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The beautiful thing about learning is nobody can take it away from you—B. B. King

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THE CAUCASUS
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THE IMPORTANCE OF BIOMARKERS IN THE MODERN DIAGNOSIS OF TRAUMATIC BRAIN INJURIES

Zhanslu Sarkulova, Ainur Tokshilykova, Marat Sarkulov, Kamila Daniyarova, Botagoz Kalieva, Marat Zhankulov
West Kazakhstan Medical University named after Marat Ospanov, Email: slu2008@mail.ru, Kazakhstan

The relevance of the problem.
Currently, they manifest themselves in the structure of acute traumatic processing of the large brain, taking the first place in the world as a cause of death and involution along with cardiovascular diseases (Ng, Xi Yun, Alan Yu Wa Lee, 2019).
To date, the concept of brain damage connects the pathogenesis and clinic of cerebral lesions with the activation of stress neuron-specific proteins. The latter damage the integrity of the blood-brain barrier with inflammatory reactions. Against this background, cerebral ischemia progresses, oxygenation and metabolism are disrupted, with an increase in brain damage (Busch D.R., Balu R., Baker W.B. 2019). Any of these listed mechanisms of brain damage should be regarded as a potential factor in the expansion of the affected area of the central nervous system.
In modern medicine, there are no unified points of view on the diagnosis of brain damage. Recording markers of brain damage with neuromonitoring should be highly specific and sensitive and represent a new concept for assessing the severity of this pathology.

The purpose of our work was to study neurobiomarkers with integral scales for diagnosis in patients with traumatic brain injuries.

Materials and methods of research.
A prospective continuous cohort study was conducted in 42 patients with traumatic brain injuries (TBI) who were treated at an Emergency Hospital. In the group of examined -22 (52.4%) men and 20 (47.6%) women (p=0.8922). The average age of the sample was 40 years (95%CI: 25.00 - 58.00); age differences by disease groups (p<0.0001, p=0.1981). According to the outcome of the diseases (p=0.3904), and by age (p=0.4287) and gender, the patients were not comparable (p=0.8921). The studies were carried out at admission and in dynamics on the 1st, 3rd and 7th days of the patient's stay in the department. To diagnose the severity of injury, we conducted studies of serum markers of brain damage - S100ß and HCE, as well as their sensitivity, specificity and correlative relationships with the integral scale of neurological GCS, as independent predictors of the severity of the functional state.

The results of the study.
As the results of the study showed, peak values of NSE conjugation are observed in patients with traumatic brain injuries as early as the 1st loan amount, followed by a decrease of 11.51%. Similar changes occurred with the concentration of S100ß. However, a significant decrease of 72.45% was observed in dynamics by the 7th day of observation. Brain damage that causes high levels of S100ß, especially in patients with severe injuries, may be strongly associated with cerebral vasospasm and ischemia, indicated in 1.2 figures.
The correlation of the concentration of neuromarkers with the neurological scale showed their relationship with different outcomes. S100ß levels were negatively correlated with GCS values (r

= -0.47; p<0.0001), respectively. Notably, patients with lower GCS levels (<8) had significantly higher levels of S100ß. Significant connections were established between the S100ß and NSE markers. The levels of S100ß were statistically significantly and positively correlated with the values of NSE - (r=0.39*; p=0.0320).
An analysis of the sensitivity and specificity of the differences between the studied bioneuromarkers in the diagnosis of the severity of brain tissue damage in the studied patients showed that, compared with HCE, the S100ß protein demonstrates higher specificity to brain tissues and better meets the requirements for determining a serum marker for brain damage by type of TBI (Van Vliet E.A., Ndode-Ekane X.E., Lehto L.J. 2020). Its sensitivity is very high in terms of cellular damage to the brain. In our studies, we noted that in some patients, even with minor trauma, serum levels of S100ß were elevated (Jassam Y.N., Izzy S. 2017).
The levels of dependent transference (S100ß and NSE) and independent transference (GCS) can be used as multimodal drugs in diastolic patients with acute traumatic brain injury.
Keywords: biomarkers, diagnostics, traumatic brain injuries.

Declarations
The manuscript has not been submitted to any other journal or conference.

Study Limitations
There are no limitations that could affect the results of the study.

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The authors declare no competing interests.

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EFFECTS OF DIFFERENT METHODS OF TREATMENT ON IMMUNE PARAMETERS AND SKIN WOUND HEALING OUTCOME

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ABSTRACT

Skin wound healing is a complex process crucial for maintaining bodily integrity and function. However, factors such as chronic diseases, infections, advanced age, medications, and nutrient deficiencies can disrupt the normal wound healing process, leading to complications such as excessive scarring. Cytokines like IL-1 and IL-6 play essential roles in wound healing. This study investigates the effects of different treatments on IL-1 and IL-6 levels during the wound healing process.

Results showed that IL-1 levels were significantly increased on the 7th day of wound healing in the epicyn and dermatix ultra-treated group, followed by a gradual decrease to normal levels by the 21st day. Flosteron treatment also normalized IL-1 levels by the 28th day, albeit with a slight delay compared to epicyn. In contrast, IL-1 levels remained elevated in the control and contractubex-treated groups. Similarly, IL-6 levels remained stable on the 7th day but increased on the 14th day in the epicyn and dermatix ultra -treated group, returning to normal by the 28th day. Flosteron treatment normalized IL-6 levels only by the 28th day. Contractubex treatment showed no significant changes in IL-6 levels compared to the control. Overall, epicyn, dermatix ultra and flosteron treatments effectively modulated the inflammatory response, as evidenced by the normalization of IL-1 and IL-6 levels by the 28th day. In contrast, the control and contractubex-treated groups exhibited prolonged elevation of cytokine levels, suggesting impaired or delayed wound healing.

Conclusion: these findings underscore the importance of choosing appropriate therapeutic interventions in wound management. Epicyn and dermatix ultra show promise in promoting wound healing, while contractubex may have limited efficacy. Further research is needed to understand the mechanisms underlying these differential effects and to explore additional markers of wound healing and tissue repair. By implementing a holistic approach to wound management that addresses the multifaceted aspects of wound healing, healthcare providers can optimize outcomes and improve the quality of life for patients with skin wounds. This study contributes to our understanding of wound healing dynamics and highlights the potential of specific treatments in promoting optimal wound healing outcomes.

Keywords: Epicyn, dermatix ultra, flosteron, contractubex, IL-1, IL-6, skin wound healing.

Introduction

Skin wound healing is of paramount importance and is crucial for maintaining the body's integrity, function, and overall well-being [1,2].

Skin wounds and their associated healing problems are a significant area of research and clinical concern. Factors that can affect the normal wound healing process include: chronic diseases (diabetes, peripheral vascular disease, autoimmune disorders, and malnutrition), bacterial, fungal, or viral infections in the wound, conditions that compromise blood circulation, advanced age, certain medications (corticosteroids, immunosuppressants, and NSAIDs), can interfere with the inflammatory response and impair wound healing, inadequate intake of essential nutrients (especially vitamin C, vitamin A and minerals), presence of foreign bodies, debris, or necrotic tissue in the wound, physical or psychological stress that can disrupt the body's immune function and hormonal balance, and many others.

Disorders of normal process of tissue repair may produce chronic wounds and excessive scarring. While scar formation is a natural part of the healing process, abnormal wound healing can lead to excessive scarring, such as hypertrophic scars or keloids. These scars may cause functional impairment, aesthetic concerns, and psychological distress.

For these reasons, treatment of skin wounds and management of healing process aimed at promoting optimal healing, reducing the risk of complications, and improving patient outcomes involve a multifaceted approach such as: wound debridement, infection control, maintaining a moist environment, promoting angiogenesis and tissue regeneration. Should be mentioned that wound healing outcome to a great extent depends on the type, severity, and underlying causes of the wound as well.

Skin wounds and their healing process are complex phenomena involving various cells, cytokines, and biochemical pathways. Cytokines such as: interleukin-1 (IL-1), interleukin-6 (IL-6), and fibroblasts play essential role in the normal wound healing process.

IL-1 is a pro-inflammatory cytokine involved in the early stages of wound healing. It is secreted by various cells, including macrophages, neutrophils, and keratinocytes, in response to tissue injury. IL-1 promotes inflammation by stimulating the expression of adhesion molecules and chemokines, which recruit immune cells to the wound site. Additionally, IL-1 stimulates the proliferation and migration of keratinocytes, promoting re-epithelialization of the wound [3,4].

IL-6 is another pro-inflammatory cytokine that plays a crucial role in the early phase of wound healing. It is secreted by various cells, including macrophages, fibroblasts, and endothelial cells, in response to tissue injury. IL-6 promotes inflammation and stimulates the recruitment of immune cells to the wound site. Moreover, IL-6 induces the production of acute-phase proteins, such as C-reactive protein (CRP), which are involved in the systemic response to injury and infection [5,6].

Summarizing could be said that the immune system plays a multifaceted role in wound healing, coordinating the inflammatory response, clearing pathogens and debris, promoting tissue repair and regeneration, and regulating the balance between inflammation and tissue remodeling. Dysregulation of immune responses can lead to impaired wound healing or excessive scarring, highlighting the importance of immune modulation in wound care.

Depending on the severity and characteristics of the wound, various therapeutic modalities such as dressings, growth factors, and tissue-engineered constructs may be employed.

At present several methods of skin wound treatment have been suggested e.g. wound dressings to protect the wound, maintain a moist environment, absorb excess exudate, and promote healing. Gauze dressings are commonly used for minor wounds and as secondary dressings for larger wounds [7]. Hydrocolloid dressings form a gel when they come into contact with wound exudate, creating a moist environment conducive to healing. Foam dressings (absorbent) help manage

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moderate to heavy exudate while protecting the wound. Alginate dressings (made from seaweed) are highly absorbent and are used for wounds with heavy exudate. Transparent film dressings provide a barrier against bacteria while allowing visualization of the wound. Antibiotic ointments are used to prevent or treat wound infections. Antiseptic solutions are used to clean the wound and prevent infection. Steroid creams reduce inflammation and itching in certain types of wounds. Silver-containing dressings have antimicrobial properties and are used for infected wounds or wounds at risk of infection. In some cases, advanced wound care therapies may be necessary for non-healing or complex wounds. These may include: negative pressure wound therapy uses suction to promote wound healing and reduce the risk of infection. Hyperbaric oxygen therapy delivers high concentrations of oxygen to the wound site to promote healing. Bioengineered skin substitutes are used to replace lost or damaged skin and promote wound closure. In cases of traumatic wounds, severe burns, or wounds with underlying tissue damage, surgical intervention (wound debridement, skin grafting, or flap reconstruction) may be necessary to repair the wound and facilitate healing. Compression therapy is used for wounds such as venous ulcers or lymphedema to improve circulation and reduce swelling [8-11]. Patients with wounds may require dietary supplements (protein, vitamins, and minerals) to support tissue repair and regeneration. Pain Management is essential for patient comfort and compliance with treatment [12, 13]. Moisturizing creams or gels may be applied to dry wounds to prevent desiccation and facilitate healing, accelerate epithelialization, reduce pain, and minimize scarring.

Considering that skin wound healing outcome to a great extant depends on selection of effective methods of treatment, in the presented article we were aimed to study and compare effects of epicyn, dermatix ultra, flosteron and contractubex on immune parameters (IL-1, IL-6) and skin wound healing process to optimize treatment outcomes and improve the quality of life for patients with skin wounds.

Material and methods.

Experiments were carried out on male white lab. Rats with the body weight range 200-250 g. The animals were purchased from the vivarium of Aleksandre Natishvili Institute of Morphology, Tbilisi, Georgia (https://www.tsu.ge/en).

All animals were allowed to become acclimatized to laboratory conditions for one week before the experiment. During this period, the animals were kept under constant environmental conditions with a light-dark cycle of 12/12 at a temperature of 23±2°C. They were fed a standard laboratory chow and given free access to water.

For modeling of skin wounds the rats were anesthetized with nembutal (50 ml/kg). After shaving and cleaning with 70% alcohol, excisional, full-thickness skin wounds were aseptically made on the dorsal skin. After, a surgical suture of 5 cm was placed on the skin at 1 cm interval.

All animals were placed in the groups. Each group involved 10 rats.

The group I - intact healthy rats;
The group II - control, untreated rats;
The group III - rats treated with epicyn;
The group IV - rats treated with dermatix ultra;
The group V - rats treated with flosteron;
The group VI - rats treated with contractubex;

Contractubex, dermatix ultra and epicin creams were applied to the wound surface as a thin layer 2-3 times a day for 4 weeks in the corresponding group animals. Flosteron (0.2 ml) was injected subcutaneously in the wound area once a week during 4 weeks.
Pro-inflammatory cytokines (IL-1, IL-6) were studied by ELISA. Blood samples for immunological investigations were collected and studied by the 7th, 14th, 21st and 28th days of experiment.
Results were analyzed statistically. Statistical significance was evaluated by using ANOVA or Mann-Whitney's U test. $p<0.05$ was accepted as statistically significant.

Results and discussion.
Investigations showed that IL-1 on the 7th day of wound healing was increased significantly compared to the data of healthy group animals. In subsequent days the IL-1 gradual decrease was detected only in the epicyn- and dermatix ultra-treated group animals and by the 21st day of wound healing it was within the normal range.
IL-1 in flosteron-treated animals was normalized by 28th day of wound healing, while in control and contractubex-treated animals it was still increased.
Increase in IL-6 was detected later, on the 14th day of wound healing. By the 21st day of wound healing IL-6 gradual decrease was obvious in epicyn, dermatix ultra and flosteron-treated animals. In epicyn and dermatix ultra-treated animals it was even within the normal range. In flosteron-treated animals IL-6 concentration was normalized only on 28th day. There was no significant difference in data of control and contratubex-treated animals and by the 28th day of healing process IL-6 was still increased compared to normal value.
IL-1 concentration on the 7th day of wound healing was increased by 19% and 16% ($p<0.05$) only in epicyn and dermatix ultra-treated group animals and on the 14th day it was decreased by 15% and 16% ($p<0.05$) compared to control group data.
On the 21st day of wound healing IL-1 in epicyn and dermatix ultra-treated groups was decreased by 32% and 35% ($p<0.001$), in flosteron-treated group – by 11% ($p<0,05$) and in contractubex-treated animals it was not changed significantly compared to control.
By the 28th day of observation, IL-1 concentration was within the normal range in epicyn, dermatix ultra and flosteron-treated groups, while in contractubex-treated group, it was slightly decreased compared to control, but this decrease was not statistically significant.
On the 7th day of wound healing IL-6 concentration unlike IL-1 was not changed significantly in all study groups compared to control.
On the 14th and 21st days of experiment IL-6 was changed only in epicin and dermatixutra-treated groups. It was increased by 17% and 25% ($p<0,02$) on the 14th day, decreased by 12% and 15% ($p<0.05$) on the 21st day and returned to normal level by the 28th day of wound healing.
In flosteron group the IL-6 returned to normal level only by the 28th day of wound healing. In contractubex-treated group, it was not changed significantly compared to control.
The results of the investigation revealed distinct patterns of IL-1 and IL-6 concentrations during the wound healing process in animals treated with different agents.
In case of treatment with epicyn and dermatix ultra on the 7th day of wound healing there was a significant increase in IL-1 concentration, suggesting a pro-inflammatory response. However, by the 14th and 21st days, IL-1 levels decreased substantially, indicating a resolution of inflammation, possibly due to the efficacy of epicyn and dermatix ultra in modulating the inflammatory response. The return to normal levels by the 21st and 28th days suggests a potential

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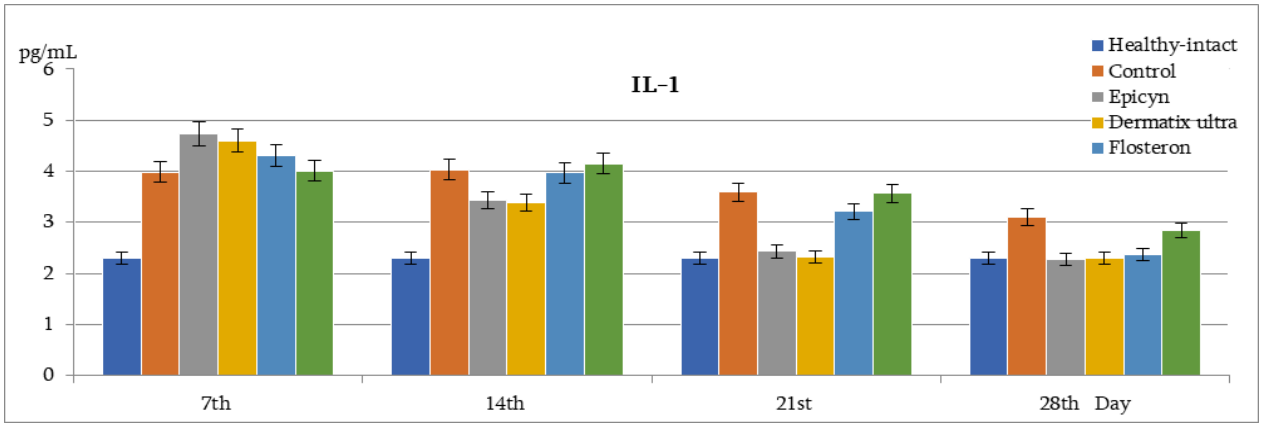
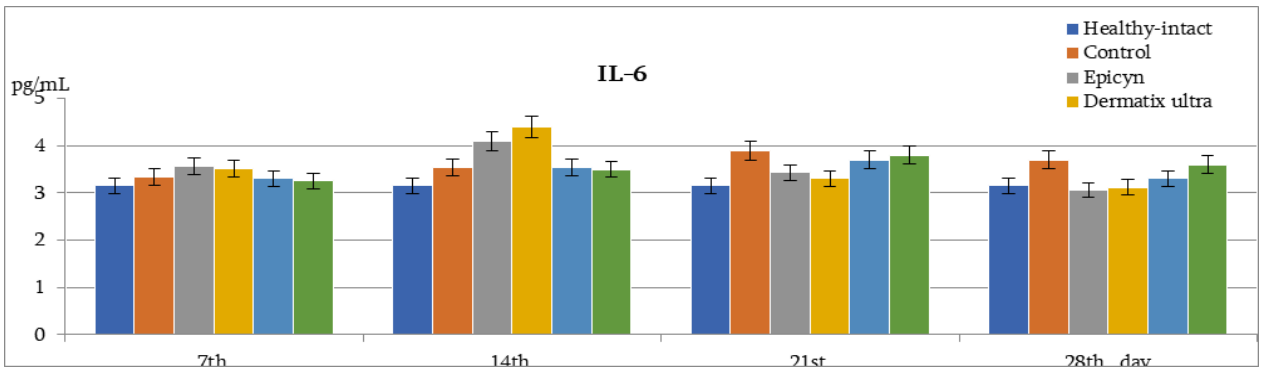
anti-inflammatory effect of treatment, successful resolution of inflammation and effective wound healing in these groups [14].

Graph. 1 IL-1 concentration in healthy, control and treated with epicyn, dermatix ultra, flosteron and contractubex group lab. rats.



Graph. 2 IL-6 concentration in healthy, control and treated with epicyn, dermatix ultra, flosteron and contractubex group lab. rats.



In case of treatment with flosteron IL-1 levls decreased by the 21st day, though not as significantly as in the epicyn and dermatix ultra-treated groups. Similar to epicyn and dermatix ultra, normalized level of IL-1 by the 28th day in flosteron-treated animals indicates that flosteron reveal moderate anti-inflammatory effect and also contributes to the resolution of inflammation, albeit with a slightly delayed effect compared to epicyn and dermatix ultra.

In case of treatment with contractubex, IL-1 level remained relatively stable throughout the observation period, with no significant changes compared to the control. This may indicate a lack of significant impact on the inflammatory response and prolonged inflammatory state by contractubex.

Regarding IL-6, treatment with epicyn increased its level on the 14th day, suggesting a secondary inflammatory response. However, by the 21st day, IL-6 levels decreased, indicating a resolution

of this secondary inflammation, aligning with the pattern observed for IL-1. The return to normal levels by the 28th day suggests successful wound healing.
In case of treatment with flosteron, IL-6 levels returned to normal only by the 28th day, indicating a delayed resolution of inflammation compared to the Epicyn and dermatix ultra groups.
At treatment with contractubex IL-6 levels remained stable throughout the observation period, similar to IL-1, suggesting a lack of significant impact on the inflammatory response.
Could be said that epicyn, dermatix ultra and flosteron treatments led to a gradual decrease and normalization of IL-6 levels by the 28th day, indicating resolution of secondary inflammation and successful wound healing [15]. In contrast, IL-6 levels remained elevated in both the control and contractubex-treated animals indicating ongoing inflammation and potentially impaired wound healing processes.

Conclusion

The results suggest that epicyn and dermatix ultra and flosteron treatments are effective in modulating the inflammatory response during wound healing, as evidenced by the normalization of IL-1 and IL-6 levels by the 28th day. This indicates their potential as therapeutic agents in promoting wound healing.
In contrast, the control group and contrcatubex-treated animals showed prolonged elevation of IL-1 and IL-6 levels, suggesting inadequate resolution of inflammation and potentially impaired, or delayed wound healing.
Overall, the findings suggest that epicyn and dermatix ultra may be more effective in modulating both the primary and secondary inflammatory responses during wound healing compared to flosteron and contractubex.
The differential effects of the treatments on inflammatory cytokine levels highlight the importance of choosing appropriate therapeutic interventions in wound management. Further studies are needed to elucidate the mechanisms underlying the observed differential effects and to assess the overall efficacy and safety of these treatments in wound healing.
Additionally, investigating other markers of wound healing and tissue repair would provide a more comprehensive understanding of the effects of these treatments.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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The author would like to express gratitude to the care support workers and elderly individuals who participated in this study, sharing their invaluable insights and experiences. Their cooperation and openness have significantly contributed to the depth and richness of the research findings.

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Competing Interests
The authors declare no competing interests.

Ethical Approval
Authors of this research received ethical approval by Tbilisi State Medical University, and Department of Pharmacology, Department of Medical Pharmacology, Department of Pathophysiology, Scientific-Research-Skills Centre.
Informed consent was obtained for all participants.
All participants were given an information leaflet to read prior to participation, and verbal consent for study participation was obtained.
All participants provided their own consent to participate.
By implementing a holistic approach to wound management that addresses the multifaceted aspects of wound healing, healthcare providers can optimize outcomes and improve the quality of life for patients with skin wounds.
Methods for all surveys were carried out in accordance with relevant guidelines and regulations in the Declaration of Helsinki.

