs focused on a dynamic detailed (by spheres and sub spheres) study of the quality of life of patients will lead to an increase in the compliance of mentally ill patients, the prevention of stigmatization and self-stigmatization, an increase in long-term remissions, as well as an improvement in their quality of life and social adaptation.

Keywords: stigmatization and self-stigmatization, spheres and sub spheres.

The relevance of the study

Rehabilitation of patients with mental disorders is the most important step in the treatment of patients, their recovery and return to society, reducing the risk of relapse. The effectiveness of treatment largely depends on the intensity and quality of rehabilitation, which has become an integral part of psychiatric care in world practice. Currently, treatment and rehabilitation programs have been developed for the management of various categories of mental patients [1, 3, 10, 11], with concomitant somatic pathology [2, 5, 7], with different levels of quality of life [4, 6]. However, all of them have some significant shortcomings, which determined the need for the study.

Purpose of the study

On the basis of the conducted research, to develop and propose rehabilitation recommendations for patients with schizophrenia with concomitant diabetes mellitus.

Material and study methods

The object of the study were 111 patients who underwent inpatient treatment in the departments of the Republican Psychiatric Hospital of the Ministry of Health of the Republic of Azerbaijan and psychosomatic department of the Clinical Psychiatric Hospital No. 3 in Baku. In accordance with the selection criteria, the main study group included 72 patients with schizophrenia and schizophrenia spectrum disorders with concomitant diabetes mellitus. The comparison group consisted of 39 patients with similar psychiatric diagnoses without concomitant diabetes mellitus.



The rehabilitation programs are based on data on the quality of life of the examined groups of patients.

The obtained results and their discussion

Summarizing the work of researchers involved in the problems of treatment and rehabilitation of patients with schizophrenic disorders, we have developed rehabilitation recommendations for patients with schizophrenia with concomitant diabetes mellitus, depending on the level of quality of life. The rehabilitation measures developed by us consist of psychopharmacotherapy, psychotherapy, and psychosocial intervention.

Studying the characteristics of the structure of the quality of life of schizophrenia patients enables the most efficient and distinct selection of the patient's psychosocial rehabilitation's directions in order to enhance their social and adaptive functioning.[6]. The tasks of conducting a complex of psychopharmacological and sociotherapeutic effects were: reduction of psychopathological symptoms with the formation of remission; restoration of disturbed social adaptation; achieving an optimal level of quality of life.

Treatment and rehabilitation of patients should include the principles of differentiation, complexity, strict adherence to the sequence of stages of therapy [8]. Unlike narrowly focused (only medicinal or only social) assistance, an integrated approach has a number of advantages, since it immediately affects all aspects of the life of patients and their immediate environment. When carrying out the whole complex of measures, the main targets of its application are distinguished:

- influence on the biological essence of a mental disorder, manifested by productive and negative psychopathological symptoms;

- treatment and prevention of exacerbations of concomitant somatic diseases;

- correction of personal deviations, the formation of a critical attitude to one's condition;

The implementation of therapeutic and rehabilitation effects was carried out through psycho and somatopharmacological, social rehabilitation, and psycho-correctional complexes. Rehabilitation measures were applied to patients in stages: the initial (adaptive-diagnostic) stage - after the relief of acute psychopathological symptoms, the diagnosis of the basic level of quality of life and the development on its basis of further tactics of treatment and rehabilitation measures; the main one (planned differentiated curation) - a complex of pharmacological and differentiated psychosocial therapeutic measures; the final stage (maintenance therapy) - during the transition from an acute to a basic or remission state.

Upon admission, the patients included in the study were divided into two groups - the main group (with concomitant diabetes mellitus) and the comparison group (somatically healthy). The revealed clinical, dynamic, and social characteristics of patients of the main group: erased psychopathological symptoms, later referral to a psychiatrist, and a lower level of quality of life in patients with schizophrenia with concomitant diabetes mellitus - testified to a greater need for this group of patients in active psychosocial therapeutic measures. After relief of psychotic symptoms, patients of the main group filled out a quality of life questionnaire in order to develop differentiated rehabilitation programs for patients with schizophrenia with concomitant diabetes mellitus.

The scheme of carrying out medical and rehabilitation measures is shown in Figure 1.