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THE MANIFESTATION OF KEY ISSUE ASPECTS OF SOME FEATURES OF GENETIC VIEWS OF CARBOHYDRATE METABOLISM DISORDER IN GLYCOGEN STORAGE DISEASE AND TREATMENT STRATEGY SUMMONS

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ABSTRACT

Aim of the research was to study key issue aspects of some features of genetic views of carbohydrate metabolism disorder in glycogen storage disease and treatment strategy summons. Glycogen storage diseases (GSDs) are a group of rare genetic disorders characterized by impaired glycogen metabolism, leading to abnormal accumulation of glycogen in various tissues. This research article aims to provide a comprehensive overview of the biochemistry underlying GSDs, exploring the molecular mechanisms, clinical manifestations and current therapeutic strategies. Through detailed investigation of the key biochemical pathways and enzymes involved in glycogen metabolism, we aim to improve our understanding of GSDs, paving the way for improved diagnosis and targeted therapy. Glycogen metabolism plays an important role in exercise and blood sugar regulation. In a fed state, insulin stimulates glycogen storage in the muscles and liver, while simultaneously stimulating glycogen synthesis and inhibiting its

breakdown. Conversely, in the fasting state or during exercise, glucagon and catecholamines promote glycogen breakdown while inhibiting its synthesis. The importance of glycogen is further emphasized by the fact that there are several congenital disorders caused by dysfunction of the enzymes that control the synthesis, regulation, and breakdown of glycogen. So, a biochemical perspective on Glycogen storage disorders, implications for precision medicine, the article provides an in-depth examination of the biochemical complexities underlying glycogen storage disorders. Glycogen storage disease type I is an inherited disorder caused by the buildup of a complex sugar called glycogen in the body's cells. The accumulation of glycogen in certain organs and tissues, including the liver, kidneys and small intestine, impairs their ability to function normally. Signs and symptoms of this condition usually appear around 3 to 4 months of age, when babies begin sleeping through the night and don't eat as often as newborns. Sick infants may have low blood sugar (low blood sugar), which can lead to seizures. They may also have a buildup of lactic acid in the body (lactic acidosis), high levels of a waste product called uric acid in the blood (hyperuricemia), and excess fats in the blood (hyperlipidemia). As children with GSDI grow, they develop thin arms and legs and a short stature. An enlarged liver can give the appearance of a protruding belly. The kidneys may also be enlarged. Patients may also experience diarrhea and cholesterol deposits on the skin (xanthomas). People with GSDI may experience delayed puberty. From young to middle age, affected people may suffer from thinning of the bones (osteoporosis), a form of arthritis caused by uric acid crystals in the joints (gout), kidney disease and high blood pressure in the blood vessels that supply the blood. lungs (pulmonary hypertension). Women with this condition may also have abnormal development of the ovaries (polycystic ovaries). In affected adolescents and adults, tumors called adenomas may form in the liver. Adenomas are usually noncancerous (benign), but these tumors can sometimes become cancerous (malignant). Researchers have described two types of GSDI that differ in their signs and symptoms and genetic cause. These types are known as glycogen storage disease type Ia (GSDIa) and glycogen storage disease type Ib (GSDIb). Two other forms of GSDI have been described, initially called type Ic and type Id. However, these types are now known to be variants of GSDIb; for this reason, GSDIb is sometimes referred to as GSD type I non-a. Many people with GSDIb have a deficiency in white blood cells (neutropenia), which can make them prone to recurrent bacterial infections. Neutropenia usually appears around the age of one year. Many patients also suffer from inflammation of the intestinal wall (inflammatory bowel disease).

Keywords: Features, genetic, glycogen, storage, disease, treatment, strategy, challenges.

Introduction

Glycogen synthesis represents a key pathway for the elimination of excess glucose, while its breakdown is critical for providing energy during exercise and on demand. The importance of glycogen metabolism is also emphasized by human genetic disorders caused by mutations in the enzymes involved. In this review, we provide an overview of glycogen metabolism and some clinical aspects of classical glycogen storage diseases. Disorders of glycogen metabolism usually result in some impairment of liver, muscle, heart, kidney, and/or brain function. In addition, the range of symptoms observed is very wide and depends on the enzyme affected. The structural maintenance aspect of glycogen metabolism, which appears to be receiving recent attention. For example, in Lafora's progressive myoclonic epilepsy, patients experience accumulation of inclusion bodies in many tissues containing glycogen with increased phosphorylation, longer chains, and irregular branch points. This abnormal structure is thought to make glycogen insoluble

and resistant to degradation. Therefore, its accumulation becomes toxic to neurons, leading to cell death. Although the genes responsible have already been identified, research over the past two decades is only beginning to shed light on their molecular functions [1-3].

Glycogen storage disease type I is an inherited disorder caused by the buildup of a complex sugar called glycogen in the body's cells. The accumulation of glycogen in certain organs and tissues, including the liver, kidneys and small intestine, impairs their ability to function normally. Signs and symptoms of this condition usually appear around 3 to 4 months of age, when babies begin sleeping through the night and don't eat as often as newborns. Sick infants may have low blood sugar (low blood sugar), which can lead to seizures. They may also have a buildup of lactic acid in the body (lactic acidosis), high levels of a waste product called uric acid in the blood (hyperuricemia), and excess fats in the blood (hyperlipidemia). As children with GSDI grow, they develop thin arms and legs and a short stature. An enlarged liver can give the appearance of a protruding belly. The kidneys may also be enlarged [4-6].

Glycogen metabolism plays an important role in exercise and blood sugar regulation. In a fed state, insulin stimulates glycogen storage in the muscles and liver, while simultaneously stimulating glycogen synthesis and inhibiting its breakdown. Conversely, in the fasting state or during exercise, glucagon and catecholamines promote glycogen breakdown while inhibiting its synthesis. The importance of glycogen is further emphasized by the fact that there are several congenital disorders caused by dysfunction of the enzymes that control the synthesis, regulation, and breakdown of glycogen. So, a biochemical perspective on Glycogen storage disorders, implications for precision medicine, the article provides an in-depth examination of the biochemical complexities underlying glycogen storage disorders. By studying the molecular basis, pathways affected, clinical manifestations, and therapeutic strategies, we think to contribute to the evolving Glycogen storage disorders research approach by offering better diagnosis and interventions and pharmacotherapy management. Glycogen storage disease is passed from parents to children (hereditarily). This happens because both parents have an abnormal gene (genetic mutation) that affects a certain way in which glycogen is stored or used. Most cases of GSD occur because both parents pass the same abnormal gene to their children. In most cases, the parents do not show any symptoms of the disease [7-9].

Glycogen storage disease (GSD, also glycogenosis and dextrinosis) is a metabolic disorder caused by a deficiency of an enzyme or transport protein that affects glycogen synthesis, glycogen breakdown, or glucose breakdown, usually in muscle and/or liver cells. GSD has two classes of causes: genetic and environmental. Genetic glycogen storage disease (GSD) is caused by any inborn error of carbohydrate metabolism (genetically defective enzymes or transport proteins) involved in these processes. In livestock, environmental GSD is caused by intoxication with the alkaloid castanospermine. However, not every congenital disorder of carbohydrate metabolism is assigned a GSD number, even if it is known to affect the muscles or liver. For example, phosphoglycerate kinase deficiency (PGK1 gene) has a myopathic form. Additionally, Fanconi-Bickel syndrome (SLC2A2 gene) and Danon disease (LAMP2 gene) have been declassified as GSD due to the fact that they represent defects in transport proteins rather than enzymes; however, GSD-1 subtypes b, c, and d are caused by defects in transport proteins (SLC37A4, SLC17A3 genes) but are still considered GSDs. Phosphoglucomutase deficiency (PGM1 gene) has been declassified as GSD because it also affects N-glycan formation; however, since it affects both glycogenolysis and glycosylation, it has been proposed to rename it GSD-XIV [10-11].

Patients diagnosed with GSD type 0 may exhibit normal or poor growth with delayed bone age during infancy. Catch-up growth has been described after the introduction of adequate dietary treatment including raw corn starch [12-14]

Glycogen storage disease (GSD) is a rare condition that changes the way the body uses and stores glycogen, a form of sugar or glucose. Glycogen is a main source of energy for the body. Glycogen is stored in the liver. When the body needs more energy, certain proteins called enzymes break down glycogen into glucose. They send the glucose out into the body. When someone has Glycogen storage disease, they are missing one of the enzymes that breaks down glycogen. When an enzyme is missing, glycogen can build up in the liver. Or glycogen may not form properly. This can cause problems in the liver or muscles, or other parts of the body. Glycogen storage disease (GSD) is passed down from parents to children (is hereditary). It is most often seen in babies or young children. But some forms of GSD may appear in adults [15-17].

Growth failure is not a feature of GDS type IV and may or may not be present depending on the causative mutation and clinical subtype [39,56,134]. Patients may also experience diarrhea and cholesterol deposits on the skin (xanthomas). People with GSDI may experience delayed puberty. From young to middle age, affected people may suffer from thinning of the bones (osteoporosis), a form of arthritis caused by uric acid crystals in the joints (gout), kidney disease and high blood pressure in the blood vessels that supply the blood. lungs (pulmonary hypertension). Women with this condition may also have abnormal development of the ovaries (polycystic ovaries). In affected adolescents and adults, tumors called adenomas may form in the liver. Adenomas are usually noncancerous (benign), but these tumors can sometimes become cancerous (malignant). Researchers have described two types of GSDI that differ in their signs and symptoms and genetic cause. These types are known as glycogen storage disease type Ia (GSDIa) and glycogen storage disease type Ib (GSDIb). Two other forms of GSDI have been described, initially called type Ic and type Id. However, these types are now known to be variants of GSDIb; for this reason, GSDIb is sometimes referred to as GSD type I non-a. Many people with GSDIb have a deficiency in white blood cells (neutropenia), which can make them prone to recurrent bacterial infections. Neutropenia usually appears around the age of one year. Many patients also suffer from inflammation of the intestinal wall (inflammatory bowel disease) [19-21].

In contrast, short stature is a common feature between GSD types VI and IX, with variability in the degree of improvement among treated patients who reach adulthood. Most individuals with PhK deficiency achieve standard adult growth parameters, but exhibit an idiosyncratic growth pattern with initial growth retardation during the first 2 to 3 years, followed by gradual normalization of linear growth. Abnormal bone mineralization with and without osteopenia has been observed in gastrointestinal diseases types VI and IX. Nutritional deficiency and chronic ketosis are suspected to be contributing factors. Rickets has been reported in GSD type IXc due to renal tubulopathy with inadequate parathyroid response [22-24].

Heart failure after orthotropic liver transplantation has been described in patients with advanced hepatic GI type IV without a history of cardiac involvement. This may be due to disease progression despite liver transplantation. Indeed, in patients who died after liver transplantation, amylopectin deposits were observed at autopsy in various organs and tissues (myocardial fibers, skeletal muscle fibers, cells of the central and peripheral nervous system, macrophages). The good clinical response to liver transplantation may be explained by the mechanism of microchimerism, in which donor cells transfer the deficient enzyme to host cells, thereby reducing amylopectin deposits [25-27].

Mild and severe myopathies and dilated cardiomyopathies have also been described in neuromuscular forms of the gastrointestinal tract type IV. It is noteworthy that in one case, cardiomyopathy was the only symptom of branched-chain enzyme deficiency. Muscle cramps or post-exercise fatigue have been reported in a minority of cases of GSD type VI, usually associated with undertreatment and protein deficiency. Muscle weakness may or may not be observed with PhK deficiency regardless of genotype [28-30].

In a recent case series, asymptomatic left ventricular and septal hypertrophy was reported in a patient with GBD type VI, and interventricular septal hypertrophy was found in a patient with GBD type IXb. The authors recommended that echocardiography be performed every 1–2 years in patients diagnosed with gastrointestinal tract types VI and IX over the age of 5 years. A systematic review of the literature did not identify any other individuals with HDD type VI or IX and heart problems. Muscle involvement can be observed in the setting of dielectrolythemia in type XI LCD, manifested by exercise intolerance and rhabdomyolysis [31-33]

Developmental delay has been described in some children with GSD type 0, while undiagnosed GSD type 0 has been associated with a higher incidence of neurodevelopmental disorders caused by severe recurrent hypoglycemia. In these patients, hypoglycemia is often asymptomatic, as loss of neuroglycopenic characteristics is noticeable with recurrent hypoglycemia. The phenomenon known as hypoglycemia-associated autonomic failure is caused by defective glucose counter-regulation with impaired sympathoadrenal and neuronal responses, resulting in decreased neurogenic and cerebral symptoms [34-36].

Purpose

Aim of the research was to study key issue aspects of some features of genetic views of carbohydrate metabolism disorder in glycogen storage disease and treatment strategy summons.

Materials And Methods

The main question of this article was to research and analyses key issue aspects of some features of genetic views of carbohydrate metabolism disorder in glycogen storage disease and treatment strategy summons. We have searched and analyzed PubMed, Web of Sciences, Clinical key, Tomson Routers and Google Scholar mostly, using search terms bases, including the words to research and study key issue aspects of some features of genetic views of carbohydrate metabolism disorder in glycogen storage disease and treatment strategy summons. We brought together all published data to comprehensively examine the effects in a systematic review and overview, to define key issue aspects of some features of genetic views of carbohydrate metabolism disorder in glycogen storage disease and treatment strategy summons.

Results and discussion

Glycogen storage disease (GSD) is a rare autosomal recessive disorder characterized by hypoglycemia, hepatosplenomegaly, seizures, and growth retardation in young children. Neutropenia and/or neutrophil dysfunction occurs in GSD1b but not in other types. GSD1b results from a deficiency of the enzyme glucose-6-phosphate translocase, and the genetic defect corresponds to chromosome 11q23. Patients with GSD1b are susceptible to recurrent bacterial infections, usually affecting the peri rectum, ears, skin, and urinary tract, although life-threatening infections such as sepsis, pneumonia, and meningitis are less common. Although the exact mechanism of neutropenia in patients with GSD1b is unknown, treatment with recombinant

human granulocyte colony-stimulating factor (G-CSF) reduced the incidence of infections and improved quality of life in these patients. Defects in neutrophil chemotaxis and intracellular bacterial killing have been described and appear to be corrected by G-CSF. To date, no cases of myelodysplasia or acute myeloid leukemia have been observed in GSD1b patients treated with G-CSF. An important complication of cytokine therapy is the development of hypersplenism, requiring either a reduction in the dose of G-CSF or splenectomy [37].

Glycogen is a branched polymer whose monomeric units are glucose. After a meal, plasma glucose levels increase and stimulate the deposition of excess glucose into cytoplasmic glycogen. The liver contains the highest percentage of glycogen by mass (around 10%), while muscle can store around 2% by mass. However, because total muscle mass is greater than liver mass, the total glycogen mass in muscle is approximately twice that in the liver. If necessary, the glycogen polymer can be broken down into glucose monomers and used to produce energy. Many enzymes and transporters of these processes play key roles in the etiology of GSD. An increasing number of GSDs are being identified, but most are very rare. Traditionally, GSDs were named after the physician who first identified the disease; However, each has a specific enzyme and gene that will be used to refer to these disorders in this article, although different diseases have their own classifications.

Glycogen storage diseases (GSDs) are a group of rare single-gene disorders characterized by a general defect in the synthesis or degradation of glycogen. This textbook describes the multiorgan clinical features of hepatic and muscle BPH, as well as their epidemiology, biochemistry and pathological mechanisms, diagnosis, treatment, quality of life, and future research directions. Some GSDs have guidelines for diagnosis and treatment. Diagnostic considerations include phenotypic characterization, biomarkers, imaging, genetic testing, enzyme activity testing, and histology. Treatment includes monitoring the development of characteristic effects of the disease, avoiding fasting for certain liver diseases, a diet prescribed by a doctor, appropriate exercise programs and emergency letters. Specific therapeutic interventions are available for certain diseases, such as enzyme replacement therapy to correct enzyme deficiency in Pompe disease and SGLT2 inhibitors for neutropenia and neutrophil dysfunction in GSD Ib. Advances in diagnostics, management and definitive treatment influence the natural history and therefore morbidity and mortality.

Diseases that disrupt neuromuscular junctions can cause abnormal muscle fatigue, such as myasthenia gravis, an autoimmune disease. Lambert-Eaton myasthenic syndrome (autoimmune) and congenital myasthenic syndrome (genetic) are similar. Diseases can alter glycogen metabolism secondary to the primary disease. Thyroid dysfunction – hypo and hyperthyroidism – may present as a myopathy with symptoms of muscle fatigue, cramping, exercise-induced muscle soreness, and may include proximal muscle weakness or hypertrophy (especially at the level of the calves). Hypothyroidism increases glycogen synthesis and suppresses glycogenolysis and glycolysis; Conversely, hyperthyroidism does the opposite: it increases glycogenolysis and glycolysis while suppressing glycogen synthesis. Long-term hypo- and hyperthyroid myopathy results in atrophy of type II (fast-twitch/glycolytic) muscle fibers and a predominance of type I (slow-twitch/oxidative) muscle fibers. Muscle biopsy shows abnormal muscle glycogen levels: high accumulation in hypothyroidism and low accumulation in hyperthyroidism. Hypothyroid myopathy includes Kocher-Debreu-Semélan syndrome (onset in childhood), Hoffman syndrome (onset in adulthood), myasthenic syndrome and the atrophic form. In patients with elevated growth hormone levels, muscle biopsies include, among other things, excessive glycogen

deposition. Interestingly, compared to hypothyroid myopathy, McArdle's disease (GSD-V), which is by far the most frequently diagnosed and therefore most studied muscular GSD, is the second most common associated endocrine disorder (mainly hypothyroidism). Late-onset Pompe disease (GSD-II) also presents with calf enlargement and hypothyroidism as comorbidities. Poor diet and malabsorption diseases (such as celiac disease) can lead to deficiencies of essential vitamins needed for glycogen metabolism in muscle cells. Malnutrition usually presents with systemic symptoms, but in rare cases it may be limited to myopathy.

Vitamin D deficiency myopathy (also known as osteomalan myopathy due to the interaction of vitamin D and calcium) results in muscle weakness, primarily of the proximal muscles; muscle biopsy shows abnormal glycogen accumulation, atrophy of type II (fast-twitch/glycolytic) muscle fibers, and decreased calcium absorption into the sarcoplasmic reticulum (necessary for muscle contraction). Although myopathy caused by vitamin D deficiency usually involves muscle atrophy, hypertrophy of the gastrocnemius muscles has rarely been reported. Exercise-induced electrically silent muscle spasms and stiffness (transient muscle contractures or "pseudomyotonia") are seen not only in GSD types V, VII, IXd, Brody, a pulsing muscle. mess. type 1 and 2 diseases and CAV3-related hyperCemia (increased serum creatine phosphokinase levels). Unlike other myopathies, in Brody's disease, muscle spasms are painless. Similar to types II, III, and V GSD, the pseudoathletic type of muscle hypertrophy is also seen in some patients with Brody disease and pulsatile muscle disease. Erythrocyte lactate transporter defect (formerly lactate transporter defect-induced myopathy) also includes exercise-induced, electrically silent painful muscle spasms and transient contractures; as well as exercise-induced muscle fatigue. However, the EMG and muscle biopsy are normal because the defect is not in the muscle, but in the red blood cells, which are supposed to eliminate lactate accumulation in exercised muscles.

Patients with GSD type 0 will experience hyperglycemia in the first two hours, then hypoglycemia may occur with prolonged OGTT, likely due to hyperglycemia-induced hyperinsulinemia. In the past, enzymatic activity was performed in cultured peripheral blood cells and skin fibroblasts. A decrease in branching enzyme activity in leukocytes, erythrocytes and fibroblasts confirmed the diagnosis of type IV cholelithiasis, but normal leukocyte activity did not allow excluding neuromuscular forms. In GDM type VI, decreased phosphorylase activity can be found in red blood cells and white blood cells. Deficiency of phosphorylase kinase activity can be demonstrated in leukocytes, erythrocytes and fibroblasts, except in forms associated with certain missense mutations of PHKA2 and PHKB. If enzyme activity in peripheral blood cells was normal, a liver biopsy was evaluated for hepatocyte enzyme analysis. More recently, molecular analysis has become the method of choice to confirm the diagnosis of each type of cholelithiasis. However, these forms may have a similar clinical and biochemical picture. Thus, performing a single gene analysis would be time-consuming and expensive. Over the past decade, next-generation sequencing technology (e.g., gene panel or clinical exome) has found widespread use in the diagnosis of inborn errors of metabolism due to the genetic heterogeneity of these conditions, allowing large-scale molecular characterization of patients. leave on time. and at a reasonable price. However, noncoding and structural variants cannot be identified using these methods, gene coverage may be variable, deletions/duplications may be missed, and identification of variants of uncertain significance poses a diagnostic challenge. In these cases, histological and enzymatic examination of a liver biopsy sample may be required to confirm the diagnosis.

Glycogen synthesis and degradation are highly regulated, multistep processes involving different sets of enzymatic reactions. Glycogen synthesis is generally thought to require an oligosaccharide

primer, which is first formed by self-glucosylation of the protein glycogenin. This process requires the nucleotide sugar, uridine diphosphate glucose (UDP-glucose), as a donor substrate. Up to seven units of glucose can be added to glycogenin, which is considered essential because the key enzyme that synthesizes glycogen, glycogen synthase (GS), can only extend the existing glucose chain.

During glycolysis, G6P is ultimately converted to pyruvate, which acts as a key metabolic intermediate for other pathways. For example, the conversion of pyruvate to acetyl-CoA creates an important substrate for the tricarboxylic acid (TCA) cycle and fatty acid synthesis. Under certain conditions, muscles can convert pyruvate to lactate (during anaerobic glycolysis) or alanine (during muscle breakdown), which are transported in the bloodstream to the liver, where they are then converted back to pyruvate (Cori cycle and alanine cycle). In the liver, pyruvate can also be converted back to glucose through gluconeogenesis. This pathway is similar to reverse glycolysis but requires the use of unique enzymes to bypass certain endergonic reactions. For example, in the liver and kidneys, the unique presence of the enzyme glucose-6-phosphatase (G6Pase) converts G6P to glucose, allowing it to be released into the bloodstream to support other tissues. This step (step 3 of gluconeogenesis) is critical because the conversion of glucose to G6P by the hexokinase enzyme in the reverse direction is energetically unfavorable.