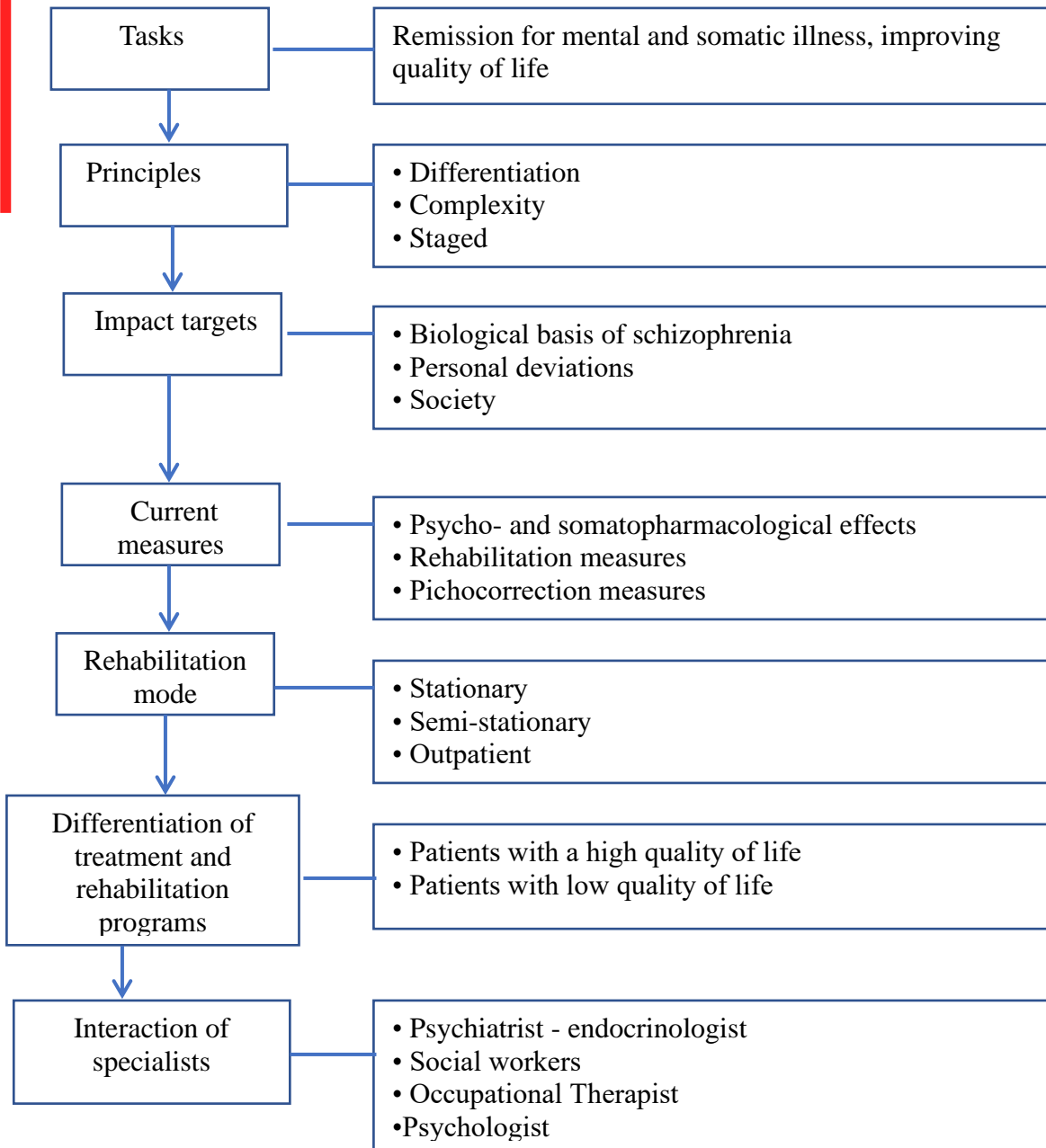


Figure 1. Scheme of treatment and rehabilitation of patients with schizophrenia with concomitant diabetes mellitus.

The implementation of therapeutic and rehabilitation effects was carried out through psycho and somatopharmacological, social rehabilitation and psycho-correctional complexes. Rehabilitation measures were applied to patients in stages: the initial (adaptive-diagnostic) stage - after the relief of acute psychopathological symptoms, the diagnosis of the basic level of quality of life and the

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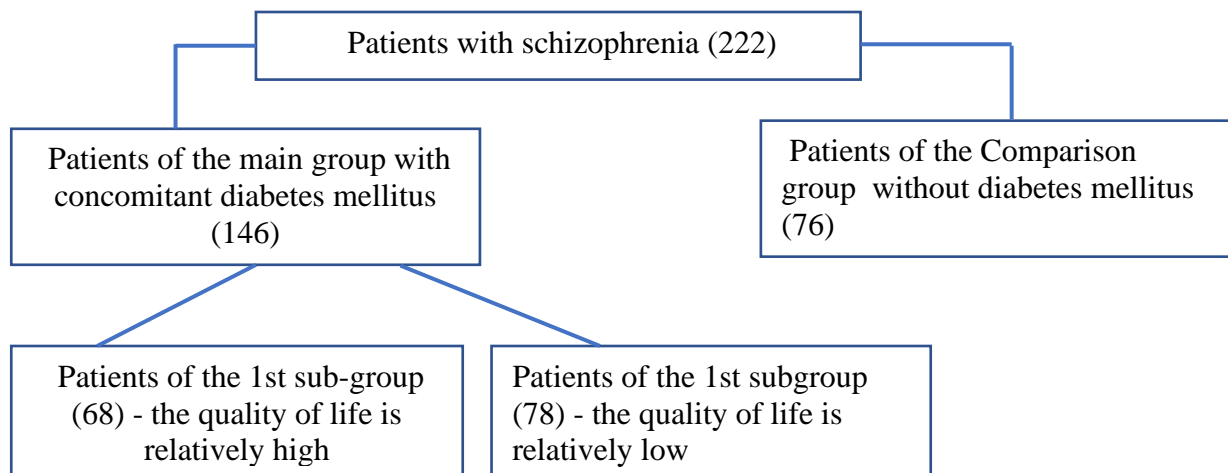


Figure 2. Division of patients of the main group into 2 subgroups depending on the level of quality of life.

Depending on the level of quality of life, the patients of the main group (146 patients) were divided into two subgroups: the 1st subgroup (68 people) - with a higher quality of life and the 2nd (78 people) - with a lower quality of life (Fig. 2) .

For the compared indicators, the average scores were taken in 6 spheres of quality of life: physical, psychological sphere, level of independence, social relations, environment and spiritual sphere. In addition, indicators on the overall quality of life and health status and the total value due to spheres were taken into account.

Our studies have revealed that QoL indicators significantly prevail in all spheres in the first grade and correspond to the level of a good quality of life (14-17 points), in the second grade, QoL indicators in all spheres correspond to the average level of QoL (11-13 points). The greatest difference between the classes was revealed in the psychological sphere (median of the first class, $Me_1=15.4$, the second, $Me_2=11.9$; $p=0.000$). Thus, it can be concluded that the most serious problems in the psychological sphere of quality of life were identified in patients of the second class. In order to identify the most significant factors affecting the level of quality of life, we studied the composition of two subgroups. There were no significant differences between the



classes in terms of gender, age, level of education, financial situation, which indicates the homogeneity of the groups in terms of the main socio-demographic characteristics. Also, there were no statistically significant differences in body mass index, neurological, allergic diseases, leading psychopathological syndrome (paranoid syndrome prevailed in both classes), premorbid personality traits (although in the second class there were slightly more patients with an unstable personality type than in first grade) suicidal behavior, alcohol and drug use.

The ratio of tobacco smoking and the level of subjective assessment of the quality of life of patients with schizophrenia is presented in Table 1.

Table 1. Smoking by patients with schizophrenia depends on the level of QoL.