Glycogen storage disease type I is an inherited disorder caused by the buildup of a complex sugar called glycogen in the body's cells. The accumulation of glycogen in certain organs and tissues, including the liver, kidneys and small intestine, impairs their ability to function normally. Signs and symptoms of this condition usually appear around 3 to 4 months of age, when babies begin sleeping through the night and don't eat as often as newborns. Sick infants may have low blood sugar (low blood sugar), which can lead to seizures. They may also have a buildup of lactic acid in the body (lactic acidosis), high levels of a waste product called uric acid in the blood (hyperuricemia), and excess fats in the blood (hyperlipidemia). As children with GSDI grow, they develop thin arms and legs and a short stature. An enlarged liver can give the appearance of a protruding belly. The kidneys may also be enlarged. Patients may also experience diarrhea and cholesterol deposits on the skin (xanthomas). People with GSDI may experience delayed puberty. From young to middle age, affected people may suffer from thinning of the bones (osteoporosis), a form of arthritis caused by uric acid crystals in the joints (gout), kidney disease and high blood pressure in the blood vessels that supply the blood. lungs (pulmonary hypertension). Women with this condition may also have abnormal development of the ovaries (polycystic ovaries). In affected adolescents and adults, tumors called adenomas may form in the liver. Adenomas are usually noncancerous (benign), but these tumors can sometimes become cancerous (malignant). Researchers have described two types of GSDI that differ in their signs and symptoms and genetic cause. These types are known as glycogen storage disease type Ia (GSDIa) and glycogen storage disease type Ib (GSDIb). Two other forms of GSDI have been described, initially called type Ic and type Id. However, these types are now known to be variants of GSDIb; for this reason, GSDIb is sometimes referred to as GSD type I non-a. Many people with GSDIb have a deficiency in white blood cells (neutropenia), which can make them prone to recurrent bacterial infections. Neutropenia usually appears around the age of one year. Many patients also suffer from inflammation of the intestinal wall (inflammatory bowel disease). People with GSDIb may suffer from oral problems, including tooth decay, gum disease (gingivitis), chronic gum disease (periodontal disease), abnormal tooth development, and open mouth sores. Neutropenia and oral problems are specific to people with GSDIb and are not usually seen in people with GSDIa.

Glycogen storage diseases (GSDs) are inherited congenital disorders of carbohydrate metabolism. Disorders of carbohydrate metabolism leading to abnormal accumulation of glycogen are classified as GSD. Their numbering is classified in order of recognition and identification of the enzymatic defect causing the disease. Clinical onset may vary from neonatal period to adulthood. Depending on the specific type, GSD may result from an inability to convert glycogen into energy and/or toxic glycogen accumulation; however, they all result in impaired glycogen utilization or storage.

In humans, glycogen is the major storage form of glucose and the primary means of non-oxidative removal of glucose in muscle and liver tissues, although significant amounts are also found in other locations, such as the brain and kidneys. When needed, glycogen is quickly broken down to form glucose. In muscles, this provides an immediate and important source of energy for exercise during the first 30 minutes. In the liver, the breakdown of glycogen during fasting promotes the production of glucose in the liver, which is critical for maintaining blood sugar levels and meeting the needs of other tissues. Although glycogen is mobilized during fasting in both the liver and muscle, the latter tissue lacks key metabolic enzymes that allow the transport of glucose into the bloodstream.

The second pathway of glycogen degradation requires the participation of the enzyme α-glucosidase (GAA). Initially assembled in the endoplasmic reticulum (ER), GAAs are transported to lysosomes via the Golgi apparatus to degrade lysosomal glycogen in an autophagy-dependent pathway, also known as glyphagy. Although studies in Drosophila suggest that glyphagy and glycogenolysis may compensate for each other, both pathways appear to be necessary for maximal glycogen breakdown.

The importance of the presence of two different pathways for glycogen breakdown is not entirely clear. Most studies have focused on GP regulation, particularly in the context of hormonal regulation (eg, insulin, glucagon, epinephrine) in response to dietary conditions and exercise. In contrast, much less is known about glicophagy, although the dominant theory suggests that it plays an important role in neonatal survival. At birth, animals were observed to have numerous glycogens containing autophagosomes, which were rapidly mobilized within the first hours. Thus, glyphagy can provide a direct source of energy for the functioning of key tissues of the newborn, such as the muscles of the heart and diaphragm.

In addition to the above processes, glycogen is a branched polysaccharide and requires the branching enzyme GBE1 to generate regularly spaced branch points (every 10–20 residues) via α (1→6) glycosidic linkages. An obvious benefit of glycogen branching is the creation of multiple sites for faster glycogenolysis. However, glycogen branching is also important for increasing the solubility and decreasing the osmotic impact of the molecule.

An additional enzyme that must be administered is glycogen debranching enzyme (GDE). Although GP is a key enzyme in glycogenolysis, it is sterically hindered when it reaches a branch point four glucose residues away. At this stage, branching occurs due to two catalytic activities of GDE. First, one of the branches passes to another chain, but at the branching site a single glucose unit remains. It is then removed to form one free glucose fragment. In contrast to GS and GP activities, little is known about the regulation of branching/disconnecting activities.

It is well known that glycogen metabolism plays an important role in exercise and blood sugar regulation. In a fed state, insulin stimulates glycogen storage in the muscles and liver, while simultaneously stimulating glycogen synthesis and inhibiting its breakdown. Conversely, in the fasting state or during exercise, glucagon and catecholamines promote glycogen breakdown while

inhibiting its synthesis. The importance of glycogen is further emphasized by the fact that there are several congenital disorders caused by dysfunction of the enzymes that control the synthesis, regulation, and breakdown of glycogen. This section will examine some aspects of these disorders, which are collectively called glycogen storage diseases (GSDs). In general, the incidence of cholelithiasis is rare, and all are inherited in an autosomal recessive manner, with the exception of cholelithiasis type IX and Danon disease (an X-linked recessive type). Although abnormal glycogen accumulation is a hallmark, there is a wide spectrum of phenotypes associated with these disorders, with age of onset ranging from fetal development to adulthood.

The etiology of GSD is best understood by following the metabolic events leading to glycogen synthesis (glycogenesis) and degradation (glycogenolysis). Excess dietary glucose is stored in glycogen, and glycogen synthesis is carried out in part by glycogen synthase (GS). There are two different forms of glycogen synthase: one in the liver, encoded by the GYS2 gene, and one in skeletal muscle, encoded by the GYS1 gene. Both forms of GS act by linking (alpha-1,4-linked) the glucose monomer to the growing glycogen polymer. Glycogen has two different types of bonds: alpha-1,4 bonds and alpha-1,6 bonds. About 95% of the bonds in glycogen are alpha-1,4 bonds. Absence or dysfunction of hepatic glycogen synthase due to mutations in the GYS2 gene prevents glycogen synthesis in the liver. This is the cause of GSD type 0a. Likewise, absence or dysfunction of muscle glycogen synthase due to mutations in the GYS1 gene will interfere with muscle glycogen synthesis, which is the cause of GSD type 0b.

Although glycogen synthase can catalyze alpha-1,4-glucose bonds in glycogen, another enzyme, glycogen branching enzyme (GBE1), is required to form alpha-1,6 branched bonds. Mutations in the glycogen branching enzyme can result in the formation of glycogen with an abnormal structure. This is the cause of HBD type IV. Abnormal glycogen structures are called polyglucosan bodies. In the type IV gastrointestinal tract, polyglucosan bodies accumulate in liver and muscle cells. Polyglucosan bodies are not efficiently glycogenolyzed, which can cause weakness and myopathy in muscle tissues. In the liver, the accumulation of polyglucosan bodies causes hepatomegaly.

Although GSD 0a and GSD 0b arise from insufficient glycogen storage, most GSDs are unable to remove glucose from glycogen (glycogenolysis), resulting in excess glycogen storage in tissues. The first step in glycogenolysis is the release of glucose-1-phosphate (G-1-P) from glycogen by the action of glycogen phosphorylase. GSD type V is caused by mutations in the muscle-specific glycogen phosphorylase (PYGM) gene. Mutations in the liver-specific glycogen phosphorylase (PYGL) gene cause GSD type VI. Glucose-1-phosphate, released by glycogen phosphorylase, is then converted to glucose-6-phosphate (G-6-P) by phosphoglucomutase. Glucose-6-phosphate present in the liver is in turn converted to glucose by glucose-6-phosphatase, encoded by the G6PC gene. The resulting glucose is released into the blood as an energy source for other tissues/organs.

It should be noted that skeletal muscle lacks glucose-6-phosphatase and therefore does not release glucose into the blood. GHD type I results from genetic disorders of glucose-6-phosphatase metabolism. GSD type Ia (also called von Gierke disease) is caused by mutations in the G6PC gene. Glucose-6-phosphate is synthesized in the cytoplasm of hepatocytes and must be transported into the lumen of the endoplasmic reticulum (ER), where it is requested by glucose-6-phosphatase to produce glucose, which is then transported into the cytoplasm and then via the hepatic transporter GLUT2 into the blood.

Glucose-6-phosphate translocase 1 (G6PT1) is a transporter protein that mediates the G-6-P channel between the cytoplasm and the ER. The G6PT protein consists of three subunits called G6PT1, G6PT2 and G6PT3. Mutations in the SLC37A4 gene, which encodes the G6PT1 protein, are responsible for GSD type Ib.Fanconi-Bickel disease is a rare disease caused by GLUT2 deficiency due to a mutation in the SLC2A2 gene. GLUT2 deficiency results in impaired glucose export, increased intracellular glucose levels, and decreased glycogen breakdown. This leads to increased glycogen stores and hepatomegaly.

As mentioned above, glycogen is a branched polymer. Although glycogen phosphorylase is good at removing glucose from alpha (1,4) bonds, it does not work at branch points. The branch points are alpha-1,6 bonds. Removal of branch points requires a glycogen decoding enzyme (GDE), called "ammylo-alpha-1,6-glucosidase, 4-alpha-glucanotransferase" in mammals, encoded by the AGL gene. GSD type III is caused by mutations in the AGL gene, resulting in either a nonfunctional GDE enzyme (GSD type IIIa or type IIIb) or decreased GDE function (GSD types IIIc and IIId).

Although most muscular dystrophies result in fixed muscle weakness rather than exercise-induced muscle fatigue and/or cramping, there are a few exceptions. Autosomal recessive limb-girdle muscular dystrophy 23 (LGMD R23) presents with calf hypertrophy and exercise-induced cramping. Myofibrillar myopathy 10 (MFM10) is characterized by exercise-induced muscle fatigue, cramping and stiffness, with hypertrophy of the neck and shoulder muscles. LGMD R28 presents with calf hypertrophy as well as exercise-induced muscle fatigue and soreness. PCMD R8 presents with pseudohypertrophy of the calves, weakness (fatigue) and exercise-induced pain. LGMD R15 (also known as MDDGC3) exhibits muscle hypertrophy, proximal muscle weakness, and muscle fatigue. The DMD-related Duchenne myopathies and Becker muscular dystrophy are known for fixed muscle weakness and pseudohypertrophy of the gastrocnemius muscles, but they also have secondary muscle mitochondrial failure leading to low ATP production; and a decrease in the number of type II (fast-twitch/glycolytic) muscle fibers, resulting in a predominance of type I (slow-twitch/oxidative) muscle fibers. Milder phenotypes associated with childhood-onset DMD include exercise-induced muscle spasms, stiffness, pain, fatigue, and elevated CPK levels. Becker muscular dystrophy is characterized by exercise-induced muscle spasms, pain, and elevated CPK levels in adulthood. Global tubular myopathy (GTM) types 1 and 2 present with muscle pain, fatigue, exercise-induced stiffness, proximal muscle weakness, and pseudohypertrophy of the gastrocnemius muscles. TAM1 exhibits seizures at rest, while TAM2 exhibits seizures during exercise. Stormorken syndrome includes the symptoms of TAM but is a more severe presentation, including short stature and other abnormalities. Satoyoshi syndrome is characterized by painful muscle spasms, muscle hypertrophy, and short stature caused by exercise. Dimethylglycine dehydrogenase deficiency leads to muscle fatigue, increased CPK levels and fishy body odor. Myopathy with myalgia, elevated serum creatine kinase levels with or without episodic rhabdomyolysis (MMCKR) leads to exercise-induced muscle cramps, pain, and fatigue; some have proximal muscle weakness.

Treatment depends on the type of glycogen storage disease. Von Gierke's disease (GSD-I) is usually treated with small, frequent meals of carbohydrates and corn starch, called modified corn starch therapy, to prevent hypoglycemia, while other treatments may include allopurinol and human granulocyte colony-stimulating factor. Modified corn starch therapy, a high-protein diet with a preference for complex carbohydrates, may be used to treat measles/Forbes disease (GSD-III). However, unlike GSD-I, gluconeogenesis is functional, so simple sugars (sucrose, fructose

and lactose) are not inhibited. The ketogenic diet has been shown to be beneficial in McArdle's disease (GSD-V) because ketones are readily converted to acetyl-CoA for oxidative phosphorylation, whereas free fatty acids take several minutes to be converted to acetyl-CoA for oxidative phosphorylation. CoA. For phosphoglucomutase (formerly GSD-XIV) deficiency, D-galactose supplementation and exercise have shown beneficial improvement in signs and symptoms.

Some patients with phosphoglucomutase deficiency also experience a “second wind” and anaerobic exercise (strength training), which follows adaptation to activity and does not cause muscle injuries, helps reduce symptoms of exercise intolerance and maintain overall health. Research has shown that regular low-to-moderate aerobic exercise increases peak power output, increases peak oxygen consumption (VO2peak), lowers heart rate, and reduces serum CPK levels in people with CD. McArdle. Whether the patient presents symptoms of muscle pain, muscle fatigue or cramps, the appearance of the second wind phenomenon is manifested by the sign of an increase in heart rate, which decreases while maintaining the same speed on the mat rolling. In sedentary patients, a second wind occurred, manifested by relief of typical symptoms and a decrease in signs of increased heart rate during low to moderate aerobic exercise (walking or brisk walking). Conversely, regularly active patients did not show typical symptoms during low to moderate aerobic exercise (walking or brisk walking), but nevertheless showed a second wind in the form of a sign of an increased decrease in cardiac frequency. In regularly active patients, more intense exercise (walking/jogging or very fast cycling) was necessary to experience both typical symptoms and their relief, as well as signs of an increase in heart rate, demonstrating a second wind. In young children (<10 years) with McArdle disease (GSD-V), the second wind phenomenon may be more difficult to detect. They may have a normal heart rate and a normal or higher maximum cardiorespiratory capacity (VO2max). However, patients with McArdle disease typically present with symptoms of exercise intolerance before the age of 10, with the average age of symptoms being 3 years.

Methods for diagnosing glycogen storage diseases include a history and physical examination to identify associated symptoms, blood tests to identify underlying metabolic disorders, and genetic testing to identify suspected mutations. It may also include a non-ischemic forearm test, an exercise test, or a 12-minute walk test (12MWT). Advances in genetic testing are gradually reducing the need for biopsies; however, if IVUS and inconclusive stress tests are present, a biopsy will be required to confirm the diagnosis.

As noted above, glycogen is the stored form of glucose and consists of long 1,4-linked glucose polymers with branch points through 1,6-linked glucose molecules. The primary physiological function of glycogen is to supply glucose through glycogenolysis to maintain glucose homeostasis. Liver stores are used to maintain serum glucose homeostasis, and muscle stores provide muscles with glucose during periods of high demand or exercise as an energy source.

When these physiological functions are disrupted, hypoglycemia, hepatomegaly, muscle cramps, exercise intolerance, and weakness develop. Some diseases also affect myocardial tissue and can lead to cardiomyopathy and cardiac conduction abnormalities. Failure to maintain glucose homeostasis triggers alternative pathways to meet metabolic needs. In type 1 GDM, for example, failure of glycogenolysis in the liver leads to increased production of lactic acid (lactic acidosis) due to intracellular accumulation of glucose-6-phosphate, which stimulates the glycolytic pathway.

GSDs are a diverse set of rare inborn errors of carbohydrate metabolism that can have different phenotypic presentations even within the same type of GSD. Obtaining a family pedigree is useful in establishing the mode of inheritance. Most GSDs show autosomal recessive inheritance, but some (type IX GSDs) show X-linked inheritance. Common symptoms include failure to thrive/poor weight gain in children, exercise intolerance, hypoglycemia, hepatomegaly, low muscle tone, acidosis, and hyperlipidemia. As noted above, the most common symptoms of these disorders are hypoglycemia and exercise intolerance [14,28].

Glycogen storage diseases (GSDs) are a group of rare genetic disorders characterized by impaired glycogen metabolism, leading to abnormal accumulation of glycogen in various tissues. This research article aims to provide a comprehensive overview of the biochemistry underlying GSDs, exploring the molecular mechanisms, clinical manifestations and current therapeutic strategies. Through detailed investigation of the key biochemical pathways and enzymes involved in glycogen metabolism, we aim to improve our understanding of GSDs, paving the way for improved diagnosis and targeted therapy. Glycogen metabolism plays an important role in exercise and blood sugar regulation. In a fed state, insulin stimulates glycogen storage in the muscles and liver, while simultaneously stimulating glycogen synthesis and inhibiting its breakdown. Conversely, in the fasting state or during exercise, glucagon and catecholamines promote glycogen breakdown while inhibiting its synthesis. The importance of glycogen is further emphasized by the fact that there are several congenital disorders caused by dysfunction of the enzymes that control the synthesis, regulation, and breakdown of glycogen. So, a biochemical perspective on Glycogen storage disorders, implications for precision medicine, the article provides an in-depth examination of the biochemical complexities underlying glycogen storage disorders. By studying the molecular basis, pathways affected, clinical manifestations, and therapeutic strategies, we think to contribute to the evolving Glycogen storage disorders research approach by offering better diagnosis and interventions and pharmacotherapy management.

Patients with impaired hepatic glycogen metabolism typically experience fasting hypoglycemia and ketosis. Their symptoms improve with the administration of glucose. Patients with abnormalities in skeletal muscle glycogen metabolism report fatigue and exercise intolerance after short periods of moderate-intensity exercise. This contrasts with patients with a defect in fatty acid metabolism, since patients with defects in this pathway typically develop symptoms after prolonged exercise. Patients with skeletal muscle-associated GSD report muscle cramps and may present with rhabdomyolysis and/or myoglobinuria. In rare cases, progressive weakness may occur. However, this is generally limited to GSD types 0, II and IV. In rare cases, GSD types III, V, and VII may present with weakness rather than muscle cramps, and fixed weakness develops over time. Patients with heart muscle abnormalities have symptoms of cardiomyopathy and rarely conduction defects [16,24].

Anthropometric measurements should be obtained and graphed in all patients with GSD to assess overall growth patterns. Short stature or poor linear growth, particularly in hypoglycemic children, should prompt investigation for glycogen storage disorders. Failure to properly release glucose from glycogen can lead to abnormal glycogen accumulation. In the liver, this leads to hepatomegaly with the potential for cirrhosis [9,37].

GHD types 0, IV, VI, IX and XI with liver involvement may have a similar clinical picture. However, these diseases present a phenotypic continuum and, even in the mildest forms, regular monitoring and dietary adjustments are necessary to slow the progression of the disease and its complications. In some cases, there may be a clinical burden related to serious organ

complications. Ensuring adequate knowledge among doctors about these rare pathologies is essential to improve the prognosis and quality of life of patients, particularly those suffering from the most serious forms. Further studies are needed to determine genotype-phenotype correlation and to guide personalized therapy and management [10,24].

Hypoglycemia is defined as the plasma glucose concentration that results in symptoms associated with hypoglycemia and is reversed by glucose administration. There is no fixed plasma glucose level above which GSD can be ruled out, especially in children. It is important to note that newborns experience a period of transient hypoglycemia during the first 48 hours of life, during which the diagnosis of cholelithiasis is impossible.

The duration of fasting that results in symptoms of hypoglycemia is an important part of the history to be taken. A short duration of fasting resulting in typical symptoms suggests a type I or type III glycogen storage disorder. If overnight fasting results in symptoms of hypoglycemia, glycogen storage disease type 0, VI, or IX should be considered [17,26].

There is currently no cure for GSD, and most treatments are aimed at relieving signs/symptoms. The main goals are the treatment or prevention of hypoglycemia, hyperlactatemia, hyperuricemia and hyperlipidemia. Hypoglycemia can be avoided by consuming starch, and an optimal, physically modified form is now commercially available. Hyperuricemia is treated with allopurinol, and hyperlipidemia with statins. Some GSDs, such as GSD type II, can now be treated with enzyme replacement therapy (ERT) using recombinant alglucosidase alpha, which breaks down lysosomal glycogen [11,25,27].

Research is currently being conducted on the use of ERT with other forms of GSD. Liver transplantation should be considered in patients with certain liver diseases with advanced forms of the liver that have progressed to malignancy or liver failure. Although liver failure and hypoglycemia can be corrected with liver transplantation, cardiomyopathy associated with GSD is not correctable and may continue to progress [13,29].

Immediate treatment of acute hypoglycemia requires rapid correction with oral carbohydrates and/or parenteral glucose. Glucagon is effective only for insulin-mediated hypoglycemia and will not benefit patients with hypoglycemia secondary to gastrointestinal symptoms.

GSDs are a group of complex metabolic disorders that are best managed by an interprofessional team consisting of clinicians, nurses, pharmacists, and dietitians. There is currently no cure for GSD, and most treatments are aimed at relieving signs/symptoms. However, even such symptomatic treatment requires vigorous patient/parent education to ensure that dietary restrictions and frequency of carbohydrate intake are followed appropriately [12,24].

Dietitians and nurse specialists play a key role in educating patients and their carers to avoid hypoglycemia. This not only reduces the risk of complications associated with hypoglycemia, but also prevents long-term consequences of the disease in most cases of cholelithiasis. Specialist pharmacists play a central role in the treatment of GDM type II by ensuring that enzyme replacement therapy is adequately administered and the drug is administered under optimal conditions. Primary care physicians, which include internists, mid-level practitioners, and pediatricians, work in coordination with specialists to help ensure that patients grow and function adequately with minimal risk of serious complications such as kidney failure or liver failure [17].

All members of the interprofessional team must be vigilant in monitoring these patients and alert other members of the team if complications arise or if the patient's condition worsens; this requires careful documentation and open communication between all members of the care team. The main overall goal is to prevent and treat hypoglycemia, hyperlactatemia, hyperuricemia and

hyperlipidemia. A well-coordinated interprofessional team can help adequately care for patients with these diseases and ensure their normal lives.

The development of experimental treatments such as gene therapy could ultimately provide therapeutic options for patients with these diseases in the future.

Seizures associated with hypoglycemia and cardiac arrest may occur in early childhood. Patients with GSD type Ia may present with growth retardation accompanied by short stature, renal dysfunction, hypertriglyceridemia, and hepatocellular carcinoma. whereas in GSD type Ib, there will be recurrent bacterial infections secondary to neutropenia. In gestational diabetes type IV, progressive liver failure accompanied by liver cirrhosis may occur. Cardiomyopathy and limb-girdle dystrophy can be seen in patients with type II cholelithiasis. Hypertrophic cardiomyopathy is a classic type III gastrointestinal complication [14,19,28].

Growth retardation and short stature are also seen in GHD types IX (a, b, c, d) and XII, but delayed cognitive development is also a feature of the latter. In headache types V and XIII, exercise intolerance and rhabdomyolysis accompanied by kidney damage may occur.

Overview Glycogen storage diseases (GSDs) are a rare group of genetic disorders characterized by abnormalities in glycogen metabolism, resulting in abnormal accumulation of glycogen in tissues. Delving into historical perspectives reveals the evolutionary trajectory of GSD research, tracing early observations, landmark discoveries, and the gradual elucidation of key complexities. Such ideas not only contextualize the current state of knowledge, but also highlight the persistence of scientific research in unraveling the mysteries of GSD. The GSD classification is essential for understanding the different enzyme disorders that characterize the different subtypes. This classification provides a framework for deciphering the intricacies of each subtype and helps tailor interventions based on specific enzyme deficiencies. At the same time, the study of the prevalence of GDM highlights the relative rarity of these pathologies, thus helping to assess their impact on society and efficiently allocate resources. Clinical manifestations make the link between genetic abnormalities and the symptoms observed. Studying the different manifestations of GSD, such as hepatomegaly, muscle weakness and hypoglycemia, provides important information for early diagnosis and targeted interventions. This comprehensive review lays the foundation for further discussions on the molecular basis, biochemical pathways and therapeutic approaches, thereby contributing to a holistic understanding of GSD [19].

Normal glycogen metabolism is a finely regulated process essential for energy homeostasis. During this stage, glucose is converted to glycogen through a series of enzymatic reactions that occur primarily in the liver and muscles. Glycogen serves as a storage form of glucose, allowing the body to release glucose when energy needs increase, such as during fasting or exercise. Understanding the intricacies of normal glycogen metabolism provides the basis for recognizing the abnormalities seen in glycogen storage diseases (GSDs), where genetic mutations disrupt this finely tuned process. Enzymes involved in the synthesis and breakdown of glycogen. Key enzymes control the synthesis and breakdown of glycogen. Glycogen synthase promotes the formation of glycogen, and glycogen phosphorylase plays a central role in its breakdown. These and other enzymes work in concert to maintain a dynamic balance, ensuring adequate glucose supply when needed and storage when there is excess.

The regulation of glycogen metabolism is tightly controlled by hormonal signals and the energy status of cells. Hormones such as insulin and glucagon modulate enzyme activity to ensure a balance between glycogen synthesis and breakdown. Cellular energy sensors such as AMP-activated protein kinase (AMPK) further contribute to this regulation, enabling adaptive responses

to varying energy demands. This tightly regulated system is fundamental to overall metabolic health and is disrupted in GSD, highlighting the importance of understanding these regulatory mechanisms. Molecular basis of ONH: genetic mutations and patterns of inheritance. Glycogen storage diseases (GSDs) result from genetic mutations in genes associated with glycogen metabolism due to autosomal recessive or dominant inheritance. Understanding these mutations is critical for prognosis and genetic counseling [9,17].

Glycogen storage diseases (GSDs) cause various enzyme dysfunctions due to specific mutations that impair glycogen metabolism. Changes in enzyme activity, substrate binding, or stability promote aberrant glycogen synthesis or degradation, the intensity of which varies among GSD subtypes. Tissue-specific manifestations: Molecular abnormalities of GCD occur in tissues where glycogen metabolism predominates, causing organ-specific symptoms. Hepatic GSDs affect the liver, while myopathic GSDs primarily affect skeletal muscles, determining the need for diagnosis and treatment. Biochemical pathways affected by GSD: - Glycogen synthesis disorders: Genetic mutations disrupt the enzymes involved in glycogen synthesis, causing abnormal glycogen accumulation. Dysregulation of glycogen breakdown: Mutations affect enzymes involved in glycogen breakdown pathways, leading to impaired glycogen utilization. Clinical manifestations and diagnosis: - Hepatic GSD: Hepatic GSD is characterized by hepatic symptoms such as hepatomegaly and metabolic abnormalities. - Myopathic GSD: Skeletal muscle weakness and fatigue are the predominant features of myopathic GSD. - Glycogen storage disease type 0 (GSD 0): GSD. 0 suggests impaired glycogen synthesis. - Diagnostic Challenges and Advances: Addressing the challenges of GSD diagnosis involves the emergence of new diagnostic technologies and a better understanding of the nuances of the disease. Therapeutic approaches: Dietary management: The formulation of dietary plans to regulate glucose intake is fundamental [12].

People with gallstones often need frequent meals, certain sources of carbohydrates, and sometimes nighttime feedings to prevent hypoglycemia. Enzyme replacement therapy: The administration of functional enzymes through therapeutic supplementation aims to alleviate deficiencies, promote improved glycogen metabolism, and reduce symptoms of certain gastrointestinal subtypes. Gene therapy and new treatment methods. Cutting-edge approaches, including gene therapy, promise to correct genetic mutations at the molecular level. These new techniques address the underlying cause, offering potential long-term solutions to GSD by restoring normal glycogen metabolism. Future directions: Advances in genomic medicine. Continuing advances in genomic medicine promise to improve our understanding of GSD through comprehensive genetic analysis to enable accurate diagnosis, predict prognosis, and target therapy. Personalized therapeutic strategies. The future involves a move toward personalized treatment plans that take into account individual genetic variations and the nuances of disease. Tailored interventions aim to optimize effectiveness and minimize side effects, reflecting a more patient-centered approach. Potential gene editing technologies. Emerging gene editing technologies such as CRISPR-Cas9 offer unprecedented opportunities to correct the genetic mutations that cause GSD. This opens the potential for therapeutic interventions, marking a paradigm shift in treatment towards direct genetic modification [13,28,36].

A strict high-protein, low-simple-carbohydrate diet, including frequent consumption of complex carbohydrates such as maltodextrin and raw cornstarch, is fundamental to preventing hypoglycemia in ketotic GSD. Indeed, metabolic imbalance leads to nocturnal hypoglycemia and ketosis, which is associated with short stature, osteopenia, and neurological complications. GSD

types 0, VI, and especially type IX will benefit from strict blood sugar control. A minority of patients with PHKA2 and PHKG2 mutations associated with a severe phenotype often require night feeding to maintain euglycemia (85). Since gluconeogenesis is maintained, protein supplementation provides gluconeogenic precursors that can be used to replenish Krebs cycle intermediates and produce endogenous glucose in GI types 0, IV, VI, and IX. By improving glucose homeostasis, hepatic glycogen accumulation and secondary complications can be limited. The diet should be rich in protein and provide 2 to 3 g of protein per kg or ~ 20 to 25% of total calories. High protein intake is especially necessary in GDM type VI to improve muscle function. Carbohydrates should provide ~ 45-50% of total calories, and complex carbohydrates and proteins should be present in every meal. A dosage of 1 g/kg raw cornstarch at bedtime helps maintain normoglycemia for 4–8 hours in infants and children. Efficacy of extended-release corn starch (glycosade) in GSD types 0, III, VI, and IX to achieve longer periods of nighttime euglycemia with stable values for other markers of metabolic control and liver function. In the United States, a long-acting corn starch preparation is approved for use at night in patients with cholelithiasis over 5 years of age. However, the use of glycosad in patients aged 2 to 5 years has been proven to be safe and effective. Adverse reactions such as bloating, diarrhea and flatulence have been reported but not reported to date in patients with cholelithiasis types 0, VI and IX.

Patients with GSD type 0 is treated with frequent meals high in carbohydrates, as well as cornstarch and protein supplements. Patients with GI type IV is prescribed a high-carbohydrate diet combined with corn starch, overnight enteral nutrition, and protein fortification to limit glycogen accumulation, prevent catabolism, and improve growth and fasting tolerance. The most serious forms are treated with liver transplantation. For the GSD type, frequent light meals with limited glucose and galactose and ingestion of raw cornstarch in the evening are used to prevent metabolic acidosis that may occur during surgery or other stresses. High cholesterol may require statin treatment after age five; Bicarbonate supplements may be necessary to balance urinary bicarbonate loss [28,36].

Based on available data, generally accepted recommendations for the management of these types of DHA have not been established. However, appropriate monitoring must be ensured to establish good metabolic control and monitor possible complications. Medical and nutritional assessments and blood tests, including complete liver and kidney function, lipid profile, calcium-phosphate metabolism, serum electrolytes, blood gases, and urinalysis, should be performed in average every 6 months; a higher frequency is recommended in younger patients and those who have not achieved metabolic balance. Continuous blood glucose monitoring may be helpful in monitoring glycemic fluctuations, particularly in younger patients. Alpha-fetoprotein levels along with abdominal ultrasound can be used to screen for hepatocellular carcinoma, although there are no validated monitoring protocols to date. Liver fibroscanning can be a useful, non-invasive tool to monitor the progression of hepatic fibrosis/cirrhosis in gastrointestinal types IV, VI, and IX [14,27].

Patients diagnosed with GSD type IV require a comprehensive evaluation of cardiac function, including an electrocardiogram and echocardiography. Patients with hypertension types VI and IX after 5 years are recommended to undergo a cardiac examination every 1-2 years.

Concerning bone metabolism, it is recommended to carefully evaluate calcium and vitamin D intake and to monitor 25-OH vitamin D levels. Calcium, phosphate and vitamin D supplementation as well as a blood test Annual DXA are necessary to prevent osteopenia and fractures, especially in cases of type XI gastrointestinal tract. as well as monitoring renal function.

Skeletal radiographs are necessary in GSD type XI to evaluate the development of rickets. Recommendations for vitamin and mineral supplementation are based on the patient's individual diet and nutritional needs.

As mentioned previously, glycogen synthase deficiency is characterized by the absence of hepatomegaly, because hepatic glycogen stores are impaired, although hepatic hypertrophy has been reported in some cases of GSD type 0. In contrast, l Hepatomegaly is a characteristic of the GSD type. IV, VI, IX and XI of varying severity, which may appear after puberty in patients treated with GSD type IX. However, despite the reduction in liver size, progression of liver disease can occur [24,37].

In type IV GI tract, the accumulation of abnormal glycogen, which is less soluble than normal glycogen, causes a foreign body reaction with subsequent osmotic edema and cell death, leading to interstitial fibrosis progressing to cirrhosis. Liver fibrosis has also been described in individuals with cholelithiasis types VI and IX. In particular, in gallstone disease, type IX fibrosis has recently been reported to range from 33 to 95% depending on the subtype, still in early childhood. In addition, liver cirrhosis has recently been described in GSD type VI. Among GSD IX subtypes, progression to cirrhosis was initially described only in patients with PHKG2 mutations. More recently, early onset cirrhosis has been reported in children with homozygous PHKB mutations.

Tumor degeneration has been described in LCD types IV, VI and IX. Hepatocellular adenomas and carcinomas have been described in type IV gastrointestinal tract. GSD type VI may rarely be complicated by focal nodular hyperplasia, and one case of hepatocellular carcinoma has been reported to date. Regarding GSD type IX, hepatocellular adenomas of subtypes IXa and IXb have been reported. In addition, the development of hepatocellular carcinoma associated with GSD type IXc has recently been described. In GDM type XI, liver histology shows marked accumulation of glycogen in hepatocytes as well as steatosis. Degeneration into liver adenomas or carcinomas is rare. The first case of hepatocellular carcinoma in a boy with Fanconi-Bickel syndrome was described in 2017 by Pogoriler and colleagues [19,24].

Conversely, individuals with PHKA2 and PHKG2 mutations may suffer from renal tubular acidosis and tubulopathy with secondary development of rickets in a patient with cholelithiasis type IXc. Implementation of adequate nutritional therapy improves tubular acidosis.

Additionally, kidney damage is a hallmark of LCD type XI, in which renal epithelial cells are damaged due to accumulation of glycogen and monosaccharides; this change leads to proximal tubular dysfunction, as evidenced by glycosuria and aminoaciduria. Although this pathology is a serious phenotype, rare cases of patients with mild renal dysfunction have been described. Normal birth length and weight are usually observed, suggesting that metabolic abnormalities do not affect fetal growth, with the exception of newborns with type XI GDM, who usually have low birth weight. the birth. GSD type II is unique among GSDs as it is also classified as a lysosomal storage disease (LSD). Lysosomes are subcellular organelles that process cellular macromolecules. Lysosomal diseases are caused by a missing or dysfunctional lysosomal enzyme. In the case of GSD II, this enzyme is lysosomal acid alpha-glucosidase, encoded by the GAA gene, which breaks down glycogen into glucose for use as a source of cellular energy. Mutation of the GAA gene leads to toxic accumulation of glycogen in lysosomes.

Glycogen storage diseases affecting skeletal muscle typically present with exercise-induced (dynamic) symptoms such as muscle fatigue rather than fixed (static) symptoms of weakness. The differential diagnosis of glycogen storage diseases accompanied by fixed muscle weakness, especially of the proximal muscles, should be made from inflammatory myopathy or muscular

dystrophy of the limb girdle. In individuals with exercise intolerance and/or proximal muscle weakness, the presence of endocrinopathies should be considered. The timing of the onset of symptoms of exercise intolerance, such as muscle fatigue and cramps, is important to distinguish it from other metabolic myopathies, such as disorders of fatty acid metabolism. Problems originating in the circulatory system, rather than in the muscles themselves, can cause exercise-induced muscle fatigue, pain and cramping, which improves with rest as a result of insufficient blood flow (ischemia) to the muscles. Ischemia, which often causes symptoms in the leg muscles, includes intermittent claudication, popliteal artery entrapment syndrome, and chronic venous insufficiency.

Conclusion

Glycogen storage diseases (GSDs) are a group of rare genetic disorders characterized by impaired glycogen metabolism, leading to abnormal accumulation of glycogen in various tissues. This research article aims to provide a comprehensive overview of the biochemistry underlying GSDs, exploring the molecular mechanisms, clinical manifestations and current therapeutic strategies. Through detailed investigation of the key biochemical pathways and enzymes involved in glycogen metabolism, we aim to improve our understanding of GSDs, paving the way for improved diagnosis and targeted therapy. Glycogen metabolism plays an important role in exercise and blood sugar regulation. In a fed state, insulin stimulates glycogen storage in the muscles and liver, while simultaneously stimulating glycogen synthesis and inhibiting its breakdown. Conversely, in the fasting state or during exercise, glucagon and catecholamines promote glycogen breakdown while inhibiting its synthesis. The importance of glycogen is further emphasized by the fact that there are several congenital disorders caused by dysfunction of the enzymes that control the synthesis, regulation, and breakdown of glycogen. So, a biochemical perspective on Glycogen storage disorders, implications for precision medicine, the article provides an in-depth examination of the biochemical complexities underlying glycogen storage disorders.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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THE MANIFESTATION OF KEY ISSUE ASPECTS OF FEATURES OF INFLUENCE OF MEDICATIONS ON THE LIVING ORGANISMS, INCLUDING HUMANS AND THEIR PHYSICAL ENVIRONMENT

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ABSTRACT

Aim of the research was to study key issue aspects of features of influence of medications on the living organisms, including humans and their physical environment. The potential consequences of the presence of pharmaceuticals in aquatic systems are unknown and have therefore received increasing attention as potential pollutants in recent years. The fact that an industrial chemical can end up in the environment is not surprising in itself. What's interesting about drug contamination is that it does not primarily arise from manufacturing, but rather from the widespread and ongoing use, isolation, and improper disposal of drugs for human and veterinary use. Pharmaceuticals are potentially ubiquitous pollutants as they are present in all human environments. There is currently little evidence that pharmaceuticals are present in the environment in sufficient quantities to cause significant harm, although their use is expected to increase as the Human Genome Project is completed and the population ages. Drugs and their metabolites are increasingly being found in water bodies in areas adjacent to anthropogenic activities. Currently, pharmaceutical compounds are regularly released into the environment in extremely large quantities, and the current emission control system is unable to control untreated or partially treated pharmaceutical wastewater. The effects of drugs permeate and impact ecosystems, biota and humans. Adverse health effects on humans, aquatic animals and livestock should be investigated through careful toxicological and safety studies. Serious efforts are needed to reduce this problem, and appropriate regulations are needed to monitor and control it. Water quality guidelines in India should include analysis of the most commonly used pharmaceutical compounds in drinking water sources. In addition,

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pharmaceutical industrial wastewater treatment plants need to implement new corrective measures to prevent long-term environmental and health risks. Regarding environmental risk assessment, include the environment in the risk-benefit analysis of pharmaceutical products for human use, improve risk management capabilities, collect data on existing pharmaceutical products, and improve environmental availability risk These assessments represent some important next steps. The biological effects to environmental exposures promise interesting results, although very few studies have been conducted on wild animals or caged organisms, such as in the wild or in ecologically significant environments. This may be due to the lack of analytical method protocols as well as the variety of pharmaceutical structural features that are not easy to handle but need to be taken into account.

Keywords: Aspects, featurs, influence medications, living, organisms, humans, physical environment.

Introduction

Currently, increasing attention is being paid to the presence and fate of active pharmaceutical ingredients, solvents, intermediates and raw materials that may be present in water and wastewater, including pharmaceutical wastewater. Traditional wastewater treatment methods, such as activated sludge, are insufficient to completely remove active pharmaceutical ingredients and other wastewater components from these waters. Pharmaceutical wastewater has direct and indirect impacts on the environment and health, especially near pharmaceutical industrial sites. Although pharmaceutical factories produce untreated or partially treated wastewater, drinking water sources are contaminated. Various classes of pharmaceutical compounds such as analgesics, antidepressants, antihypertensives, contraceptives, antibiotics, steroids, hormones, etc. To protect the environment and lifestyles from health risks, the concentration of pharmaceutical compounds in medical wastewater entering drinking water sources should be regularly monitored. This article highlights the toxicity, health risks, and environmental risk assessments associated with pharmaceutical contaminants. To reduce contamination levels when consuming medicines should be: Creation of a system for collecting drug waste generated by the population; Conducting awareness-raising work with the population, employees of healthcare institutions and other target groups on the topic of environmental pollution by drug waste; Taking into account environmental factors when choosing and prescribing treatment. At the same time, there is no need to put environmental protection above the human need for treatment; Development and implementation of wastewater treatment systems. It should be taken into account that urban wastewater has an unstable composition in terms of names and concentrations of drugs. A higher priority is to prevent drug residues from entering the city sewer system [1-3].

The chemical pollutants such as pesticides, biocides or industrial chemicals, the release of pharmaceuticals into the environment must be regulated to ensure adequate information and transparency about the environmental impacts of pharmaceuticals; adequate and reliable assessment of environmental risks of pharmaceutical products; prevent pharmaceutical products from entering the environment throughout their entire life cycle and control releases of pharmaceuticals into the environment when prevention is not possible [5-7].

Consumption of medicinal products for human and veterinary purposes has impacts on terrestrial and marine environments and ecosystems. Increased environmental awareness regarding pharmaceutical activities has led to the development of policies and measures aimed at mitigating negative environmental impacts. Various measures have been taken to promote environmentally

friendly production and practices, leading to the development of alternative methods and processes benefiting both the environment and industry. Distributors and pharmacists can make a difference by effectively managing daily operations, including improving inventory and rotation, consolidating supplies and reducing unused medications [8-10].

Incorporating green practices into the pharmacy curriculum provides future pharmacists with the skills and competencies needed in the field to reduce the environmental impact of processes and medications. A more environmentally conscious workforce in the pharmaceutical industry is creating the necessary ripple effect for the adoption and implementation of green principles across various pharmaceutical environments. Patients should also learn to avoid accumulating medications and disposing of them safely and correctly. Adopting environmentally friendly practices leads to a reduction in the use of chemicals and waste generation, which in turn leads to a reduction in the pollutants that contribute to climate change [11-13].

The increasing production and use of pharmaceutical and veterinary products has had an impact on the environment over time. Drug production processes have a significant impact on the environment, which affects the value of chemistry to society. The pharmaceutical industry impacts the environment through the carbon footprint generated during the production of pharmaceutical products and throughout the supply chain, which can lead to climate change. Climate change may alter the incidence of vector-borne diseases by altering the population of species that act as disease vectors. Another consequence of climate change is the emergence of infectious diseases caused by pathogens that would otherwise be dormant [14-16].

Diseases and conditions caused by climate change will also impact demand in the healthcare system and pharmaceutical industry. The pharmaceutical industry may see a change or increase in demand for drugs. For example, an increase in temperature can trigger asthma due to increased pollen levels. This increase in asthma cases will, in turn, lead to an increase in demand for medications to control asthma. Changing demand for medicines could create opportunities for the pharmaceutical industry to make the most of climate change and incorporate green chemistry principles into the development of new medicines [18-20].

The production and consumption of pharmaceuticals results in the presence of active pharmaceutical ingredients (APIs) in the ecosystem. Active ingredients enter the marine and terrestrial environment through release from manufacturing facilities, into wastewater after consumption of the drug in question, or through improper disposal of expired or unused drugs. The use of medicinal products in veterinary medicine may also result in the release of active substances into the environment, for example through the use of wastewater for irrigation, agriculture, aquaculture or the disposal of animal carcasses treated with veterinary drugs. The presence of APIs in the ecosystem can have a number of side effects, such as: Bacterial resistance to antibiotics and changes in the activity of digestive glands in marine life, reproductive toxicity in amphibians and feminization of fish. Another striking example of the impact of APIs on the ecosystem is the sharp decline in vulture populations due to the presence of diclofenac residues in cattle carcasses [21-23].

Around the world, the drug residues in the environment poses risks to humans, aquatic animals and wildlife and is becoming a major concern for both regulatory authorities and the pharmaceutical industry. Significant progress on this issue is simply not possible with the current limited knowledge about the transport, fate, and environmental impact of pharmaceuticals. It is necessary to take into account the possible potentiating effects of different drugs acting on the same receptors. Risk assessment of pharmaceutical chemicals involves identifying the hazards

associated with each step and assessing the risks associated with those hazards. Currently, pharmaceutical compounds are regularly released into the environment in extremely large quantities, and the current emission control system is unable to control untreated or partially treated pharmaceutical wastewater. The effects of drugs permeate and impact ecosystems, biota and humans. Adverse health effects on humans, aquatic animals and livestock should be investigated through careful toxicological and safety studies. Serious efforts are needed to reduce this problem, and appropriate regulations are needed to monitor and control it. Water quality guidelines in India should include analysis of the most commonly used pharmaceutical compounds in drinking water sources. In addition, pharmaceutical industrial wastewater treatment plants need to implement new corrective measures to prevent long-term environmental and health risks [25-27].

Goal

Aim of the research was to study and analyzed key issue aspects of features of influence of medications on the living organisms, including humans and their physical environment.

Methodology

The material of the article was the data from scientific publications, which were processed, analyzed, overviewed and reviewed by generalization and systematization. research studies are based on a review/overview assessment of the development of critical visibility and overlook of the modern scientific literature. Were use the following databases: (for extensive literature searches to identify key issue aspects of features of influence of medications on the living organisms, including humans and their physical environment.). PubMed, Medline, Web of Science, Scopus, Web of Knowledge, Clinical Key, Tomson Reuters, Google Scholar, Cochrane library, and Elsevier foundations, national and international policies and guidelines were also reviewed and as well as grey literature.