Smoking	I subgroup (QoL is higher)		II group (QoL is lower)		p
	Abs., pers.	%	Abs., pers.	%	
No smoking	37	54,4	20	25,6	<0,005
Occasionally and less than a pack a day	16	23,5	25	30,1	>0,05
A pack or more per day	15	22,1	33	34,3	<0,05
Total	68	100	78	100	

As can be seen from Table 1, the second subgroup - with a lower quality of life - included statistically significantly fewer non-smokers (25.6%) than the first subgroup - with a higher quality of life (54.4%). Also, the second subgroup was dominated by patients who smoked a pack or more of cigarettes per day (34.3%), compared with the first subgroup, in which a pack or more were smoked by 22.1% of patients. Differences in these indicators were statistically significant. The smallest difference between the two subgroups was observed among patients who smoked occasionally and less than a pack of cigarettes per day (23.5% in the first and 30.1% in the second subgroup). The differences did not reach the level of statistical significance ($p > 0.05$). This fact indicates the significance of the impact on the quality of life of patients not only the presence of tobacco dependence, but also the frequency of smoking.

Statistically significant differences between classes were observed in marital status (Table 2).

Table 2. Marital status of patients with schizophrenia depending on the level of QoL.

Marital status	I subgroup (QoL is higher)		II group (QoL is lower)		p
	Abs., pers.	%	Abs., pers.	%	
Not married	25	36,7	49	62,8	<0,005
Married	22	32,4	8	10,3	<0,001
Divorced	21	30,9	21	26,9	>0,05
Total	68	100	78	100	

As can be seen from Table 2, in the first subgroup (with a higher quality of life) there were more patients who were married (32.4%) than in the second subgroup (10.3%); $p < 0.005$. Undoubtedly, this fact indicates a significant positive impact of family lifestyle on the quality of life of patients with schizophrenia.

The clinical severity of schizophrenia symptoms was assessed using the PANSS scale. The medians of positive (P), negative (N), general psychopathological (G) symptoms, as well as the composite index (the difference between positive and negative P-N syndromes) and the sum of positive, negative and general psychopathological symptoms (P+N+G) were compared. A comparative analysis of the severity of psychopathological symptoms according to the PANSS scale is presented in Table 3.

Table 3. Comparison of the severity of psychopathological symptoms in patients of I and II subgroups according to the PANSS scale.

Scales of psychopathological symptoms	Me ₁ , subgroup I, points	Me ₂ , II subgroup, points	P
P - positive symptoms	25,0	23,0	<0,005
N - negative symptoms	18,5	22,0	<0,005
P - N	7,0	2,0	<0,001
G - general psychopathological symptoms	48	51,0	<0,05
P+N+G	93,5	95,0	>0,2

As can be seen from Table 3, in patients of the first subgroup, positive symptoms prevailed (median of subgroup I Me₁=25.0 points; subgroup II Me₂ - 23.0 points; <0.005), in patients of the second subgroup - negative (Me₁=18.5 points ; Me₂ - 22.0 points; <0.005). Differences in these indicators were close to statistically significant. In terms of the sum of positive, negative and general psychopathological symptoms, as well as the scale of general psychopathological symptoms, the differences were not so significant, the indicators somewhat prevailed in the second subgroup. Statistically significant differences between the two subgroups were identified by the difference between positive and negative symptoms (Me₁=7.0 points; Me₂ - 2.0 points; p<0.005). Thus, there is a fairly clear direct relationship between negative symptoms and lower quality of life scores, and between positive symptoms and higher quality of life scores. Of course, when assessing the quality of life, not only the presence of diabetes mellitus is important, but also its exacerbation, i.e. the physical condition of the patient, his well-being at the time of the examination. The presence of exacerbations of diabetes mellitus during hospitalization is presented in Table 4.

Table 4. Exacerbation of concomitant diabetes mellitus during the period hospitalizations in patients of two subgroups.

Exacerbation of diabetes	I subgroup (QoL is higher)		II group (QoL is lower)		P
	Abs., pers.	%	Abs., pers.	%	
Have	15	22,1	44	56,4	<0,005
Don't have	53	77,9	30	43,6	
Total	68	100	78	100	



As can be seen from Table 4, exacerbations of diabetes mellitus were statistically significantly more common in patients of the second subgroup (56.4%) than in patients of the first subgroup (22.1%), $p < 0.005$. Thus, diabetes mellitus in a state of exacerbation significantly reduces the quality of life of patients with schizophrenia.

Side effects of ongoing antipsychotic therapy in patients of two subgroups are presented in Table 5.

Table 5. Side effects of ongoing antipsychotic therapy in patients of the first and second subgroups.

Side effects of psychopharmacotherapy	I subgroup (QoL is higher)		II group (QoL is lower)		P
	Abs., pers.	%	Abs., pers.	%	
Don't have	41	60,5	41	52,5	<0,05
Extrapyramidal disorders	12	17,5	16	20,5	<0,05
Body weight gain	9	13,2	13	16,7	<0,05
Over-sedation	3	4,4	6	7,7	<0,05
A combination of two or more side effects	3	4,4	2	2,6	<0,05
Total	68	100	78	100	

As can be seen from Table 5, side effects of antipsychotic therapy were more common in the group of patients with a lower level of quality of life, but the differences between the classes did not reach the level of statistical significance. In general, a rather large number of patients without side effects attracts attention (60.5% of patients in the first and 52.5% of the second subgroup). This fact can be explained by the fact that in most cases, patients were prescribed atypical antipsychotic drugs, as well as prescribing, in some cases, correctors of antipsychotic therapy with a preventive purpose. The most frequently observed extrapyramidal disorders (17.5% of patients of the first and 20.5% of the second subgroup) and body weight gain (13.2% of patients of the first and 16.7% of the second subgroup), isolated cases were represented by excessive sedation and combined side effects. It can be assumed that the absence of statistically significant differences between subgroups is due to the insufficient number of patients experiencing the side effects of psychopharmacotherapy.

Thus, in the study, the factors most influencing the quality of life of patients with schizophrenia with concomitant diabetes mellitus were identified. The factors most significantly reducing the quality of life of this category of patients were the absence of one's own family, smoking more than a pack of cigarettes per day, exacerbation of diabetes at the time of the examination, and the prevalence of negative symptoms in the clinic of schizophrenia.

The treatment of patients is based on an integrated approach, which implies the unity of psychopharmacotherapy and various methods of psychosocial treatment and psychosocial rehabilitation. Assistance is provided by a multi-professional team of specialists (with the participation of a psychiatrist, endocrinologist, clinical psychologist, psychotherapist and social work specialist), each of which has its own tasks, coordinated with other members of the "team". Middle and junior medical staff, as members of the therapeutic team, should be active in this work, motivating patients and their relatives for a positive attitude towards therapy, creating an appropriate psychotherapeutic environment in the department, monitoring and consolidating the results of group and individual forms of work.