Results and Discussion

Pharmaceutical products intended for human use are included in the UNESCO list of emerging pollutants. Their identification and elimination represent a decisive step towards achieving the goals of the Sustainable Development Program. Concentrations of drugs found in the environment are below therapeutic levels. In waters receiving treated wastewater, drugs are found at concentrations below 100 ng/L. These low concentrations make it difficult to assess their toxic effects on ecosystems and human health. The vast majority of pharmaceutical products have not been adequately studied regarding their long-term toxic effects, presence and fate in the environment. However, certain classes of drugs, such as beta blockers, antibiotics, anticancer drugs, and endocrine disruptors, have been shown to have devastating effects on the ecosystem, including increased mortality and disruption of the physiological and reproductive functions of aquatic species. Moreover, since it is impossible to separate humans from nature, this has devastating consequences for human health. However, the extent of the problem remains largely unknown due to the large number of drugs available and difficulties in assessing the risks associated with exposure to multiple compounds at low doses over long periods of time. The drugs on the market pose a potential risk to the environment. Although there is no established method for detecting all pharmaceuticals entering an ecosystem, some are widespread and have

been shown to have negative impacts on ecosystems. These groups include hormones, antibiotics, antidepressants, anti-inflammatory and pain relievers, beta blockers and anti-cancer drugs [28-30]. Antibiotic resistance is a global public health problem, especially given the increased use of antibiotics during the COVID-19 pandemic, which has led to the exhaustion of the last line of antibiotics. It has been established that the use of antibiotics in medicine, veterinary medicine and agriculture is associated with pollution of various parts of the environment, which has contributed to increased antibiotic resistance and the occurrence of ecotoxicological effects. Failure to properly dispose of antibiotics through sewers by patients also poses a growing environmental threat to public health. Additionally, high levels of antibiotic contamination after long-term exposure can negatively impact human health, especially in patients with chronic diseases such as obesity, diabetes and asthma [31-32].

Antidepressant contamination has increased significantly worldwide during the COVID-19 pandemic. To this day, antidepressants can be found in urban and suburban water supplies. Many aquatic animal species bioaccumulate various antidepressants in their tissues, resulting in cytotoxicity, genotoxicity, impaired stress response, weight and length gain/loss, and liver and kidney damage. Because there is significant overlap between human and animal environments, exposure to antidepressants (sertraline, fluoxetine) in the environment also affects human neurological development and various mental illnesses. Although psychotropic drugs are usually present in wastewater at subtherapeutic levels, they can have biological effects at low doses, and combinations of multiple psychotropic drugs are often present, especially in the environment, increasing the risk of toxic effects [33-35].

Pharmaceutical compounds are used in modern society for various beneficial purposes, but at the same time, the pharmaceutical industry releases highly toxic pollutants into the environment either directly or after chemical modification. Additionally, pharmaceutical compounds can enter the environment through various routes such as treated wastewater discharge, seepage into landfills, sewer pipes, animal waste, etc. Although a number of physical and biological processes occur in an aquatic ecosystem, they can lead to depletion of many lead to pharmaceutical compounds. Traces of human and veterinary drugs and their metabolites were found in several bodies of water. Objects such as surface water, groundwater and drinking water sources. Several industries, including pharmaceuticals, chemicals, paints, etc., are rapidly developing in India, with wastewater being discharged into water bodies either directly or after partial treatment. Pharmaceutical compounds have been found to be released into the environment and may be considered environmental pollutants. Several pharmaceutical plants have been found to be sources of much higher concentrations in the environment than those resulting from drug use. Typically, the pharmaceutical industry generates a large amount of waste during production and service. Drugs have been found in sewage treatment plant wastewater and drinking water. Trace amounts of drugs in drinking water can have serious adverse effects on human health and aquatic life over long periods of time, even when drug concentrations in drinking water (in the nanogram per liter range) are orders of magnitude below the minimum therapeutic dose [36].

Pathways through which drugs may be exposed to the environment include manufacturing plants and hospital wastewater, land use (eg, biosolids and water reuse), etc. Wastewater treatment services are not always successful in removing active chemicals from wastewater. Therefore, drugs enter the aquatic environment, where they have a direct effect on aquatic organisms and can be absorbed into the food chain.

Higher concentrations of antibiotics can lead to changes in microbial community structure and ultimately affect food chains. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen and diclofenac, are widely used and therefore often found in wastewater systems, both surface and groundwater. Ibuprofen, ketoprofen, naproxen, indomethacin, diclofenac, acetylsalicylic acid and phenazone were detected in the surface water system. However, after clofibric acid, the most common drugs found in aquatic environments are diclofenac, ibuprofen and propyphenazone. Diclofenac has also been shown to be highly toxic to vultures and livestock. NSAIDs such as ibuprofen, naproxen, and aspirin are the most commonly used medications and are often found in effective amounts in municipal wastewater.

Many pharmaceutical companies are responsible for the generation of toxic wastewater during their operations. The wastewater generated from these facilities contains solids, biodegradable and non-degradable organic compounds, etc. Pharmaceutical wastewater provides basic information about the reliability of the aquatic environment of the rivers and streams into which it is discharged. An important indicator of industrial wastewater contamination is the oxygen content of chemical oxygen demand (COD) and biological oxygen demand (BOD), with nutritional status measured by the amount of nitrogen and phosphorus in the wastewater.

Long-term exposure of coastal biota to lower concentrations of complex drug mixtures can result in acute and chronic damage, behavioral changes, tissue accumulation, reproductive impairment, and inhibition of cell proliferation. Several studies have shown that fish exposed to sewage may experience reproductive problems. In addition, fish exposed to trace amounts of contraceptive drugs in the concentration range found in the environment show dramatic reductions in reproductive success, suggesting that population-level effects may be possible. Around the world, the drug residues in the environment poses risks to humans, aquatic animals and wildlife and is becoming a major concern for both regulatory authorities and the pharmaceutical industry. Significant progress on this issue is simply not possible with the current limited knowledge about the transport, fate, and environmental impact of pharmaceuticals. It is necessary to take into account the possible potentiating effects of different drugs acting on the same receptors. Risk assessment of pharmaceutical chemicals involves identifying the hazards associated with each step and assessing the risks associated with those hazards.

Currently, pharmaceutical compounds are regularly released into the environment in extremely large quantities, and the current emission control system is unable to control untreated or partially treated pharmaceutical wastewater. The effects of drugs permeate and impact ecosystems, biota and humans. Adverse health effects on humans, aquatic animals and livestock should be investigated through careful toxicological and safety studies. Serious efforts are needed to reduce this problem, and appropriate regulations are needed to monitor and control it. Water quality guidelines in India should include analysis of the most commonly used pharmaceutical compounds in drinking water sources. In addition, pharmaceutical industrial wastewater treatment plants need to implement new corrective measures to prevent long-term environmental and health risks.

Water sources contaminated with pharmaceutical contaminants are found in agricultural lands, surface water, groundwater, and drinking water. Water flows to plants, which affects the quality of soil and crops grown using this contaminated water. Pharmaceutical contaminants are considered external environmental factors that affect crop quality. Drugs enter plants as pollutants, either through the soil or the air. Pollutants enter the plant from the soil through the roots and are transported through the stem. Plants also absorb pollutants from the air, and leaves

can absorb pollutants from the atmosphere. Pharmaceutical contaminants such as B-lactams, aminoglycosides, macrolides, tetracyclines, sulfonamides, herbicides including sulfonylureas, triazines, imidazolinone, phenylurea and bisphenol (BPA) have been found to cause toxicity in plants. Polychlorinated biphenyls (PCBs) affect plant growth, reproduction and productivity.

Most pharmaceuticals we use are excreted via urine and feces in unchanged form or as metabolites and eventually end up in the drain. The pharmaceutical residues can then reach lakes, the sea and groundwater, despite passage through wastewater treatment plants, as the wastewater treatment plants are not built to clear pharmaceuticals. Pharmaceuticals affect biological processes. They are also often designed to withstand biodegradation and can therefore remain in the environment for a long time. There are reports of effects on fish, as well as that measured concentrations of antibiotics in wastewater treatment plants can select for antibiotic resistance. Various policies need to be implemented throughout the life cycle of pharmaceutical products, including source-oriented, consumer-oriented and waste management-oriented activities. The most effective solutions must be implemented at the source, before drugs enter the environment. These measures include rational drug consumption, prescribing more environmentally friendly drugs and developing harmless and easily biodegradable drugs. Improved disease prevention, personalized medicine, improved package sizes, and PC redistribution markets may go some way to avoiding drug waste.

The next step is to prevent unavoidable waste from entering the environment. Therefore, correct collection and disposal of is critical and must be adapted to national and local conditions. Finally, education of health care professionals and the public, as well as partnerships between environmental scientists and clinicians, paharmacists are important at all stages of the pharmaceutical product life cycle. All joint efforts must be guided by a One Health approach to combat pharmaceutical waste and improve the health of people, animals and the environment, which are closely linked. To reduce contamination levels when consuming medicines should be: Creation of a system for collecting drug waste generated by the population; Conducting awareness-raising work with the population, employees of healthcare institutions and other target groups on the topic of environmental pollution by drug waste; Taking into account environmental factors when choosing and prescribing treatment. At the same time, there is no need to put environmental protection above the human need for treatment; Development and implementation of wastewater treatment systems. It should be taken into account that urban wastewater has an unstable composition in terms of names and concentrations of drugs. A higher priority is to prevent drug residues from entering the city sewer system.

Ecology, which directly affects the health of society, is one of the most important factors in the modern era of civilization. Factors affecting population health are the biggest social problem. The health and illness of society are determined by the environment in which a living organism is located and develops. Man is a biosocial being. Environmental factors affect organisms in different ways. It can be irritating, limiting or determining the existence of the organism in specific conditions; the danger of disturbing the natural balance is associated with pollution of the atmosphere, water, soil and food products with nitrates, pesticides, radionuclides and other harmful substances. The environment is saturated with psychotoxins, chemical waste, biological damaging agents (drug-resistant bacteria, fungi, viruses, parasites resulting from mutations). causing death of plants and animals and illness in humans. Therefore, it is clear what a great danger an environmental disaster poses.

Based on data from the World Health Organization, an analysis of the impact of environmental factors on human health was published, which revealed large differences between countries and showed that human health can be improved by reducing exposure to environmental factors such as: pollution, ultraviolet radiation, noise, climate, ecosystem change and dangerous work environment. More than 10% of deaths in 23 countries of the world are related to the environment with two risk factors: Polluted air and water; Low sanitary and hygienic indicators. An environmental disaster has a direct impact on public health. Society and the environment are in constant relationship. Therefore, the health and illness of society are determined by the environment in which a living organism is located and develops. Factors affecting population health are the biggest social problem.

There is a danger of disturbing the natural balance. Pollution of the atmosphere, water, soil and food products with nitrates, pesticides, radionuclides and other harmful substances leads to the death of plants and animals and diseases of people. Therefore, it is clear what a great danger ecological disaster causes. The most serious consequence of biosphere pollution is the manifestation of genetic disorders. As a result of increased radioactive background and chemical pollution of the environment, the number of pathologies, malignant tumors, mental disorders, etc. increases. number. Mutagens in the form of chemical compounds, ionizing radiation penetrate the cell and cause disruption of the genetic program, causing mutations in somatic cells.

Human activity has the most negative impact by releasing pollutants. Pollutants are considered to be all those substances that enter the atmosphere, soil, natural waters and cause disruption of the biological, physical or chemical processes taking place there. Radiation and thermal radiation are also pollutants. As a result of human activities, carbon dioxide (CO_2), carbon dioxide (CO), sulfur dioxide (SO_2), methane (CH_4), nitrogen oxides NO_2, NO, N_2O are released into the atmosphere. As a result of aerosol use, chlorofluorocarbon enters the atmosphere, and hydrocarbons from transport emissions. Water bodies are polluted not only by waste from industrial production, but also by organic and mineral fertilizers and pesticides used in agriculture. In the same way, sea water is being polluted. Rivers carry millions of tons of chemical waste into the sea every year. Millions of tons of oil spill into the oceans every year as a result of tanker and oil rig accidents, killing marine animals. Burial of nuclear waste at the bottom of the sea, sunken ships with nuclear reactors and weapons also pose a danger.

Radioactive contamination of the soil creates a great danger, since radioactive substances from the soil enter plants, and from there into the body of humans and animals, where they accumulate and cause various diseases. Chemicals pose a particular danger, specifically, organic compounds used in agriculture to control weeds, pests and diseases.

Currently, increasing attention is being paid to the presence and fate of active pharmaceutical ingredients, solvents, intermediates and raw materials that may be present in water and wastewater, including pharmaceutical wastewater. Traditional wastewater treatment methods, such as activated sludge, are insufficient to completely remove active pharmaceutical ingredients and other wastewater components from these waters. Pharmaceutical wastewater has direct and indirect impacts on the environment and health, especially near pharmaceutical industrial sites. Although pharmaceutical factories produce untreated or partially treated wastewater, drinking water sources are contaminated. Various classes of pharmaceutical compounds such as analgesics, antidepressants, antihypertensives, contraceptives, antibiotics, steroids, hormones, etc. were detected in water samples ranging from mg/L to μg/L. Although the quantities detected are very small, they are highly toxic to humans, animals and aquatic life. To protect the environment and

lifestyles from health risks, the concentration of pharmaceutical compounds in medical wastewater entering drinking water sources should be regularly monitored. This article highlights the toxicity, health risks, and environmental risk assessments associated with pharmaceutical contaminants.

Regarding environmental risk assessment, include the environment in the risk-benefit analysis of pharmaceutical products for human use, improve risk management capabilities, (iii) collect data on existing pharmaceutical products, and improve environmental availability risk These assessments represent some important next steps. The biological effects to environmental exposures promise interesting results, although very few studies have been conducted on wild animals or caged organisms, such as in the wild or in ecologically significant environments. This may be due to the lack of analytical method protocols as well as the variety of pharmaceutical structural features that are not easy to handle but need to be taken into account.

Demographic, epidemiological and lifestyle changes, such as the aging of the population, the increase in chronic diseases, the availability of cheap generic treatments and easy access to a large number of over-the-counter medications, have become key factors in the growth of the pharmaceutical industry. The global increase in drug consumption has led to greater international awareness of the problem of unused pharmaceuticals (UPs) in households and the harmful environmental and health consequences of their improper disposal. Drugs in the environment are challenging because they are designed to interact with a living system and produce a pharmacological response at low doses, making them dangerous to the environment even at low concentrations. Secondly, drugs are designed to be stable in reaching and interacting with their target molecules, meaning that they degrade very slowly or that their continued use results in a constant, slower release into the environment, that is, as quickly like decomposition. In addition, conventional wastewater treatment plants are not designed to completely remove pharmaceuticals from wastewater.

Pharmaceutical products enter the environment through two main routes: excretion and insufficient elimination. In both cases, pharmaceuticals end up in sewage treatment plants, which are generally not designed to remove these pollutants from wastewater. Drugs have been found mainly in surface water, but also in groundwater, soil, manure and even drinking water. The presence of drugs in freshwater and terrestrial ecosystems can lead to the release of drugs into wildlife with the possibility of bioaccumulation. People are then exposed to drugs through drinking water and their residues in crops, fish, dairy products and meat. The effects of pharmaceuticals entering aquatic environments are of increasing concern, with impacts ranging from molecular changes to population-level effects.

The environment is everything that surrounds us: the air we breathe, the water we drink, and the land on which all living creatures live, the plants we use for food thrive. Development is what we do with these resources to improve lives. Our actions to make our lives more comfortable change the environment. One of the achievements of the United Nations in the field of environmental protection is the Kyoto Resolution on the Climate Change Convention (1997). In 2004, it passed into law, requiring countries to reduce emissions of dangerous greenhouse gases by 5.2% by 2012. The United Nations Convention on Biological Diversity (1992) obliges states to preserve the rich diversity of plants and animals necessary for human existence.

Environmental pollution leads to the increase of toxic substances in the human body and its environment - air, water, soil, animal and plant world - beyond the permissible norm, which is followed by a sharp increase in various chronic diseases. The interaction between the organism

and the environment takes place in two main directions. One of them refers to those biochemical changes in human organisms that are caused by the demands of environmental conditions or arise in the process of human impact on the environment. It is necessary to specify the impact processes of men, women, children and entire groups. The environment is that part of living and non-living nature that surrounds organisms and directly or indirectly affects their existence, development and reproduction.

Pharmaceutical and personal care products (PPCP) in the environment are a hot topic. Veterinary antibiotics, prescription drugs and cosmetic products are discarded from a variety of sources and regularly enter the environment, where they occur in small quantities in wastewater, surface and ground water, silt-laden agricultural soils, aquatic and terrestrial biota, and wet drinks Water. The public should become aware of this and is calling on the scientific and regulatory community to assess the potential risks to human health and the environment and take appropriate action if necessar.

Chemical pollutants are known to have specific effects on organisms, for example: Organotin compounds (used in anti-fouling paints on ships) affect marine life. However, there is another very diverse group of chemical compounds that can be harmful but have received relatively little attention as potential environmental pollutants. These include drugs, including drugs for humans and animals, as well as illegal (recreational) drugs.

Thousands of tons of pharmacologically active substances are used worldwide every year, but surprisingly little is known about the fate of most drugs after their intended use. Most of the administered dose is excreted unchanged from the body, and metabolites can be converted back into the active ingredient by bacteria. In addition, the public often throws unused medicines down the drain. Based on published prevalence data, it is likely that a significant portion of municipal wastewater is contaminated with narcotic compounds that vary only in the type and content of substances present.

Modern research has shown that many drugs are not completely eliminated from the body in wastewater treatment plants. The presence of drugs in surface systems, soil and even marine systems has been confirmed in concentrations ranging from high ng/liter to low mg/liter, which are similar to the concentrations of some pesticides. Pharmaceutical compounds discarded in household waste can end up in landfills and pose a risk to surface and ground water. Additionally, unlike more regulated contaminants, which often have a longer half-life in the environment, pharmaceuticals can become pseudopersistent due to prolonged exposure to wastewater, with unknown consequences for aquatic organisms that may be continuously exposed.

The potential consequences of the presence of pharmaceuticals in aquatic systems are unknown and have therefore received increasing attention as potential pollutants in recent years. The fact that an industrial chemical can end up in the environment is not surprising in itself. What's interesting about drug contamination is that it does not primarily arise from manufacturing, but rather from the widespread and ongoing use, isolation, and improper disposal of drugs for human and veterinary use.

Pharmaceuticals are potentially ubiquitous pollutants as they are present in all human environments. There is currently little evidence that pharmaceuticals are present in the environment in sufficient quantities to cause significant harm, although their use is expected to increase as the Human Genome Project is completed and the population ages. Drugs and their metabolites are increasingly being found in water bodies in areas adjacent to anthropogenic activities.

The biggest concern at the moment is that antibiotics in wastewater treatment plants may lead to increased resistance of natural bacterial populations. There are many isolates of microorganisms resistant to antibiotics in the environment, and although the issue remains controversial, the significant increase in the number of bacterial strains resistant to multiple antibiotics is often attributed to the misuse of antibiotics and the increase in their discharge into wastewater. Three known mechanisms of gene transfer (conjugation, transduction, and transformation) are thought to occur in aquatic environments; As a result, streams and rivers can become a source and reservoir of resistant genes, as well as a means of their dissemination. In addition, some non-target organisms (eg cyanobacteria) may be exposed to antibiotics, which may have indirect negative effects on the aquatic food.

The problem is further complicated by the fact that exposure to only one drug or toxic substance at a time is likely to be a rare event. Laboratory studies have shown that mixtures of just a few compounds have effects on ecosystems, but it is unknown what happens in the wider environment. Most organisms are constantly exposed to various substances, the concentrations of which vary little in time and space. Therefore, the limits of your tolerance depend on the duration of exposure to chemical and non-chemical stressors, many of which have the same mechanism of action and whose effects can result in additive effects. Thus, risk estimates that ignore possible cumulative drug effects will almost certainly lead to significant underestimation of risk.

Increasing demand for global water sources will likely lead to increased indirect and direct water reuse in the future. Drinking water is a direct route to the human body, including drugs and other contaminants that may be present there. Advanced water treatment technologies such as granular activated carbon (GAC) and reverse osmosis (RO) can remove drugs from drinking water until they are invisible, but these processes are not widely used. Due to the lack of appropriate technology and the need for significant economic investment, municipal wastewater is never treated in this way. In addition, large-scale monitoring programs to test these compounds would be extremely expensive and time-consuming due to the large number of different compounds and the diversity of their properties and effects.

Given that the extent and consequences of the presence of drugs in aquatic environments is largely unknown, more research is needed before a clear picture of the true nature and importance of the problem can be formed. Therefore, it would be unwise to claim that these compounds have significant environmental impacts until convincing evidence is available. To this end, future emphasis should be on adequate and sufficient scientific knowledge to determine occurrence, exposure, sensitivity and consequences in order to make informed decisions regarding human health and the environment.

When evaluating drugs, benefits to human health must take precedence over potential harm to the environment. Therefore, it may be beneficial to focus on reducing or eliminating problems at their source by developing clearer drug labeling and more effective guidelines for the disposal of pharmaceutical compounds by patients and healthcare professionals. The potential benefit of this approach would be improved consumer health (by minimizing the consumption of active substances) as well as reduced healthcare costs. Given the enormous importance of the pharmaceutical industry to both human health and the economy, any increased control could have serious economic and social consequences. If pharmaceuticals turn out to be problematic contaminants, collaboration between health professionals and environmentalists will be mutually beneficial, as much research remains to be done before the problem can be fully understood.

The industrial agriculture, municipal wastewater treatment, and the introduction of municipal sewage sludge (biosolids) as major sources of pharmaceuticals and personal care products in the environment. To compensate for this, indicators of veterinary antibiotic use are provided by both the agricultural industry and interested scientists. Personal care products are divided into fragrances and musks, cleansers and disinfectants.

Chemicals play an important role in healthcare as they can be used as disinfectants, cleaning agents, laboratory reagents, sterilants, pesticides, pharmaceuticals, and in medical devices and equipment. They also offer great animal welfare benefits. However, there is growing awareness and concern about the consequences of mishandling drugs and chemicals on human health and the environment.

Pharmaceuticals are also biologically active substances specifically designed to provide pharmacological effects on living organisms. They affect the health of wildlife and ecosystems if not managed in an environmentally sound manner.

Active pharmaceutical ingredients (APIs) are the biologically active components of a drug. These APIs are sold to pharmaceutical companies that manufacture end products for patients around the world. More than 5,000 active pharmaceutical ingredients are used in prescription, over-the-counter and veterinary products worldwide.From a chemical and waste management perspective, environmental and health issues in this sector are mainly related to the release of pharmaceuticals into the environment: Waste ends up in rivers, lakes and underground aquifers. In addition, when used in livestock production and when manure is used as fertilizer, veterinary drugs end up in the soil and environment. This leads to soil contamination and biomagnification due to leaching of drugs into food crops.

Sources of drug release into the environment include direct emissions from drug manufacturing, patient and animal feces, aquatic agriculture, and disposal of unused or expired drugs. Medicines designed to degrade slowly, or even non-degradate to resist chemical breakdown as they pass through the human or animal body, pose a particular risk if ingested, stored, or distributed into the environment. When released into the environment, the biological activity of persistent pharmaceutical pollutants in the environment can have direct negative effects on non-target organisms such as wildlife and have long-term impacts on the health and sustainability of ecosystems. The latter occurs through population-level reproductive effects that persist into future generations of non-target organisms. Pharmaceutical contaminants that are persistent in the environment are frequently and increasingly used in consumer products. However, significant gaps remain in knowledge about the environmental and health impacts of these pollutants [36].

Some pharmaceuticals have been found in low concentrations in drinking water, which is a warning sign that the current handling of pharmaceuticals may lead to health and environmental problems in the future.

Access to healthy water is a prerequisite for good health. Since society’s use of chemicals, including pharmaceuticals, is continuously growing, the risk is also increasing that these chemicals will return to us in our food and water supply through nature’s ecocycle.

There are little knowledge of the long term effects that continuously supplied trace quantities of pharmaceuticals and other chemicals could have on our development, our ability to resist disease and wellness in general. Therefore caution is advisable. The pharmaceuticals in nature can cause health problems. According to the precautionary principle, measures can be taken if there is reason to believe that a product or a method of production involves unacceptable risks to the

health of human beings, animals, plants and the environment – even if there is no definitive scientific proof of such an effect [15].

Drug residues are found in various environmental components around the world, and there is growing concern about the harm they may cause to human health and the environment. In nature, drug residues were found in urban wastewater, rivers and lakes. Effective measures must be taken to prevent further contamination of the environment by drugs. First of all, it is necessary to create a system for collecting drug waste from the population. Undoubtedly, drugs enter the environment during the production process through wastewater from pharmaceutical plants, municipal wastewater through natural human excretion, wastewater and manure from the use of veterinary drugs and as a result of improper handling of drug waste [2].

The review defines each of these sources and steps that can be taken to reduce drugs' environmental impacts. In the European Union, since 2004, the obligation to organize a system for collecting drug waste from the population has been established. For the successful operation of such a system, information work with the population about how drugs affect the environment and how to properly dispose of them is important. Residents of all European countries can bring drug waste to a pharmacy or hazardous waste collection point. However, in some countries there is a lack of widespread awareness-raising, which leads to inefficient collection systems and most waste ends up in the trash or drained into sewers. In some countries, drug waste generated by medical and pharmaceutical organizations is neutralized in pharmacies, clinics, hospitals and manufacturers. At the same time, pharmacies and hospitals have the right to transfer expired medicines to the manufacturer [28].

In most countries where the system operates successfully, the costs of collecting and neutralizing drug waste are shared by pharmaceutical companies, drug manufacturers and local authorities. The main problem is the very existence of unused drugs. So, generally many patients buy more medicines than they need. The best way to reduce their number is seen in optimizing the practice of prescribing drugs, so that only the necessary amount of drugs is prescribed, giving preference to more environmentally friendly ones, as well as improving information interaction between doctors and patients. The pharmaceutical industry must also provide for the production of drug packaging adapted to various treatment regimens [13,22].

Every participant in the drug supply chain, from the pharmaceutical industry to the patient, plays an important role in reducing the environmental impact of pharmaceutical activities. The International Pharmaceutical Federation has highlighted the different roles that each person plays in the pharmaceutical supply chain to minimize the environmental impact of pharmaceutical products. The pharmaceutical industry plays an important role in the environmental impact of pharmaceutical products.

Educating pharmaceutical personnel and the public is an important aspect of helping to create a healthy environment and reduce activities that contribute to climate change. The implementation of green practices in the pharmaceutical sector is already included in the curricula of EU Countries countries universities. Pedagogical input helps to recognize the importance of such practice early in professional development.

Consumer education is also important as it plays an important role in reducing the amount of drugs in the environment. Consumers should be discouraged from storing medications to avoid wasting them when not in use. They should also be taught how to properly store and dispose of unused and expired medications that may end up down the drain [19].

The world's population is aging, which will lead to an increase in drug use. Various measures need to be taken to minimize the release of active pharmaceutical ingredients into the environment and reduce the carbon footprint of the pharmaceutical sector. Small contributions from many people can synergistically have a positive impact on the environment.

There are several sources of release of active pharmaceutical ingredients (APIs) into the environment. The main ones are: wastewater from cities, hospitals, pharmaceutical plants and landfills. The vast majority of the active pharmaceutical ingredients (API) of drugs taken orally is excreted in the urine of animals and humans. Some pollution comes from the use of veterinary drugs in livestock and fish farming. However, it is not yet possible to evaluate this contribution, because there is no control and accessible reporting of the use of veterinary drugs. The most vulnerable to the effects of active pharmaceutical ingredients (APIs) are amphibians, fish, some animals and birds.

The main source of drugs entering the environment is wastewater from pharmaceutical enterprises (from product washing, waste acidic and alkaline wastewater, wastewater from cleaning equipment and production facilities, etc.) and liquid waste that is allowed to be discharged into the sewer system. Currently monitored parameters in pharmaceutical wastewater are biological oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids, ammonia and ammonium ions, phosphates, chlorides, sulfates, petroleum products, iron, anionic surfactants and pH value. This list may include other chemical compounds, including active pharmaceutical ingredients (APIs), but their content is not regulated or controlled at this time. Currently, the countries of the European Union have prioritized the most environmentally stable active pharmaceutical ingredients (APIs) - diclofenac, hormonal drugs of the estrogen group (ethinyl estradiol), antibiotics of the macrolide class (erythromycin, clarithromycin, azithromycin) and etc [14, 29].

Assessment of environmental risks of both original and generic drugs. In European countries, for some drugs such an assessment is carried out, as well as an assessment of the level of resistance, bioaccumulation potential and toxicity. Currently, providing information about environmental hazards when registering drugs in the countries of the European Union is voluntary. In some countries has been created an online database of drugs, which describes their environmental risks and expanding the responsibility of drug manufacturers throughout the entire cycle from production to neutralization.

After drugs enter the body, they are destroyed, neutralized, metabolized and converted into new compounds. However, some of them are excreted unchanged or in the form of metabolites, ending up in the sewer system. Municipal wastewater treatment does not involve removal of APIs. Some of them are concentrated in sewage sludge from treatment plants, which is stored in filtration fields, while the rest ends up in rivers. The Challenges in this matter are also hospitals, where there is a high level of drug consumption. In the absence of an established system for collecting drug waste generated by the population, it either ends up in the sewer or is thrown into the trash. From landfills, drugs can be carried by animals, birds, or migrate into the soil and groundwater.

To raise animals and fish on an industrial scale, hormonal drugs, antibiotics and other drugs can be used, which can be excreted from the animal’s body naturally. Hormones can be used in veterinary medicine and animal husbandry to stimulate the development and growth of animals, improve fertility, digestibility of feed, accelerate puberty, regulate the timing of pregnancy, etc. According to studies in some countries, antibiotic residues were found in manure, in plants grown in fields fertilized with manure, in soils, and in small quantities in groundwater. The use of

veterinary drugs in should be regulated by veterinary and sanitary rules for the use, sale and storage of veterinary drugs [36].

European experience in collecting hazardous waste from the population shows that waste collection is carried out effectively if such collection is organized by a company specializing in the collection of hazardous waste. The same practice works in our country. In the EU, pharmacies are considered only as an area for the installation of appropriate containers and containers for collecting hazardous waste from the population. The containers themselves are installed by specialized companies interested in collecting hazardous waste. It is inappropriate to oblige pharmacies, healthcare institutions or other trade organizations to organize the collection of drug waste from the population [3].

Pharmacies and medical institutions are places where consumers can obtain the most complete information about drug waste, since these organizations employ personnel with the relevant knowledge. In the country, many pharmacies themselves are located on the territory of various retail facilities, so there may not be places in pharmacies to install a special container for collecting drug waste. When determining places for collecting waste from the population, it is necessary to comply with the criterion of step-by-step accessibility of such places from the places of residence of citizens. In this regard, retail facilities should also be considered as places for installing special containers for collecting drug waste. The decision to organize collection points for drug waste from the population in pharmacies should be made by Health care institutions in every countries.

In the vast majority of countries, all drug waste collected from the population is sent for incineration. At the same time, pharmacies, for example, in Sweden and Lithuania, can only accept medications without packaging, because it belongs to secondary resources and must be sent for recycling. Low-temperature, medium-temperature (up to 850°C) and high-temperature (at least 1200°C) combustion is used for waste. Hazardous waste, which includes most drugs, cannot be burned at low temperatures. At medium temperatures it is possible in limited quantities and in the absence of high-temperature combustion technology. Cytostatic drugs for cancer treatment can only be burned at temperatures above 1200°C, but the generation of such waste in household use is unlikely. Currently, there is a steady trend towards a decrease in the number of thermal installations for the neutralization of pharmaceutical waste. Incineration of waste is contrary to three principles of international law: precaution, prevention and limitation of transboundary effects. In Europe, resistance to waste incineration manifests itself in the form of the introduction of alternative technologies. Any combustion method requires monitoring of pollutant emissions and the resulting ash. An alternative to conventional methods of thermal treatment of pharmaceutical waste are technologies that provide for the preliminary decomposition of the organic component of the waste in an oxygen-free atmosphere (pyrolysis). When carrying out microwave pyrolysis with heating using microwave waves, toxic gaseous products are converted into less dangerous ones [11,25,36].

In countries where there are no incineration plants or their use is limited geographically, drug waste is disposed of. The main disadvantage of this method is the high probability of soil and groundwater contamination. According recommendations of the World Health Organization, only non-hazardous drug waste (vitamins, herbal-based drugs, biodegradable drugs) can be sent to the landfill. Hazardous waste, including cytotoxic drugs, must be pre-sealed, i.e. placed in a metal capsule and filled with plaster and cement [22].

Some drugs pass through the human body, exit unchanged or in the form of metabolites, while maintaining their stability in wastewater and the environment for a long time. In addition, improper disposal of medications and disposing of them down the drain increases the concentration of hazardous APIs in water. Wastewater from pharmaceutical plants is also discharged into the city sewer system after local treatment. The active pharmaceutical ingredients are present in municipal wastewater above detection limits. Traditional mechanical and biological wastewater cleaning methods are unable to neutralize the active pharmaceutical ingredients in water. The issue of purification efficiency, the formation of drug metabolites and their behavior, the interaction of some drugs with others is still under study. Among the methods being developed and implemented in the countries of the European Union one can highlight physicochemical methods, aerobic/anaerobic biological cleaning in membrane bioreactors. Effective technologies for purifying wastewater from medicinal components include oxidation with ozone or hydrogen peroxide and the use of carbon filters. However, such technologies are currently expensive to implement and use. At the same time, more and more attention is being paid to preventing the entry of drugs into wastewater, including during production. The main problem is the very existence of unused drugs [12,16].

One of the most obvious sources of uncontrolled release of drugs into the environment may be wastewater and atmospheric emissions from enterprises producing finished drugs and pharmaceutical substances. The environmental safety of such production should be usually regulated by law. However, accidental releases of drugs into the environment or those that violate existing norms and rules that occur in industry, are nevertheless not systematic. Moreover, there is a general trend towards a reduction in the environmental load on the part of pharmaceutical production, primarily in developed countries of the world, due to a consistent increase in the technological effectiveness and organization of the production process, the introduction of increasing standards of quality and environmental safety, and control by authorized government agencies. It is also necessary to take into account that pharmaceutical production is localized geographically and if an accident occurs at the enterprise or there are violations of environmental legislation, then such emissions are exclusively local in nature and pose a danger only to specific regions. Other sources of drugs that are practically uncontrollable and are formed mainly by people who use drugs for medical purposes, as well as in animals, pose a great danger to the environment.

For the most part, drugs are xenobiotics, and many of them are metabolized in the human body. The task of metabolism, as a rule, is to impart polarity to lipophilic substances in order to facilitate subsequent excretion. Metabolic parameters are individual for each substance and depend on gender, race, age and physiological state of the human body. There are two phases of metabolism, the numbering of which does not necessarily reflect their actual sequence. In the first phase of metabolism, a redox or hydrolytic transformation of the molecule occurs, increasing its polarity. In the second phase of metabolism, the xenobiotic is conjugated with endogenous molecules that improve the transport properties of the metabolite. During metabolism, inactivation of the active substance often occurs, which can lead to its inability to further exert a biological effect. However, many drugs are either not subject to metabolism or are subject to it only to some extent. And this leads to the fact that the active molecule of the active substance is excreted unchanged either in the urine or in the feces and is capable of further exerting a biological effect. In addition, as research results show, glucuronide transport complexes of active molecules of some drugs, formed during the second phase of metabolism, are easily destroyed during sewage

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treatment processes and release unchanged active substance into the aqueous phase or sewer sludge. We can also mention the route of release of drugs into aquatic environments due to their transport through the skin or leaching of drugs for external use during swimming in open waters. But from the point of view of quantitative indicators, this path is of little significance [34].

During metabolism, inactivation of the active substance often occurs, which can lead to its inability to further exert a biological effect. However, many drugs are either not metabolized or only to some extent. And this leads to the fact that the active molecule of the active substance is excreted unchanged either in the urine or in the feces and is capable of further exerting a biological effect. In addition, as research results show, glucuronide transport complexes of active molecules of some drugs, formed during the second phase of metabolism, are easily destroyed during sewage treatment processes and release unchanged active substance into the aqueous phase or into sewage sludge.

We can also mention the route of release of drugs into aquatic environments due to their transport through the skin or leaching of drugs for external use during swimming in open waters. But from the point of view of quantitative indicators, this path is of little significance.

The increasing the availability of drugs, for the general development of health care systems, the consumption of drugs for medical purposes increases and, as a result, their content in the environment increases. This process is poorly managed and poses a potential danger to human health and other biological organisms. Contamination of the environment with drug residues has a global character and is actively studied in the developed countries of the world. However, this problem remains insufficiently worldwide [25,28].

The best ways to reduce their number are to optimize the practice of prescribing drugs, so that only the required amount of drugs is prescribed, giving preference to the least environmentally hazardous ones, as well as improving information interaction between doctors and patients. The pharmaceutical industry must also consider producing drug package sizes tailored to different treatment regimens. One key measure is to encourage the pharmaceutical industry to develop harmless drugs that quickly break down into harmless compounds in the environment. For example, currently in European countries, when registering a new drug, environmental characteristics such as ecotoxicity, biodegradability are indicated.

The comparing drugs that are equally safe and well suited for treating a patient, it is recommended to take into account, in addition to their pharmaceutical properties, their environmental impact. To do this, recommend using environmental drug classifiers.

Large quantities of nonsteroidal anti-inflammatory drugs, including acetaminophen, acetylsalicylic acid, ibuprofen, diclofenac, and naproxen, are significant contributors to environmental pollution, especially because they have been detected in nanogram and microgram quantities in soil, wastewater, surface water, and drinking water, groundwater. These drugs have chronic ecotoxic effects because their stable chemical structure makes them very resistant to biological changes in the environment. It is now known that they primarily damage the organs of invertebrate and vertebrate animals, cause oxidative stress and interfere with the activity of detoxification enzymes. These drugs may also cause cardiovascular effects, hepatotoxicity and affect oocyte maturation through unknown mechanisms [5,12,28].

Beta blockers are very long-acting drugs that are toxic to the environment. Although there is no data on their adsorption in the environment, these drugs are known to have moderately high water solubility and are present in surface waters at µg/L concentrations. These compounds are extremely resistant to hydrolysis, bioavailable and mobile in the environment. Therefore, its

accumulation in the environment can have unexpected consequences for many living organisms. According to European Union Directive, metoprolol and propranolol are compounds harmful to aquatic organisms. This is evidenced by the results of tests with green algae.

Anticancer drugs interfere with cell growth and division, and when released into the environment, they disrupt the ecosystem, impair fertility and cause significant genetic changes in living organisms. Anticancer drugs are prescribed in smaller quantities, but their effects are destructive even at concentrations in the ng/L range and include mutagenic, carcinogenic and teratogenic effects on aquatic life. Cytostatics are frequently found in the pharmaceutical industry and hospital wastewater due to improper use and disposal. The detection rate of anti-cancer drugs in oncological hospitals wastewater is big amount and cisplatin is considered one of the most dangerous drugs. The presence of cisplatin in water, even at concentrations of ng/l, can have a toxic effect on aquatic flora and fauna [28].

Environmental pollution caused by pharmaceuticals is a complex public health problem that is scientifically controversial and affects multiple stakeholders with different interests and at different organizational levels: governments, non-governmental organizations, academic institutions, manufacturers, industries and families.

In keeping with the idea of protecting the environment, the pharmaceutical industry must develop promising concepts to minimize secretions while still ensuring sufficient pharmacologically effective concentrations in the patient. The potential of developing new pharmaceutical products that are more biodegradable and less harmful to the environment. There are already some examples of the development of greener pharmaceuticals, such as glufosfamide and green drug delivery systems. Scientists are currently developing an effective and environmentally friendly version of the antibiotic ciprofloxacin, a very stable drug. Using computer modeling, an existing active ingredient is analyzed and theoretically modified to improve biodegradability and reduce toxicological effects. The most promising candidates have been synthesized and tested in vitro [37].

Limited consumer awareness of best recycling practices weakens their influence on recycling practices in many countries. Information campaigns can increase awareness and use of environmentally friendly pharmaceutical waste disposal methods in households. A good example is the Meds disposal campaign, a European initiative jointly coordinated by several European health and supply chain organizations and supported by media campaigns in different languages. The aim of the initiative was to combat the negative impact of mishandling of pharmaceutical products on the environment, raising consumer awareness of correct disposal routes and collection systems in a number of European countries.

In addition, greater awareness and behavior change can be achieved through specific recycling instructions on the product's outer packaging or information leaflet, which are mandatory in EU countries. In addition, eco-labels that reflect the environmental impact of various pharmaceutical products can influence consumer choice and awareness, as well as help physicians make prescribing decisions. Instructions on how to properly dispose of medications should also accompany medication dispensing at regular intervals. Pharmacists can play a key role in educating their patients about proper medication disposal [18,29].

Human drugs, hormones, antibiotics, analgesics, antidepressants and anticancer drugs indicate environmental risks. When it comes to veterinary products, hormones, antibiotics and parasiticides are often considered environmentally sensitive. These results are consistent with findings from the open scientific literature on approaches to environmental drug prioritization.

Promising approaches such as environmental risk assessment of pharmaceuticals play an important role in minimizing the problems caused by pharmaceuticals in the environment. However, the regulatory framework for environmental risk assessment can be improved by integrating the environment into the risk-benefit analysis of drugs for human use, improving risk management capabilities, collecting data on existing drugs, and improving the availability of data for environmental risk assessment. In addition, more general and integrative stages of regulation, legislation and research have been developed and presented in this article. To minimize the amount of pharmaceuticals in the environment, they should strive to improve existing pharmaceutical legislation, prioritize pharmaceuticals present in the environment, and improve the availability and collection of pharmaceutical data.

Over the past three decades, the presence of pharmaceuticals in the environment has received increasing attention. Medicines are released into the environment and can have harmful effects [36,48,67]. It is clear that priority must be given to environmentally relevant pharmaceutical substances. Existing pharmaceutical substances for which environmental data are lacking, as well as substances being considered for monitoring campaigns, need to be given priority attention to identify and minimize their environmental risk. According to the World Health Organization, concentrations of pharmaceuticals in water systems are expected to increase as the use of pharmaceuticals is expected to increase as they become more accessible to a growing world population. To be proactive, it is necessary to identify and prioritize the most important substances for the environment, which has become a challenge in recent years. Depending on the chemical properties of the substances, different approaches have been proposed. Most often, a combination of exposure and exposure data is used to prioritize environmentally significant chemicals. Several approaches have proposed using toxicological data to predict adverse effects on aquatic organisms (comparisons of several, but not all, approaches are included). Most published approaches to prioritization indicate the high environmental potential of various drug classes. Human medicines are often a priority, with all attention paid to hormones, antibiotics, psychotropic, anti-inflammatory and cytostatic substances, as well as beta blockers. In addition to hormones, antibiotics and parasiticides have proven to be environmentally important in veterinary medicines [12,17,33].

The origin and possible effects of human and veterinary drugs on aquatic and terrestrial organisms are relatively new topics. However, in recent decades, a large number of studies have been published indicating the varied effects of drugs on organisms and the occurrence of drugs in different environmental areas on a global scale. It is now recognized that the environmental impact of pharmaceuticals is a global issue and not just a problem in developed countries. The general public, industry, research or regulatory authorities, do not want bioactive drugs to end up in the environment and therefore potentially in their drinking water. Therefore, the amount of pharmaceuticals in the environment needs to be minimized using all available strategies. Promising approaches such as ERA play an important role in minimizing problems before drugs enter the environment. These strategies need to be strengthened and adapted to minimize the amount of pharmaceuticals entering the environment.

Liquid waste of drugs classified as non-hazardous (syrups, herbal preparations, solutions based on salts, amino acids, lipids or glucose) can be poured into the sewer after diluting with water. It is necessary to prevent the discharge of large quantities of disinfectants into the sewer system, because they can affect the quality of biological wastewater treatment. Discharge of drugs that are persistent in the environment, capable of biological accumulation and have toxic properties into

the sewer system leads to environmental pollution with active pharmaceutical ingredients. According to studies conducted in many countries, existing wastewater treatment systems do not eliminate such pollution and drug residues are found in wastewater cleaning sludge, and to a greater extent in water after cleaning, which is discharged into natural watercourses.

Residues of many pharmaceutical products can be found in drinking water, plants and fruits, as well as in the tissues of fish and shellfish. Thus, people are exposed to these residues when they drink contaminated water and eat contaminated food. Pharmaceuticals in the environment can also influence the provision of important ecosystem services and have indirect effects on human health and well-being. Found the evidence that drug residues in drinking water and food affect human health, as well as the indirect effects of drugs on human health. Available evidence suggests that the risks of direct toxicity are low, but there are scenarios in which indirect effects are possible. Much remains to be done regarding the wider range of drugs and exposure pathways, and the links between the presence of drugs in the environment and the provision of ecosystem services [16,25].