It should be noted the need for long-term management of patients after discharge from the department. To this end, it is recommended that patients discharged from the hospital continue to be observed by a local psychiatrist and endocrinologist in a polyclinic to assess the mental and somatic state, the implementation of supportive psycho and somatic pharmacotherapy in the form of a monthly examination and monitoring of the patients' condition.

The main treatment for schizophrenia and schizophrenia spectrum disorders is, of course, medicamentous therapy. However, along with pharmacological treatment, a special role is now given to psychocorrectional and social work with the patient, his family, relatives and immediate environment, which reduces the risk of recurrence of the disease and significantly affects his quality of life. Psychosocial rehabilitation is one of the fundamental parts in a modern comprehensive program of care for patients with mental disorders.

As a set of programs for teaching patients with mental disorders how to behave rationally both in the hospital and at home, psychosocial rehabilitation is aimed at developing the social skills necessary in everyday life, such as interacting with other people, accounting for one's own finances, cleaning the house, committing shopping, using public transport, etc. Psychotherapy helps the mentally ill feel better about themselves, especially those who experience feelings of inferiority due to their illness and those who deny their own illness. Although psychotherapy alone cannot cure the symptoms of schizophrenia spectrum disorders, individual and group sessions can provide important moral support and create a friendly atmosphere that is very beneficial for both the patients themselves and their loved ones.

An important element of social rehabilitation is participation in the work of mutual support groups led by patients who have undergone hospitalization. This allows other patients to feel help in understanding their problems, to realize that they are not alone in their misfortune, to see the possibilities of personal participation in rehabilitation activities and in public life.

Psychosocial rehabilitation involves various systems of influence, including individual conversations (psychotherapy), family and group therapy, rehabilitation, support groups, etc. In addition to family therapy, individual psychotherapeutic treatment is carried out, which consists in regular meetings of the patient with a professional, which can be a psychiatrist, psychologist or social worker with special training. In conversations, various topics of concern to the patient are discussed: past experience and existing difficulties, thoughts, feelings and relationship systems. The patient and his mentor jointly discuss the problems that are relevant to the patient, separate the real from the fictitious and try to find the optimal solution to the existing problems.

By analyzing their past with an experienced and accommodating mentor, the patient receives additional information to develop a new perspective on himself and his problems. In contrast to psychotherapy for other mental conditions, people on the schizophrenia spectrum benefit in particular from conversations about the real world and daily concerns. These conversations provide them with the support they need and a steady "connection to reality." At the same time, it is also important to develop personal connections of patients, to support the aspirations for their creation and preservation.

An important principle of rehabilitation measures is the inclusion of the patient himself in the treatment and recovery process, involving him as much as possible in complicity in the restoration of certain impaired functions (for example, memory or attention) or social ties: labor, family, etc. This principle of rehabilitation of the mentally ill can be called the principle of partnership.

In accordance with these principles, we propose a scheme of three successive stages in the rehabilitation of the mentally ill. The first stage is the initial one (adaptive-diagnostic), the second



is the main one (planned differentiated therapy using various rehabilitation programs), and the third one is the final stage of maintenance therapy.

The main task of the initial (adaptive-diagnostic) stage is the elimination or mitigation of the manifestations of the disease, the prevention of the formation of a mental defect, the patient's adaptation to the changed environmental conditions, and the formation of adherence to therapy. The main role at this stage belongs to medicamentous therapy. At the end of this stage, the patient's quality of life is assessed, the results of which determine the further tactics of treatment and rehabilitation measures.

The task of the main stage of rehabilitation is to prevent the phenomena of hospitalism and self-stigmatization, as well as to form the patient's motivation for work, for an active lifestyle, interpersonal relationships, etc. At this stage, medicamentous therapy and psychosocial, psychotherapeutic measures are equally applied, which are differentiated depending on the basic level of quality of life determined at the first stage. Patients are actively involved in psycho-educational, working groups. Here it is necessary to connect the methods of leisure, labor, sports and art therapy developed on the basis of the Clinical Psychiatric Hospital No. 1 of the Ministry of Health of the Republic of Azerbaijan. Psychotherapeutically oriented work is carried out not only with patients, but also with their relatives.

The final stage of rehabilitation (the stage of maintenance therapy) is aimed at the fullest possible restoration of the patient's rights, the restoration of the individual and social value of the individual, the restoration of pre-painful relationships with the surrounding reality. Medicamentous treatment at this stage of readaptation is limited, as a rule, to "maintenance" doses of psychotropic drugs or those that stop the exacerbation. A very difficult and at the same time very important thing that contributes to the success of rehabilitation is the organization of the correct attitude towards patients from the side of the environment in the family, the prevention of its stigmatization. In the process of rehabilitation, group work is widely used, which is aimed at changing the relationship of attitudes and the range of the patient's abilities. It allows stimulation of activity, formation of the patient's responsibility for his social behavior, increase of his social competence.

Patients with concomitant diabetes mellitus, of course, need adequate and timely somatotropic therapy. Individuals with severe mental illness (including those with schizophrenia) are prescribed significantly fewer drugs for the treatment of somatic disorders [9]. And this is true despite the fact that somatic diseases in mentally ill patients are more common than in the general population. The most likely reason for this fact is the lack of alertness of therapists in relation to patients of this risk group.

Patients with schizophrenia who have undergone rehabilitation are characterized by a more adequate perception of the world, they develop a relatively critical attitude towards the violation of their health, a positive attitude towards life, family and society appears, the level of perception of their quality of life increases or normalizes. Based on the clinical-pathogenetic and clinical-dynamic results obtained by us, the main principles and methodological approaches to the treatment and rehabilitation of patients with schizophrenia with concomitant diabetes mellitus and differentiated recommendations depending on the basic level of QoL were developed.



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SARS-COV-2-INDUCED HYPERGLYCEMIC STATUS AND DIABETES MELLITUS - CORRELATION POSSIBILITY

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ABSTRACT

Diabetes mellitus, its treatment and prevention of complications still remain a serious challenge in modern medicine. In recent years, the number of people with diabetes has not only increased, but also rejuvenated. At present, COVID-19 drastically worsened the statistics of diabetes. Has been proposed that development of diabetes mellitus in Covid-19 infected patients should be caused by severe "cytokine storm", stress-induced and/or corticosteroid-induced hyperglycemia, SARS-CoV-2 direct or indirect damaging effects on various organs and systems, especially pancreatic β -cells. Nowadays, studies are still scarce and precise mechanisms of development of diabetes mellitus in covid-patients are not known. There is not much data available specific to COVID-19 and prediabetes. Remains unclear also whether SARS-CoV-2 can cause changes in glucose metabolism. Further researches are required to detect correlation between SARS-CoV-2-induced hyperglycemic state and state pathogenesis of development of diabetes mellitus in post-covid patients. It is very important for better management of Covid-patients to reduce the number of complications and the rate of disability and mortality caused by diabetes mellitus.

Keywords: COVID-19, hyperglycemic status, diabetes mellitus.

Diabetes mellitus, its treatment and prevention of complications still remain a serious challenge in modern medicine. In recent years, the number of people with diabetes has not only increased, but also rejuvenated, which is caused probably due to the modern lifestyle (chronic stressful



situations, increased consumption of products high in both, calories and sugar, hypodynamics etc.) [1]. High rate of patients with metabolic syndrome noteworthy as well that increases the risk of cardiovascular pathology, especially, diabetes mellitus [2, 3].

The current epidemiologic and negative situations caused by the pandemic have drastically worsened the statistics of diabetes. This is indicative of the fact that the first cases of development of diabetes mellitus in patients with COVID-19 have been described at the time of epidemic broke-out in Wuhan [4].

COVID-19 is a new and potentially serious coronavirus. The World Health Organization (WHO) has declared the COVID-19 outbreak to be a public health emergency of international concern. COVID-19 is proving to be a more serious illness than seasonal flu in everyone, including people with diabetes.

There are studies, where a new-onset diabetes mellitus was associated with SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) [5-9]. It has been proposed that the development of diabetes mellitus in these patients should be caused by severe "cytokine storm", stress-induced and/or corticosteroid-induced hyperglycemia, SARS-CoV-2 direct or indirect damaging effects on various organs and systems, especially pancreatic β -cells [10].

People who get COVID-19 have a greater risk of developing diabetes up to a year later, even after a mild SARS-CoV-2 infection, compared with those who never had the disease, a massive study of almost 200,000 people shows [11]. The research, published in *The Lancet Diabetes & Endocrinology* earlier this month, is one of a growing number of studies showing that COVID-19 can increase a person's risk of diabetes, months after infection [12].

About two years after the emergence of the COVID-19 virus, researchers continue to learn more about its impact on diabetes: There is an increased risk of COVID-19 infection in people with diabetes, which was recognized early on. However, there was concern about statistical methods and the retrospective nature of those initial studies; subsequent, higher quality studies have confirmed this association. Therefore, diabetes is recognized as a risk factor for COVID-19 infection [13].

The mentioned correlations have been confirmed by scientists/researchers in the United States, Great Britain and other countries [14,15,16,17]. A global registry of patients with Covid-19-induced diabetes mellitus has been created. However, it should be emphasized that nowadays, studies are still scarce and precise mechanisms of development of diabetes mellitus in covid-patients are not known and further researches are required.

There is not much data available specific to COVID-19 and prediabetes, but concerning risks factors still include obesity and other chronic medical conditions — particularly lung, heart or kidney issues [18].

Prevalence of similar cases occurring in our medical practice, especially at treatment with glucocorticoids, indicates the relevance of the issue and the need for further research [19].

An increasing body of evidence suggests that COVID-19 is associated with new diabetes diagnoses. However, it is unclear whether COVID-19 detects pre-existing diabetes or induces new-onset diabetes. Many clinics are reporting people diagnosed with diabetes during or soon after an infection with the coronavirus. COVID-19 is notorious for sometimes leaving an after math of puzzling symptoms, such as fatigue or concentration difficulties. But doctors are also worried about the coronavirus triggering a more familiar condition: diabetes [18,19].

COVID-19 has been shown to exacerbate pre-existing diabetes. This likely occurs because COVID-19 is associated with low-grade inflammation, which may initiate or worsen insulin



resistance. In addition, numerous studies have also demonstrated that SARS-CoV-2 can infest and multiply within insulin-producing pancreatic beta-cells, thus impairing insulin synthesis and secretion. Some studies have shown that these cells have the ACE2 receptor that the virus uses to enter cells. Or the pancreas cells could be harmed by the raised level of inflammation caused by the immune system's response to the virus [20].

Although previous research reported high blood-sugar levels and metabolic consequences resulting from pre-existing diabetes following COVID-19 hospitalization, studies correlating the disease to new-onset diabetes mellitus are scarce. Diabetes is an umbrella term for several conditions that involve high blood sugar, and can lead to serious complications, such as heart attacks. The body normally keeps blood sugar within a narrow window, as too high a level can damage organs and blood vessels. Currently unknown also and is an area of ongoing study whether COVID-19 infection can result in type 1 diabetes [21].

Most of the studies on this link so far have been descriptive ones, looking at people who go to hospital for covid-19 and are diagnosed with diabetes while there. More recently, researchers have begun estimating how often diabetes arises after the infection, including in people who did not go to hospital, who account for most covid-19 cases [22].

A large US study published last month, for instance, estimated that anyone with a positive covid-19 test has about a 40 per cent higher chance of developing any kind of diabetes in the following year, compared with uninfected people. A similar German study found an increased risk for type 2 diabetes of 28 per cent over about four months. The picture for type 1 diabetes is less clear as some specialist clinics have reported rises in new diagnoses since the pandemic began, but not all have.

Remains unclear also whether SARS-CoV-2 can cause clinically meaningful changes in glucose metabolism. Nevertheless, it may be possible to find an answer by characterizing the clinical symptoms of COVID-19-related diabetes and by determining the period between the onset of hyperglycemia and that of the infection [23]. Confusing matters further, there have been some reports of people with signs of both type 1 and type 2 diabetes after a covid-19 infection. These include people who already had type 2 diabetes, but covid-19 seemed to trigger a syndrome called ketoacidosis, usually a hallmark of type 1 diabetes [20].