The uncontrolled release drugs into the environment may be wastewater and atmospheric emissions from enterprises producing finished drugs and pharmaceutical substances. the environmental safety of such production is usually regulated by law. However, accidental releases of drugs into the environment or those that violate existing norms and regulations that occur in industry, are nevertheless not systematic. Moreover, there is a general trend towards a reduction in the environmental load on the part of pharmaceutical production, primarily in developed countries of the world, due to a consistent increase in the technological effectiveness and organization of the production process, the introduction of increasing quality standards and environmental safety, and control by authorized government bodies . It is also necessary to take into account that pharmaceutical production is localized geographically, and if an accident occurs at the enterprise or there are violations of environmental legislation, then such emissions are exclusively local in nature and pose a danger only to specific regions. For all the reasons listed above, such sources are not the subject of analysis in this review, although they contribute to environmental pollution. Other sources of drugs that are practically uncontrollable and are formed mainly by people who use drugs for medical purposes, as well as in animals, pose a great danger to the environment [14].

For the most part, drugs are xenobiotics, and many of them are metabolized in the human body. The task of metabolism is generally to impart polarity to lipophilic substances in order to facilitate subsequent excretion. Metabolic parameters are individual for each substance and depend on gender, race, age and the physiological state of the human body. There are two phases of metabolism, the numbering of which does not necessarily reflect their actual sequence. In the first phase of metabolism, a redox or hydrolytic transformation of the molecule occurs, increasing its polarity. In the second phase of metabolism, the xenobiotic is conjugated with endogenous molecules that improve the transport properties of the metabolite [22,29].

Pharmaceutical products are essential to human health, but they become an environmental problem when they enter the environment, which occurs when residues are excreted from the body after consumption or when unused pharmaceutical products are improperly disposed of. Although no method has been developed to detect all drugs entering an ecosystem, certain groups have been shown to have negative impacts on ecosystems, including increased mortality of aquatic species and changes in physiology, behavior, or reproduction. Particular attention is paid to these groups of drugs and their impact on the environment. In this review, the authors propose

measures to reduce the amount of unused pharmaceutical products in the environment, with a focus on prevention. Various policy measures are recommended throughout the life cycle, including source-oriented, user-oriented and waste management measures, to prevent the generation of household pharmaceutical waste and ensure environmentally sound disposal of household pharmaceutical waste. Preventive measures include rational drug consumption, prescribing more environmentally friendly drugs or developing safe and easily biodegradable drugs, better disease prevention, personalized medicines, better packaging sizes and markets for the redistribution of unsafe drugs. The next step is to prevent inevitable waste from entering the environment. Therefore, it is extremely important to collect and properly dispose of unused medicines. Finally, education of healthcare professionals and the public, as well as partnerships between environmental scientists and clinicians, are essential at all stages of the pharmaceutical life cycle. Reducing drug levels in the environment will benefit human life.

Conclusions

Drugs and their metabolites are increasingly being found in water bodies in areas adjacent to anthropogenic activities. Currently, pharmaceutical compounds are regularly released into the environment in extremely large quantities, and the current emission control system is unable to control untreated or partially treated pharmaceutical wastewater. The effects of drugs permeate and impact ecosystems, biota and humans. Adverse health effects on humans, aquatic animals and livestock should be investigated through careful toxicological and safety studies. Serious efforts are needed to reduce this problem, and appropriate regulations are needed to monitor and control it. Water quality guidelines in India should include analysis of the most commonly used pharmaceutical compounds in drinking water sources. In addition, pharmaceutical industrial wastewater treatment plants need to implement new corrective measures to prevent long-term environmental and health risks. Regarding environmental risk assessment, include the environment in the risk-benefit analysis of pharmaceutical products for human use, improve risk management capabilities, collect data on existing pharmaceutical products, and improve environmental availability risk These assessments represent some important next steps. The biological effects to environmental exposures promise interesting results, although very few studies have been conducted on wild animals or caged organisms, such as in the wild or in ecologically significant environments. This may be due to the lack of analytical method protocols as well as the variety of pharmaceutical structural features that are not easy to handle but need to be taken into account.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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О РИСКЕ РАЗВИТИЯ АНЕУПЛОДИИ ЭМБРИОНОВ В ЗАВИСИМОСТИ ОТ ПАТОЗООСПЕРМИИ МУЖЧИН В ПРОГРАММЕ ВСПОМОГАТЕЛЬНЫХ РЕПРОДУКТИВНЫХ ТЕХНОЛОГИЙ

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Вопрос мужского бесплодия с каждым днём приобретает все большую актуальность. Согласно различным статистическим источникам в настоящее время в структуре бесплодия мужской фактор составляет 50-60. Хотя всего пару десятков лет назад это цифра была всего 30. Рассматривая этиологические и патогенетические аспекты мужского бесплодия необходимо отметить ,что речь идет не только о количественном изменении числа и степени подвижности сперматозоидов ,но и о морфологических,генетических и функциональных нарушениях.Кроме всего у мужчин с различными видами патозооспермии (олигоспермия,астеноспермия,тератоспермия,азооспермия и сочетанные формы патологии)значительно увеличен риск анеуплодии сперматозооидов и следовательно анеуплодии эмбрионов даже в программах вспомогательных репродуктивных технологий.При изучении результатов экстра корпорального оплодотворения(ЭКО)у мужчин с различными формами патозооспермии были обнаружены показатели наступления беременности и более высокая частота репродуктивных потерь по сравнению с парами ,в которых у мужчин были нормальные показатели спермограмм.Только широкое внедрение в практику предимплатационной генетичеческой диагностики позволило проводить выбор генетически полноценных эмбрионов,что естественно приведет к увеличению частоты наступления беременности и рождении генетически здоровых детей в программах ВРТ.Проводя анамнез мировой литературы в плане мужского бесплодия важно отметить ,что до сих пор все еще остались открытыми вопросы относительно некоторых этиологических аспектов ьужского бесплодия,а также частоты и типов анеуплодии эмбрионов,получившихся от пар с наличием патооспермии у женщин в циклах ЭКО.Целью настоящего исследования явилась изучение частоты развития различных форм анеуплодии эмбрионов в зависимости от видов патозооспермии мужчин в программе ВРТ.

Материал и методы

Нами были обследованы 325 супружеских пар с мужским фактором бесплодия ,обратившихся в центральную клинику города Баку за период с 2008-го по 2020годы для экстракорпорального оплодотворения.Все пациенты были разделены на 3 группы.Группу А составили 110 супружеских пар с пазооспермией у мужчин ,которым было произведено экстракорпоральное оплодотворение с предимплатационной генетической диагностикой(ПГД).В группу В были включены 110 супружеских пар с патозооспермией,которым ЭКО проводилась без ПГД(пациенты не дали согласия на ПГД).Группу С составили 105 супружеских пар с нормальными показателями спермаграмм,которым роводилась ЭКО с ПГД по их собственному желанию.Все мужчины

имели нормальный кариотип.Женщины имели нормальные данные УЗИ, ГСГ, гормональных и инфекционных анализов,а также имели нормальный набор хромосом.
Контролируемая гиперстимуляция яичников проводилась по стандартному антогонист протоколу со 2-3 го дня менструального цикла препаратами рекомбинантного фолликулостимулирующего гормона в сочетании с препаратами человеческого менопаузального гормона.Ультразвуковой мониторинг роста фолликулов осуществляли трансвагинальным ультразвуковым исследованиям 4-5 раз в течении стимуляции.При достижении максимального фолликула 14-15 мм вводился препарат антогониста гонадотропин –ризинг гормона в дозе 0,25мг. Забор яйцеклеток проводили через 35-36 часов после введения тригера овуляции. Всем больным проводилась интрацитоплазматическая иньекция сперматозоидов (метод icsi). Оценка качества эмбрионов проводилась через 40-42 часа (2 сутки), 72-74 часа (3 сутки), 20 часов – 5 сутки после оплодотворения. Биопсия эмбрионов производилась на 3-й день после оплодотворения на стадии 6-10 бластомеров или бластоциды(использовался лазерный аппарат). Для выявления числовых и структурных хромосомных нарушений применялся метод FISH(флуоресцентная гибридизация in situ).В этом методе используются ДНК-зонды,которые представляют собой нуклеотидную последовательность ограниченного размера,комлементарную определенному участку ядерной ДНК.Зонд несет ,,метку,, ,то есть содержит нуклеотид,связаннй с флуороформом (молекулу,способную к флуоресценции). После процедуры гибридизации в случае образования гибридной молекулы ДНК-зонд и ДНК мишени,на исследуемом цитогенетическом препарате можно наблюдать свечение специфических последовательностей ДНК на хромосомах или в ядрах при помощи флуоресцентного микроскопа.
Предимплатационная генетическая диагностика проводилась по хромосомам 13, 15, 16, 17, 18, 21, 22 X,Y. Анеупродия определялась как наличие менее или более 2-х копий исследуемых аутосом или отсутствие одной половой хромосы.Эуплодия определялась как полный набор ,гаплоидия –как одинарный набор и полиплодия –как тройной и более набор исследуемых хромосом.Комплексной патологией считалось наличие более 2-х из выше указанных нарушений.Сочетанная патология определялась при выявлении трех и более хромосом с нормальным числом копий.На 4-й 5-й день проводился трансфер только нормальным ,т.е.эуплоидным эмбрионам .Беременность определялась по данным ХГЧ в крови на 13-15-й день после переноса эмбрионов и в дальнейшем по данным УЗИ при выявлении плодного яйца и сердцебиения эмбриона.

Статистическая обработка

Результаты собственных исследований

Возраст женщин ,включающих в исследования были 21-43 года,возраст мужчин 27-52 года.Пары с дисфункцией щитовидной железы ,сахарным диабетом ,аутоиммунными заболеваниями,раком,дисфункцией яичников,курением или зависимостью были исключены из исследования.

Таблица 1. Виды патозооспермии у исследуемых пациентов.

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Виды патозооспермии	Группа А n=110	Группа В n=110	P
Олигозооспермия	11	9	
Астенозооспермия	14	12	
Олигоастенозооспермия	16	21	
Тератозооспермия	32	29	
Олигоастенотератозооспермия	37	39	

Как видно из таблицы частота анеуплоидии чаще встречается в группе болыных с тератозооспермией. Это прослеживается и в основной ,и в контрольной группе.
Нами были изучен характер экстрагенитальной патологии у мужчин.Пациенты с дисфункцией щитовидной железы ,сахарным диабетом были исключены из исследования.

Таблица 2. Характер экстрагенитальной патологии у мужчин, включенных в исследования.

Характер экстрагенитальной патологии	Группа А n=110	Группа В n=110	Группа С n=105	P
Заболевания сердечно-сосудистой системы	11	8	5	
Заболевания мочевыделительной системы	28	30	25	
Заболевания опорно-двигательного аппарата	5	7	1	
Заболевания нервной системы	17	13	20	

Также нами были изучены инфекционный статус мужчин.

Таблица 3. Инфекционный статус исследуемых пациентов.

Виды инфекции	Группа А n=110	Группа В n=110	Группа С n=105	P
Уреаплазмоз	21	27	29	
Микоплазмоз	20	22	19	
Хламидиоз	15	9	17	
Гарднереллёз	27	22	24	
Трихомониаз	3	1	1	
Кандидоз	11	13	9	
Вирус папилломы человека	7	4	3	
Генитальный герпес	14	2	5	

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В результате проведённых работ нами были отобраны эмбрионы у исследуемых 215 пар (группа А и группа С), 880 эмбрионов в группе А и 890 эмбрионов в группе С. Интерпретация результатов FISH проводилась путем оценки хромосомных строений эмбрионов в отношении числовых аномалий в 9-ти хромосомах - 13, 15, 16, 17, 18, 21, 22, X, Y.

Таблица 4. Частота обнаруженных хромосомных аномалий в исследуемых группах.

Хромосомные числовые аномалии	**Группа А 880 эмбрионов**	**Группа С 890 эмбрионов**	**P**
Синдром Клайнфельтера (XXY)	5	1	
Синдром Шершевского-Тернера (X0)	7	3	
Синдром Дауна (Трисомия 21)	12	7	
Синдром Патау (Трисомия 13)	6	5	
Синдром Патау (Моносомия 13)	3	3	
Синдром Эдвардса (Трисомия 18)	8	3	
Синдром Эдвардса (Моносомия 18)	5	1	
(Трисомия 15)	3	-	
(Моносомия 15)	4	1	
(Трисомия 16)	6	2	
(Моносомия 16)	4	1	
(Трисомия 17)	3	1	
(Моносомия 17)	3	-	
Синдром Джейкобса (Трисомия XYY)	4	2	
(Трисомия 22)	8	3	
(Моносомия 22)	7	3	
Комплекс (Трисомия)	9	4	
Комплекс Анеуплодия	12	6	
Комплекс Моносомия	11	6	

В ходе исследования нами также было изучено влияние возраста мужчин на частоту патологии эмбрионов, что показало прямую зависимость между ними.

Таблица 5. Зависимость частоты патологии эмбрионов от возраста мужчин в исследуемых группах.

,	**Частота патологии эмбрионов**			
	Группа А n=110	Группа С n=105	Группа А 120 эмбрион	Группа С 52 эмбрион
24-30 лет	30	29	12	5

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30-35 лет	28	27	25	9
35-40 лет	32	31	38	15
Старше 40 лет	20	18	45	23

Таблица 6. Результаты ЭКО с ПГД мужчин в исследуемых группах.

Результаты ЭКО	**Группа А n=110**	**Группа В n=110**	**Группа С n=105**	**P**
Частота наступления беременности	52	31	59	
Частота отрицательного результата ЭКО	58	79	46	
Рождение здорового ребёнка	39	11	52	
Прерывание беременности (выкидыши, неразвивающиеся беременности)	13	20	7	

Обсуждение

Появление ИКСИ в сочетании с ПГД произвело революцию в лечении мужчин с сильно нарушенными параметрами спермы и повысило их шансы на достижение нормальной доношенной беременности. Это связано с тем, что ИКСИ значительно снижает требования к качеству спермы, подвижности и способности к оплодотворению, в то время как ПГД позволяет анализировать хромосомный набор эмбрионов бесплодных мужчин, позволяя переносить только хромосомно нормальные эмбрионы, что повышает вероятность успеха и устраняет потенциальные риски использования субоптимальных сперм для оплодотворения.

За последние два десятилетия методологии, используемые для анализа доимплантационных эмбрионов человека, претерпели революционные изменения. В некоторых из первых исследований, посвященных анализу доимплантационных эмбрионов человека, использовался анализ кариотипа, который, хотя и позволяет анализировать все хромосомы, требует делящихся клеток на стадии метафазы. Это серьезный недостаток, поскольку только 24–36% эмбрионов, проанализированных с помощью кариотипирования, продуцируют метафазы достаточного качества для точного анализа хромосом. Другие недостатки включают то, что он способен анализировать только развивающиеся клетки, потому что арестованные клетки не производят метафазы и не могут быть проанализированы, и трудности с идентификацией отдельных хромосом, поскольку трудно получить оптимальное распределение хромосом и возможную потерю хромосом во время фиксации ядер.

Однако кариотипирование больше не используется для анализа хромосомных анеуплоидий в преимплантационных эмбрионах человека, а метод, который наиболее часто используется для анализа хромосомных анеуплоидий у человеческих преимплантационных эмбрионов - это флуоресцентная гибридизация in situ (FISH). FISH обычно предпочитают, потому что он дает информацию о цитогенном статусе каждой клетки и может

применяться к отдельным клеткам, позволяя анализировать количество хромосом как в метафазных, так и в интерфазных ядрах.

В настоящем исследовании мы обнаружили, что более низкие концентрации сперматозоидов, по-видимому, сопровождаются более высокими показателями патозооспермии. Это согласуется с данными Levron et al (2013), которые документально подтвердили, что тяжелая патозооспермия связана с более низкими концентрациями сперматозоидов вместе с олигоспермией. Более низкие концентрации сперматозоидов у пациентов с тяжелой патозооспермией были хорошо документированы результатами анализа различных стадий гаметогенеза, которые предположили, что контрольная точка пахитена I вызывает мейотическую остановку аномальных клеток, которые более распространены у пациентов с тяжелой патозооспермией, ведущей к олигоспермии или азооспермии. Однако другие мейотические исследования показали, что небольшое количество домейотических аномальных клеток может ускользать от контрольной точки пахитены, достигать мейоза и производить хромосомно аномальные сперматозоиды, процент которых прямо пропорционален уровню патозооспермии.

Была выдвинута гипотеза, что разные типы эмбриональных аномалий человека могут иметь мейотическое или митотическое происхождение. Мейотические аномалии до оплодотворения являются наиболее вероятным механизмом анеуплоидии, который универсален для всех клеток эмбриона. Это может происходить из-за нерасхождения целых хромосом во время мейоза I или II или преждевременного деления хромосомы на две сестринские хроматиды во время мейоза I с последующим их случайным разделением. Митотические нарушения могут возникать из-за отсутствия расхождения, эндоредупликации или запаздывания анафазы, которые чаще всего возникают во время первых трех делений после оплодотворения, которые контролируются центриолями сперматозоидов. Следовательно, целостность сперматозоидов явно необходима для нормального митотического деления и раннего развития эмбриона. Анеуплоидии могут возникать по разным механизмам, таким как преждевременное деление клеток, слияние клеток и разрыв хромосом. Было продемонстрировано, что трисомии и моносомии в основном имеют мейотическое происхождение. Половые хромосомы особенно подвержены мейотическому недифференцированию; который считается механизмом анеуплоидии сперматозоидов из-за их уникальной структуры, которая обеспечивает лишь несколько сайтов рекомбинации. Обычно аномальные клетки, страдающие от нерасхождения половых хромосом во время мейоза I или II, подвергаются полному или частичному аресту мейоза с помощью механизма контрольных точек пахитена. Иногда мутации одного или нескольких генов, участвующих в этих механизмах репарации ДНК, производят хромосомные аномальные клетки, которые избегают контрольной точки пахитены и приводят к образованию сперматозоидов с дисомией половых хромосом.

В настоящем исследовании общее количество обнаруженных хромосомных аномалий было значительно выше у эмбрионов группы Б (34,09%), чем у эмбрионов группы А(28,57%) Аномалия возникает преимущественно также из-за митотических ошибок в первых нескольких делениях эмбриона после оплодотворения из-за аномального количества мужских центриолей или субоптимальной функции центриолей, которые значительно увеличиваются пропорционально уровню патозооспермии. В таком случае первое митотическое веретено не сформируется должным образом, что приведет к нарушению цитокинеза, создавая две хромосомно аномальные клетки. Митотические ошибки также

могут быть связаны со сниженной экспрессией определенных генов контрольных точек клеточного цикла во время раннего эмбрионального развития или менее функциональными механизмами контрольных точек клеточного цикла, которые могут приводить к ошибкам хромосомной сегрегации при первых расщеплениях доимплантационных эмбрионов человекаю.

Оптимистично, эти результаты вселяют надежду в пациентов с абсолютной патозооспермией и других пациентов с различной степенью патозооспермии и вынуждают как клиницистов, так и генетиков, которые обязаны предложить этим пациентам отцовство. Пара должна получить недирективное, объективное генетическое консультирование относительно потенциальных репродуктивных рисков для аномального потомства и должна быть обеспечена необходимой информацией о возможных репродуктивных вариантах и доступных методологиях генетического тестирования, чтобы иметь возможность принять информативное решение о том, хотят ли они нормального зачатия и будущие пренатальные генетические тесты с учетом возможного риска выкидыша, или они хотят продолжить вспомогательную репродукцию (ИКСИ / ЭКО) в сочетании с пренатальным генетическим скринингом.

Заключение

Результаты, полученные в текущем исследовании, добавляют дополнительные доказательства того, что пациенты с тяжелой патозооспермией, подвергающиеся лечению ИКСИ, могут иметь более высокий уровень анеуплоидий половых хромосом у эмбрионов, чем пациенты с умеренной патозооспермией. Пациентам с патозооспермией следует предлагать надлежащее и тщательное генетическое консультирование с акцентом на повышенный риск анеуплоидии половых хромосом у их потомков и важность ПГД для предотвращения этого потенциального риска. FISH-анализ - это быстрый, надежный и относительно дешевый метод оценки половых хромосомных аномалий у доимплантационных эмбрионов. Для оценки реального влияния патозооспермии на уровни хромосомных аномалий у эмбрионов ИКСИ необходимы дополнительные исследования с большим количеством случаев.

Декларации

Рукопись не была представлена в какой-либо другой журнал или на конференцию.

Ограничения исследования

Ограничений, которые могли бы повлиять на результаты исследования, нет.

Подтверждение

Автор хотел бы выразить благодарность работникам службы поддержки и пожилым людям, которые приняли участие в этом исследовании, поделившись своими бесценными знаниями и опытом. Их сотрудничество и открытость в значительной степени способствовали глубине и богатству результатов исследований.

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CORRELATIONAL ANALYSIS OF THE INTERRELATIONSHIP BETWEEN THE THYMUS GLAND AND PERIPHERAL ORGANS OF THE IMMUNE SYSTEM IN EARLY ONTOGENESIS

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ABSTRACT

Relevance. The morphology of the thymus gland reflects the functional state of the immune system of children and adults to the fullest extent [1,2,3]. We know from the main directions of the evolution of the organs of the immune system that the development of the organs of immunogenesis begins with the development of the thymus gland, then in the spleen [4-10]. It was found that regardless of the duration and causes of clinical death, morphological changes in the thymus develop faster than in the peripheral organs of the immune system [11].
However, in the issue of inter-organ interaction of the organs of the immune system, a lot remains unresolved, in particular, in early ontogenesis, since there is practically no data in the available literature on the interrelationship between the central and peripheral organs of the immune system in early ontogenesis in children.
The purpose of the study. To carry out a correlation analysis of the assessment of the relationship of immunomorphological changes between the thymus gland and the spleen, mesenteric lymph nodes of fetuses and newborns born under the conditions of the physiological course of pregnancy.
Research materials and methods. The material for the immunomorphological study was the thymus gland, spleen and mesenteric lymph nodes of fetuses and newborns who developed during physiological pregnancy and died as a result of intracranial birth trauma. Each group is divided into four subgroups according to the terms of the perinatal period: 1st stillbirths at 28-36 weeks of pregnancy; II – stillbirths at 37-40 weeks of pregnancy; III – newborns who died on 1-4 days of life; IV – newborns who died on 5-7 days of life.
The research methods described in the classical histomorphology manuals [12,13,14] were applied in the work: anatomical – dissection, macroscopic description, weighing of the thymus gland, spleen; calculation of the weight coefficient of the thymus (TWiC) and spleen (SWI), fixation; histological – staining with hematoxylin and eosin, azure II – eosin, according to the Foot method; histochemical – CHIC reaction; morphometric – measurement of morphological parameters of the thymus gland, spleen and mesenteric lymph nodes using an ocular micrometer MOV 1-15 and an Avtandilov ocular measuring grid under an MBI–3 microscope with an AU-12 binocular nozzle; statistical analysis method - the degree of reliability of the difference was determined using the the Student's t-test ($p \leq 0.05$).
The association and magnitude between two variables were assessed using the correlation coefficient which is calculated according to the formula proposed by K. Pearson:

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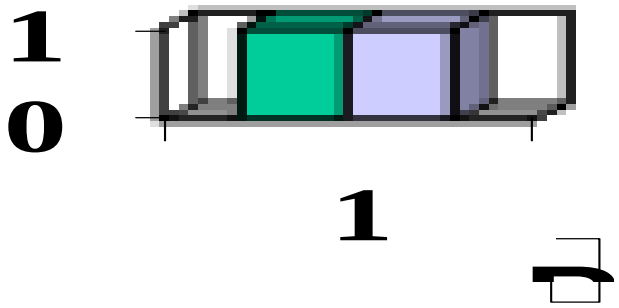
$$r_{xy} = \frac{\sum(x_i - x)(y_i - y)}{\sqrt{\sum(x_i - x)^2 \sum(y_i - y)^2}} \qquad (4)$$

where: r_{xy} – correlation coefficient

The results of the study. The mass of the thymus gland shows a pronounced positive correlation with the mass of the spleen (Figure). Small lymphocytes of the cortical substance of the thymus gland exhibit two positive associations: a strong positive correlation with the volume of the periarterial coupling (r= 0.87) and a moderate positive one with plasmocytes and macrophages (r=0.54) of the spleen. A moderate positive relationship (r=0.67) was established between the differentiation values of the thymus gland parenchyma and the volume of the spleen's white pulp. A strong positive relationship was determined between the medulla of the thymus gland and the lymphoid nodules of the spleen, with the correlation coefficient of r=0.73.