It is imperative to establish a causal relationship between COVID-19 and diabetes since both diseases are prevalent throughout the world. Furthermore, establishing a causal relationship will have significant implications for diagnosis, management, public health, and scientific research [23]. Furthermore, detection of correlation between SARS-CoV-2-induced hyperglycemic state, early diagnosis of latent diabetes and pathogenesis of development of diabetes mellitus in post-covid patients with- and without metabolic syndrome is very important that will provide better management of covid-patients and help to elaborate preventive measures. It will increase the effectiveness of treatment of post-Covid-19 patients, reduce the number of complications and the rate of disability and mortality caused by diabetes mellitus.

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STUDY OF HEPATOPROTECTIVE ACTIVITY OF GRAPE SEED POLYPHENOL EXTRACTS IN A MODEL OF ACUTE PARACETAMOL-INDUCED HEPATITIS

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ABSTRACT

Aim

Drug-induced liver injury is a significant problem, so the aim of our research was to study the hepatoprotective properties of polyphenolic extracts from "Rkatsiteli" and "Caberne" grape seeds in a model of acute medical liver injury caused by the administration of paracetamol. Acute drug-induced hepatitis was simulated using one of the most popular antipyretic analgesics, paracetamol, known to be hepatotoxic. Experiments were performed on 24 nonlinear mature male white rats weighing 200-240 g. The experimental animals were orally administered paracetamol at a dose of 1250 mg/kg once a day for a 24-hour period. The experimental animals were divided into five groups: the intact control group; the control pathology group; animals in the third group, in which against the background of paracetamol liver damage the reference preparation Silibor was administered at a dose of 25 mg/kg; animals in the fourth and fifth experimental groups, in which against the background of paracetamol hepatitis were administered polyphenolic extracts from "Rkatsiteli" and "Caberne" grape seeds at a dose of 0.5 ml/kg. The administration of paracetamol in toxic doses resulted in severe damage to the hepatic parenchyma, which was accompanied by the formation of necrotic cells in the central and middle sections of the hepatic lobes. Increase of ALT activity in serum of experimental animals by 2.1 times indicated the development of a pronounced cytolytic syndrome. Administration of polyphenolic extracts from "Caberne" and "Rkatsiteli" grape seeds to the tested animals was accompanied by normalization of the indices characterizing the state of LPO/AOS. Thus, the content of TBA-AP in liver tissue of the experimental animals decreased by 35.7% and 31.2%, respectively, and the level of reduced glutathione normalized similarly, increasing by 59.9% and 52.3%. Although the increase of catalase activity in serum of animals in the control pathology group was not statistically significant, it was statistically lower in animals treated with the studied polyphenol complexes from grape seeds than in untreated animals, which was not observed when using the comparison drug. Consequently, the obtained experimental data indicate that polyphenolic extracts from "Caberne" and "Rkatsiteli" grapes seeds show high



therapeutic efficacy in conditions of acute toxic liver injury by paracetamol, have a distinct effect on peroxidation syndrome development, normalizing LPO/AOS balance, syndrome and significantly improving the functional state of the liver.

Introduction

Redox reactions are involved in numerous physiological and pathological processes; moreover, cellular homeostasis depends on the interaction between oxidants and the defense system, which includes reductants and antioxidant enzymes. The prevalence of free radicals, such as reactive oxygen species and reactive nitrogen species, at a desirable level can contribute to cell growth and differentiation. However, the overproduction of free radicals is destructive, resulting in oxidative stress and contributing to various diseases, such as cardiovascular diseases, cancer, diabetes, obesity, neurodegenerative disorders, and liver diseases.

In many cases, toxic liver damage develops as a complication of drug therapy. A significant number of medications exhibit hepatotoxic effects. These include NSAIDs (Indomethacin, Paracetamol), oral antidiabetic drugs (similar Sulfonylurea, Biguanides), antituberculous drugs (Isoniazid), antibiotics (Tetracyclines, Macrolides - Erythromycin, Oleandomycin, Rifampicin), diuretics (Furosemide), indirect-duty anticoagulants (Phenylin), Phenothiazine neuroleptics. Paracetamol is widely used in practical medicine and is an effective and relatively safe antipyretic and analgesic agent, but its prolonged use can be accompanied by toxic liver damage. This led to the relevance of investigating the therapeutic effect of polyphenolic extracts of grape seed in comparison with a hepatoprotective drug called Silibor on the model of hepatitis caused by paracetamol.

Paracetamol is an effective analgesic/antipyretic drug when used at therapeutic doses. However, the overdose of paracetamol can cause severe liver injury and liver necrosis. The mechanism of paracetamol-induced liver injury is still not completely understood. Reactive metabolite formation, depletion of glutathione and alkylation of proteins are the triggers of inhibition of mitochondrial respiration, adenosine triphosphate depletion and mitochondrial oxidant stress leading to hepatocellular necrosis. Role of oxidative stress in paracetamol-induced liver injury: The importance of oxidative stress in paracetamol hepatotoxicity is controversial. Paracetamol-induced liver injury cause the formation of reactive oxygen species. The potent sources of reactive oxygen are mitochondria, neutrophils, Kupffer cells and the enzyme xanthine oxidase. Free radicals lead to lipid peroxidation, enzymatic inactivation and protein oxidation. Role of mitochondria in paracetamol-induced oxidative stress: The production of mitochondrial reactive oxygen species is increased, and the glutathione content is decreased in paracetamol overdose. Oxidative stress in mitochondria leads to mitochondrial dysfunction with adenosine triphosphate depletion, increase mitochondrial permeability transition, deoxyribonucleic acid fragmentation which contribute to the development of hepatocellular necrosis in the liver after paracetamol overdose. Role of Kupffer cells in paracetamol-induced liver injury: Paracetamol activates Kupffer cells, which then release numerous cytokines and signalling molecules, including nitric oxide and superoxide. Kupffer cells are important in peroxynitrite formation. On the other hand, the activated Kupffer cells release anti-inflammatory cytokines. Role of neutrophils in paracetamol-induced liver injury: Paracetamol-induced liver injury leads to the accumulation of neutrophils, which release lysosomal enzymes and generate superoxide anion radicals through the enzyme nicotinamide adenine dinucleotide phosphate oxidase. Hydrogen peroxide, which is influenced by the neutrophil-derived enzyme myeloperoxidase, generates hypochlorous acid as a potent oxidant.



Role of peroxynitrite in paracetamol-induced oxidative stress: Superoxide can react with nitric oxide to form peroxynitrite, as a potent oxidant. Nitrotyrosine is formed by the reaction of tyrosine with peroxynitrite in paracetamol hepatotoxicity.

Aim

Drug-induced liver injury is a significant problem, so the aim of our research was to study the hepatoprotective properties of polyphenolic extracts from "Rkatsiteli" and "Caberne" grape seeds in a model of acute medical liver injury caused by the administration of paracetamol.

Materials and methods Acute drug-induced hepatitis was simulated using one of the most popular antipyretic analgesics, paracetamol, known to be hepatotoxic. Experiments were performed on 24 nonlinear mature male white rats weighing 200-240 g. The experimental animals were orally administered paracetamol at a dose of 1250 mg/kg once a day for a 24-hour period. The experimental animals were divided into five groups: the intact control group; the control pathology group; animals in the third group, in which against the background of paracetamol liver damage the reference preparation Silibor was administered at a dose of 25 mg/kg; animals in the fourth and fifth experimental groups, in which against the background of paracetamol hepatitis were administered polyphenolic extracts from "Rkatsiteli" and "Caberne" grape seeds at a dose of 0.5 ml/kg. Extracts studied were administered intragastrical one hour after administration of the toxic agent. The comparison drug Silibor was administered according to the same scheme: the first two days in parallel with paracetamol, and then one more day. On the third day, the animals were removed from the experiment by decapitation. In liver tissue, the content of TBA-active products (TBA-AP), reduced glutathione (RG) and catalase activity were determined, and the activity of alanine transaminase (ALT), γ -glutamyl transpeptidase (GGTP), alkaline phosphatase (ALP), total protein (TP) and urea were determined in the serum of the test animals.

Results and discussion

The results of the experiment on hepatoprotective effect of polyphenolic extracts from grape plant under conditions of acute paracetamol hepatitis, given in Table 1, showed that administration of paracetamol in toxic doses led to a marked increase in intensity of lipid peroxidation processes. Intensity of lipid peroxidation was manifested by the increase of the amount of TBA-AP in the liver tissue of the control group by 36.0% and the reduced level of renewed glutathione by 35.9%. At the same time, the increase in catalase activity was not statistically significant and showed little trend.

The administration of paracetamol in toxic doses resulted in severe damage to the hepatic parenchyma, which was accompanied by the formation of necrotic cells in the central and middle sections of the hepatic lobes. Increase of ALT activity in serum of experimental animals by 2.1 times indicated the development of a pronounced cytolytic syndrome.

Table 1. Study of the hepatoprotective effect of polyphenolic extracts from grape seeds in a paracetamol-induced hepatitis model (n=6).

Indicator/	Intact control	Control	Caberne,	Rkatsiteli,	Silibor,
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Group		pathology	0.5ml/kg	0.5ml/kg	25 мг/кг
In the liver tissue					
TBA-AP, $\mu\text{mol/g}$	63.03 \pm 4.80	85.74 \pm 4.41*	55.13 \pm 6.28**	58.97 \pm 5.13**	69.23 \pm 4.71**
RG, r.u.	44.85 \pm 4.38	28.73 \pm 2.63*	45.95 \pm 3.71**	43.76 \pm 1.73**	40.48 \pm 2.19**
Catalase, mkat/l	2.64 \pm 0.19	3.18 \pm 0.19	2.42 \pm 0.18**	2.45 \pm 0.26**	2.50 \pm 0.26
In the serum					
ALT, $\mu\text{mol/h}\cdot\text{l}$	0.76 \pm 0.07	1.58 \pm 0.07*	1.17 \pm 0.10*/**	1.15 \pm 0.10*/**	0.99 \pm 0.05*/**
GGTP, $\mu\text{mol/h}\cdot\text{l}$	3.09 \pm 0.21	6.55 \pm 0.75*	4.67 \pm 0.25*/**	4.71 \pm 0.31*/**	3.74 \pm 0.28**
ALP, mkat/l	3.25 \pm 0.24	4.63 \pm 0.32*	3.74 \pm 0.15**	3.78 \pm 0.26	3.53 \pm 0.27**
TP, g/l	59.20 \pm 1.91	53.60 \pm 1.57*	60.00 \pm 1.58**	59.40 \pm 2.11**	60.80 \pm 1.88**
Urea, mol/l	7.36 \pm 0.50	6.20 \pm 0.39	7.08 \pm 0.38	6.94 \pm 0.61	7.80 \pm 0.64

Notes:

- * – differences that are statistically reliable on intact control, $p > 0.05$;
- ** – differences that are statistically reliable on control pathology, $p > 0.05$;
- n – number of animals in the group.

Functional abnormalities developing against the background of paracetamol damage to the liver are obviously a consequence of metabolic changes and necrotic changes that occurred in the hepatic parenchyma. Signs of cholestatic syndrome development were observed, which was manifested by significant increase of ALP and GGTP activity in serum of animals of control pathology group.

There was also disruption of biosynthetic processes, in particular protein biosynthesis in hepatocytes, as evidenced by a significant decrease in serum protein levels. At the same time there were no significant violations of detoxification (ammonia-depleting) function of the liver (the level of urea in blood serum did not change statistically), which allows to estimate the severity of hepatocellular syndrome as moderate. The severity of the pathological changes was significantly reduced by the application of grape polyphenolic extracts and the Silibor comparison. Administration of polyphenolic extracts from "Caberne" and "Rkatsiteli" grape seeds to the tested animals was accompanied by normalization of the indices characterizing the state of LPO/AOS. Thus, the content of TBA-AP in liver tissue of the experimental animals decreased by 35.7% and 31.2%, respectively, and the level of reduced glutathione normalized similarly, increasing by 59.9% and 52.3%. Although the increase of catalase activity in serum of animals in the control pathology group was not statistically significant, it was statistically lower in animals treated with the studied polyphenol complexes from grape seeds than in untreated animals, which was not observed when using the comparison drug. Although the overall effect of the comparison drug on LPO processes and the state of the antioxidant system was less pronounced, Silibor also led to normalization of the oxidative balance. The level of TBA-AP decreased by 19.3% and the content of reduced glutathione increased by 40.1% with the use of Silibor. Although the application of the studied agents resulted in normalization of the LPO/AOS indices, the signs of cytolytic syndrome persisted. Administration of polyphenol extracts from "Caberne" and "Rkatsiteli" grape seeds to experimental animals led to a decrease in ALT activity in blood serum by 25.9% and 27.2% respectively, but enzyme activity remained elevated compared with intact control. Silibor exhibited a slightly more pronounced anticytolytic effect, reducing ALT activity by 37.3%, but also did not lead to its complete normalization.



A significant improvement in the functional state of the liver was observed during treatment with Silibor and polyphenol complexes from grape seeds, which proved to be a normalization of protein synthesis function and restoration of serum proteins. At the same time, a significant decrease in GGTP activity was observed. When polyphenolic extracts from grape seeds "Caberne" and "Rkatsiteli" were applied, GGTP activity decreased by 28.7% and 28.1%, respectively. When polyphenolic extract from grape seeds "Caberne" was administered, ALP activity was completely normalized, and in animals treated with polyphenolic extract from grape seeds "Rkatsiteli", it did not differ from the parameters of animals of intact control and control pathology groups. The changes revealed suggest a reduction in the severity of the cholestatic syndrome when using the studied polyphenolic extracts from grape seeds. At the same time, administration of Silibor resulted in complete normalization of ALP and GGTP activity, indicating the superiority of the comparison drug in its effect on the development of cholestasis syndrome.

Conclusions

Consequently, the obtained experimental data indicate that polyphenolic extracts from "Caberne" and "Rkatsiteli" grapes seeds show high therapeutic efficacy in conditions of acute toxic liver injury by paracetamol, have a distinct effect on peroxidation syndrome development, normalizing LPO/AOS balance, syndrome and significantly improving the functional state of the liver. It is also established that the reference preparation Silibor shows in conditions of acute paracetamol hepatitis somewhat more distinct influence, in comparison with the investigated polyphenol complexes from grape seeds, on development of cytolytic and cholestatic syndrome.

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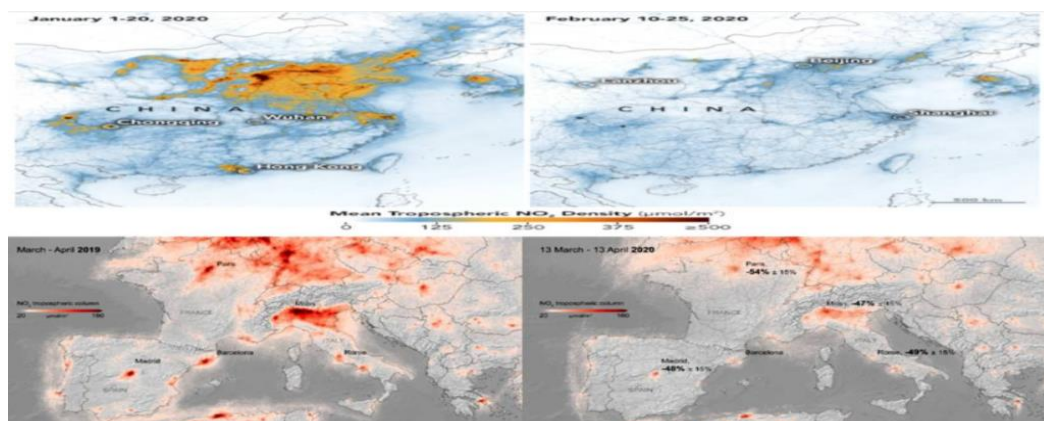


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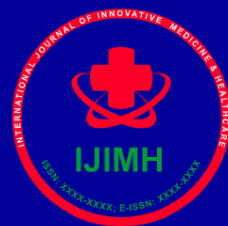
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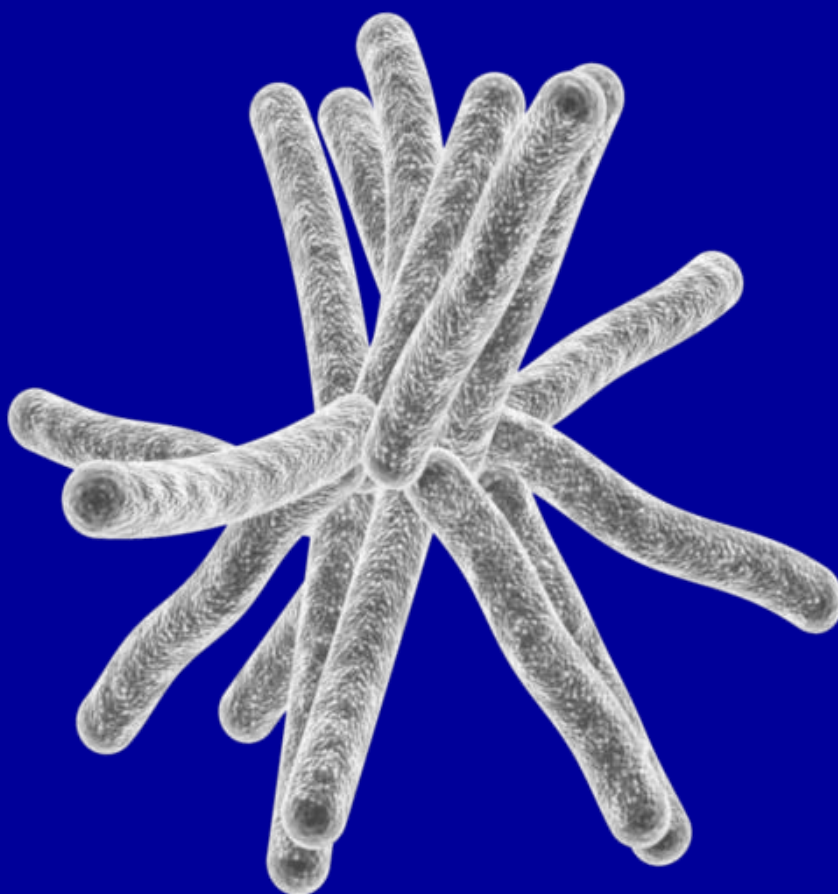
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