The correlation relationship between the thymus gland and mesenteric lymph nodes was also found to be positive. When differentiating the parenchyma of the thymus gland and the formation of lymphoid nodules with light centers, the correlation coefficient was r =0.09, i.e. weakly positive. The interrelationships of small lymphocytes of the cortical substance of the thymus gland with plasmocytes and macrophages of the medulla of the lymph nodes were moderately positive – r is equal to 0.44 and 0.58, respectively. The correlation coefficient (r) between the medulla with the thymus gland Ghassal corpuscles and the lymphoid nodule with light centers was 0.72, i.e. a strong positive relationship. Strong positive correlations were found between the differentiation of the parenchyma of the thymus gland and the paracortical zone (r=0.79) and the cortical plateau (r=0.40) of lymph nodes.

Thus, a correlation analysis of the inter-organ relationships between the thymus gland and peripheral lymphoid organs shows that certain functional interdependencies arise in the organs of immunogenesis and between them in fetuses and newborns in the perinatal period during physiological vital activity.



PD - periods of fetal and newborn development:
I – 27-36 weeks of antenatal development;**II** – 37-40 weeks of antenatal development; **III** –1-4 days after birth; **IV** – 5-7 days after birth.

A-body weight/thymus gland mass;
B- body weight/spleen weight;
Figure – Correlation of organometric parameters of the thymus gland and spleen with body weight at birth of fetuses and newborns in the perinatal period of development during the physiological course of pregnancy.

Conclusions. 1.The established facts of the timely formation of differentiation of the parenchyma of the thymus gland and the thymus-dependent zone of peripheral lymphoid organs, an increase in the number of small lymphocytes, increased mitosis, macrophage and plasmocyte reactions allow the presence of correlations between these processes under normal conditions.
2. The conducted studies allow us to better understand the patterns of structure and development of organs of immunogenesis, allowing us to standardize morphological data in the process of physiological ontogenesis.
3. The data obtained can be used by morphologists, immunologists, pathologists, forensic experts to assess the condition of the thymus gland and peripheral lymphoid organs when exposed to various extreme destabilizing factors on the body, and can also be used as a reference for studies of immunogenesis organs and modeling biological experiments.

Declarations
The manuscript has not been submitted to any other journal or conference.

Study Limitations
There are no limitations that could affect the results of the study.

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İQLİM DƏYİŞMƏLƏRİNİN FƏSADLARINA QARŞI ƏTRAF MÜHİTİN FORMALAŞMASINDA CİS-İN ROLU

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ABSTRACT

The article provides information about climate changes, which have become one of the global problems, and their impact on the living world, which worries the world community more and more. Unstable weather conditions are felt not only in Azerbaijan but also in several countries of the world and create problems. Increasing attention to these problems is manifested in the holding of a number of international events, including scientific and practical conferences. According to the latest assessment report of the Intergovernmental Panel on Climate Change, the average temperature on Earth has increased by 0.8 degrees in the last 100 years. The increase in temperature is mainly due to anthropogenic factors. The basis of anthropogenic factors are gases that create a thermal effect: carbon, methane, nitrogen oxide, nitrogen 1 oxide and chlorine-fluorine compounds. Space observations of the last 100 years show that the intensity and frequency of storms and blizzards have increased. Hot winds, hurricanes, and precipitation have intensified. At the same time, the number of flood events has also increased. If the surface of the ocean used to heat up to a depth of 1000 meters, then the warming reaches up to a depth of 2000 meters; resulting in hot currents becoming even hotter. That is, the main factor in the increase of all these natural disasters is climate change.

Azerbaijan has not been left out of the influence of global climate changes. In the last 100 years, average annual temperatures in the territory of Azerbaijan have increased by 0.4-1.3^0 C. The increase in temperature is unevenly distributed depending on the regions. In the last 10 years, the number and power of floods in small mountain rivers in the territory of Azerbaijan has increased. The issue of effective use of climate resources in agricultural production is one of the important tasks to solve the food problem. In order to implement it, it is necessary to deeply study the characteristics of our territory, to reveal the potential opportunities that ensure more efficient and rapid development of agriculture.

In this direction, the possibilities offered by Geographical Information Systems (GIS) are appreciated by think tanks of the world. Due to the capabilities of GIS, action plans can be prepared in the direction of preventing the consequences of global climate change, as well as the danger that may arise at a later stage.

GIS is the most efficient way to present information about geographic objects and to determine their position more quickly. GIS allows to analyze and model any geographical phenomenon - weather forecast, environmental changes, movement of lithospheric plates. It helps to solve the problem by connecting geographic information from different sources.

For this, GIS is the most accurate and perfect system that must be used to detect climate change in various areas and eliminate its consequences.

Keywords: Climate changes, environmental formation, GIS, average annual temperature, ecological crisis

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Məqalədə qlobal problemlərdən birinə çevrilmiş olan iqlim dəyişiklikləri və onların canlı aləmə təsiri dünya birliyini getdikcə daha çox narahat etməsi haqqında məlumat verilir. Qeyri-sabit hava şəraiti tək Azərbaycanda deyil dünyanın bir sıra ölkələrində hiss olunmaqda və problemlər yaratmaqdadır. Bu problemlərə diqqətin artması özünü bir sıra beynəlxalq tədbirlərin, o cümlədən elmi və praktiki konfransların keçirilməsində göstərir. İqlim Dəyişmələri üzrə Hökümətlərarası Ekspertlər qrupunun son qiymətləndirmə hesabatına görə son 100 ildə Yer kürəsində orta temperatur 0,8 dərəcə artıb. Temperaturun artması isə əsasən antropogen amillərlə bağlıdır. Antropogen amillərin əsasını istilik effekti yaradan qazlar: karbon, metan, azot oksidi, azot 1 oksid və xlor-flüor birləşmələri təşkil edir. Son 100 illik kosmik müşahidələr göstərir ki, tufanların, çovğunların həm intensivliyi, həm də tezliyi artıb. İsti küləklər, qasırğalar, yağıntılar güclənib. Eyni zamanda, sel, daşqın hadisələrinin də sayı artıb. Okeanın səthi əvvəllər 1000 metr dərinliyə qədər qızırdısa, artıq qızma 2000 metr dərinliyə qədər çatır; nəticədə isti axınların daha da qızmasına səbəb olur. Yəni bütün bu təbii fəlakətlərin artmasında əsas amil iqlim dəyişmələridir.

Azərbaycan da qlobal iqlim dəyişmələrinin təsirindən kənarda qalmamışdır. Son 100 ildə Azərbaycan ərazisində orta illik temperaturlar 0,4-1,3^{0}C-yə qədər artmışdır. Temperatur artımı regionlardan asılı olaraq qeyri-bərabər paylanır. Son 10 illiklərdə Azərbaycan ərazisində kiçik dağ çaylarında sel və daşqınların sayı və gücü artmışdır. İqlim ehtiyyatlarından kənd təsərrüfatı istehsalında səmərəli istifadə məsələsi ərzaq problemini həll etmək üçün qarşıya qoyulmuş mühüm vəzifələrdən biridir. Onu həyata keçirmək üçün ərazimizin xüsusiyyətlərini dərindən öyrənmək, kənd təsərrüfatının daha səmərəli və sürətli inkişafını təmin edən potensial imkanları aşkara çıxarmaq tələb olunur.

Bu istiqamətdə Coğrafi İnformasiya Sistemlərinin (CİS) təklif etdiyi imkanlar dünyanın beyin mərkəzləri tərəfindən təqdir edilir. Çünki CİS-in imkanları hesabına qlobal iqlim dəyişikliyinin yaratdığı fəsadların, həmçinin sonrakı mərhələdə yarana biləcək təhlükənin qarşısının alınması istiqamətində tədbirlər planları hazırlana bilər.

CİS coğrafi obyektlər haqqında informasiyaları təqdim etmək və onların mövqeyini daha tez təyin etmək üçün ən səmərəli üsuldur. CİS istənilən coğrafi hadisəni - hava proqnozunu, ətraf mühitdə baş verən dəyişiklikləri, litosfer tavalarının hərəkətini təhlil etməyə və onları modelləşdirməyə imkan verir. O, müxtəlif mənbələrdən alınan coğrafi informasiyaları bir-biri ilə əlaqələndirməklə problemin həllinə yardım edir.

Bunun üçün CİS iqlim dəyişikliyinin müxtəlif sahələr üzrə aşkarlanması və yaratdığı fəsadların aradan qaldırılması istiqamətində istifadəsi labüd olan ən dəqiq və mükəmməl sistemdir.

Açar sözlər: İqlim dəyişmələri, ətraf mühitin formalaşması, CİS, orta illik temperatur, ekoloji böhran.

Geniş müzakirə mövzularından birinə çevrilən iqlim dəyişmələrinin fəsadlarına qarşı mübarizə tədbirləri sosial və iqtisadi islahatların aparılmasına diqqəti artırır.

Dünyada fəaliyyət göstərən 6500-dən artıq beyin mərkəzləri müasir effektiv kommunikasiyanın qurulması, onların təsir imkanlarının artırılması və əldə edilmiş nəticələrin ölçü meyarları barədə standartların müəyyənləşdirilməsi üçün araşdırmalar aparır. Son 30 ildə iqlim dəyişmələrinin fəsadlarına qarşı; beynəlxalq iqtisadiyyat, ətraf mühit problemləri, yoxsulluğun azaldılması, informasiya və cəmiyyət kimi mühüm sahələrdə bilik və siyasət arasında körpü yaratmaqla,

ölkələrin inkişaf xəttinə, qlobal iqtisadiyyatın təkamülünə və adi insanların həyat tərzinə göstərdiyi təsirlərin minimuma endirilməsinə kömək edən bir sıra qlobal təşəbbüslər irəli sürüblər. Beyin mərkəzləri beynəlxalq əməkdaşlıq səylərini artırmaqla bütün dünyada siyasi qərarların qəbul edilməsi prosesini təkmilləşdirir, regional və beynəlxalq şəbəkələr yaratmaqla müasir layihələrin regionlar üzrə yaradılmasına və həyata keçirilməsinə yardımçı olurlar.

Qlobal problemlərdən birinə çevrilmiş olan İqlim dəyişiklikləri və onların canlı aləmə təsiri dünya birliyini getdikcə daha çox narahat etməkdədir. Qeyri-sabit hava şəraiti tək Azərbaycanda deyil dünyanın bir sıra ölkələrində hiss olunmaqda və problemlər yaratmaqdadır. Bu problemlərə diqqətin artması özünü bir sıra beynəlxalq tədbirlərin, o cümlədən elmi və praktiki konfransların keçirilməsində göstərir. İqlim Dəyişmələri üzrə Hökümətlərarası Ekspertlər qrupunun son qiymətləndirmə hesabatına görə son 100 ildə Yer kürəsində orta temperatur 0,8 dərəcə artıb. Temperaturun artması isə əsasən antropogen amillərlə bağlıdır. Antropogen amillərin əsasını istilik effekti yaradan qazlar: karbon, metan, azot oksidi, azot 1 oksid və xlor-flüor birləşmələri təşkil edir. Son 100 illik kosmik müşahidələr göstərir ki, tufanların, çovğunların həm intensivliyi, həm də tezliyi artıb. İsti küləklər, qasırğalar, yağıntılar güclənib. Eyni zamanda, sel, daşqın hadisələrinin də sayı artıb. Okeanın səthi əvvəllər 1000 metr dərinliyə qədər qızırdısa, artıq qızma 2000 metr dərinliyə qədər çatır; nəticədə isti axınların daha da qızmasına səbəb olur. Yəni bütün bu təbii fəlakətlərin artmasında əsas amil iqlim dəyişmələridir.

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Azərbaycan ərazisi düzənlik və dağlıq relyefə malik olduğundan təbii amillərin məkan-zaman bölgüsü, iqlimin ayrı-ayrı ünsürlərinin kəmiyyət əlaqələri, aqroiqlim göstəricilərinin hündürlükdən, girintili-çıxıntılı relyef şəraitindən, yamacların ekspozisiyasından asılı olaraq paylanmasının öyrənilməsi böyük elmi və praktiki əhəmiyyət kəsb edir. Respublikamız Şərqi Avropa və Qərbi Asiyanın sərhədində yerləşən transcontinental ölkə olmaqla, cənub en dairələrində yerləşdiyi üçün böyük miqdarda günəş işığı və istisi alır. Kür-Araz ovalığında günəş işıqlandırmasının davamiyyəti il ərzində 2200-2400 saat, FFR-in (foto-sintetik fəal radiasiya) illik kəmiyyəti isə 64 kkal/sm^2-dən çox olur. Bu göstəricilərin maksimum qiyməti Arazboyu düzənlikdə müşahidə olunur (müvafiq olaraq 2800 saatdan və 76 kkal/sm^2-dən çox). Ərazidə günəş enerjisininin illik gedişi də yaxşı ifadə olunmuşdur. İyuldan sentyabradək respublikanın düzənlik rayonları tropik zonada (150^0 şimal en dairəsi) olduğu qədər, qışda isə Sank-Peterburq enliyindəkindən iki dəfə çox günəş enerjisi alır. Günəş enerjisinin ən çox toplandığı bir dövrdə (aprel-oktyabr) ümumi FFR Kür-Araz ovalığında 50-54kkal/sm^2 , Naxçıvan Muxtar Respublikasının düzən hissələrində isə 59-60 kkal/sm^2-dir. Yayda işıqlanma şəraiti şərq yamaclarda qərb yamaclara nisbətən yaxşı olur.

İqlim dəyişmələri, onun müasir dünyamızdakı müxtəlif ölkələrin inkişaf xəttinə, qlobal iqtisadiyyatın təkamülünə, habelə adi insanların həyat tərzinə göstərdiyi təsiri barədə yazılmış ədəbiyyatın sayı artıq yüz minlərlədir. İqlim dəyişmələri mövzusunu araşdıran elmi cəmiyyət özü iki cəbhəyə bölünmüşdür. Birinci cəbhə iqlim dəyişmələrinin bir qrup maraqlı tərəf, xüsusən də

inkişaf etmiş ölkələr tərəfindən inkişaf etməkdə olan ölkələrdəki tərəqqinin sürətinin qarşısının alınması üçün ortaya atılmış boş iddia olduğuna söykənir. Dünyanın ətraf mühit sahəsində tanınmış alimlərini özündə birləşdirən ikinci cəbhə isə iqlim dəyişmələrinin bəşəriyyət qarşısında duran ən ciddi problem olduğunu öz elmi mülahizələri və tədqiqatları ilə izah etməyə çalışır. İqlim dəyişmələrinin həqiqətən də baş verdiyini iddia edən alimlərin fikrinə əsasən problemin kökündə Yer kürəsinin karbon-dioksid (CO_2) və digər istilik effekti yaradan (parnik) qazların udulması potensialı durur.

Müxtəlif növ tərəvəz və bitkilərin yetişməsi üçün lazımi temperaturu yaradan istilikxanalar kimi, atmosferdəki qazlar da günəşdən gələn istiliyi tutub saxlayaraq planetimizdə yaşamağımız üçün zəruri istiliyi yaradır. Alimlərin hesablamalarına əsasən, əgər atmosferdə bu qazlar olmasaydı, onda Yer kürəsində orta illik temperatur təxminən 19° C olardı. Məhz buna görə həmin qazlar istilik effekti yaradan qazlar adlandırılır. CO_2 və digər qazlar atmosferin üst qatlarında günəşdən gələn istiliyi tutub saxlamaqla bizi hədsiz istilikdən mühafizə edərək bir növ görünməz mühafizə zolağı yaradırlar.

Beləliklə, onlar dünyada insanların normal yaşaması və fəaliyyət göstərməsi üçün zəruri temperaturun formalaşdırılmasında müstəsna rol oynayırlar. CO_2 atmosferə müxtəlif mənbələrdən daxil olur: kənd təsərrüfatı, landşaftdan istifadədə olan dəyişikliklər, sənaye, tullantılar, energetika və sair. Bütün dünya ölkələri kimi, bu gün Azərbaycan da çoxsaylı ekoloji böhranlarla üzə-üzədir. Qlobal iqlim dəyişmələri nəticəsində Yer kürəsində temperaturun tədricən artması və dünyanın müxtəlif bölgələrində atmosfer yağıntılarının azalması müşahidə olunur ki, bu hal ölkəmizdə də özünü göstərir. Nəticədə çaylarda və su anbarlarında suyun səviyyəsi azalır.

XX əsrin ortalarından etibarən sənayenin inkişafı və enerji əldə etmək məqsədilə üzvi maddələrin yandırılması nəticəsində atmosferdə CO_2 və digər istilikxana qazlarının həcmi sürətlə artmışdır. Bu da öz növbəsində günəş istiliyinin atmosferdə daha çox miqdarda saxlanmasına səbəb olur.

Belə ki, günün ikinci yarısında qərb yamaclar daha çox radiasiya almalı olduğu halda, tez-tez baş verən konvektiv hərəkətlər nəticəsində buludluluq əmələ gəlir, işıqlanma şəraiti zəifləyir və Günəş radiasiyasının gərginliyi azalır. Xüsusi ölçmə işləri göstərmişdir ki, Kiçik Qafqazda səpələnən radiasiyanın gündəlik cəmi buludsuz havada şərq yamaclarda qərb yamaclara nisbətən çox olur. Müxtəlif səmtli yamaclar da şaxtavurma hadisələrinə görə bir-birindən fərqlənir. Bitkilər şərq yamaclarda qalan yamacalara nisbətən şaxtadan daha çox zərər çəkirlər. Yüksəkliyə doğru Günəş radiasiyasının qızdırma effekti artdığına görə bitkilər dağlarda fazalararası dövrdə düzənliyə nisbətən daha az temperatur cəmi tələb edirlər. Mədəni bitkilərin dağ rayonlarına köçürülməsi işində bu effektin nəzərə alınmasının praktiki əhəmiyyəti var. Ərazinin xeyli hissəsində yüksək termik rejim, yağıntının az olması, bəzi yerlərdə isə çox qıtlığı səciyyəvidir.

Demək olar ki, bütün Kür-Araz ovalığına, Abşeron yarımadasına və Arazboyu düzənliyə il ərzində cəmisi 110-350 mm yağıntı düşür. Bir qayda olaraq, dağlıq zonada yağıntıların miqdarı hündürlükdən asılı olaraq artır. Buna uyğun və havanın temperaturunun azalması ilə əlaqədar olaraq yağıntıların rütubətlənmədə rolu da artır. Ilk baxışda elə təsəvvür yaranır ki, yağıntıların ümumi miqdarı bir çox rayonlarda bitkinin rütubətə olan tələbatını ödəmək üçün kifayət qədərdir. Lakin, yağıntı miqdarının illik rejimi elədir ki, bitkinin intensiv inkişaf etdiyi və transpirasiyanın gücləndiyi bir dövrdə o rütubətlə kifayət qədər təmin olunmur.

Dünyanın heç bir ölkəsi, coğrafi məkanı genişlənməkdə olan iqlim dəyişikliyinin mənfi təsirlərindən sığortalanmayıb. Lakin etiraf etməliyik ki, bu gün həm də qlobal dünyamızda elmi-texniki inkişaf da tərəqqi dövründədir. Müasir texnalogiyaların imkanları sayəsində əvvəllər həlli

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imkansız hesab olunan problemlər də öz həllini tapır. Yəni, bu gün iqlim dəyişlikliyi səbəbindən yaranan fəsadların aradan qaldırılmasını şərtləndirən imkanlar mövcuddur.

Bu istiqamətdə Coğrafi İnformasiya Sistemlərinin (CİS) təklif etdiyi imkanlar dünyanın beyin mərkəzləri tərəfindən təqdir edilir. Çünki CİS-in imkanları hesabına qlobal iqlim dəyişikliyinin yaratdığı fəsadların, həmçinin sonrakı mərhələdə yarana biləcək təhlükənin qarşısının alınması istiqamətində tədbirlər planları hazırlana bilər.

CİS coğrafi obyektlər haqqında informasiyaları təqdim etmək və onların mövqeyini daha tez təyin etmək üçün ən səmərəli üsuldur. CİS istənilən coğrafi hadisəni - hava proqnozunu, ətraf mühitdə baş verən dəyişiklikləri, litosfer tavalarının hərəkətini təhlil etməyə və onları modelləşdirməyə imkan verir. O, müxtəlif mənbələrdən alınan coğrafi informasiyaları bir-biri ilə əlaqələndirməklə problemin həllinə yardım edir.

CİS həmçinin, iqlim dəyişikliyi səbəbindən yararsız hala düşən torpaqların təyinatının dəyişdirilərək başqa sahə üzrə yenidən yararlı hala gətirilməsi istiqamətində də çox dəyərli, qiymətli təkliflər təqdim etmək imkanına malikdir.

Hazırda CİS Ətraf Mühit üzrə müxtəlif obyekt və hadisələrin daha dəqiq təhlilini aparmaq üçün istifadə oluna biləcək ən mükəmməl alətdir, verilmiş kəskin ekoloji vəziyyətə baxış keçirilməsinə və gələcəkdə fiziki vəziyyəti haqqında fikir irəli sürülməsinə şərait yaradır. Verilənlərin emalı başa çatdıqdan sonra CİS ətraf mühitdə olan risk və təhlükələrin planlaşdırlmasına və onların idarə olunmasına imkan verir.

Ətraf mühit dedikdə insanları əhatə edən, onlarla qarşılıqlı əlaqədə olan günəş şüaları, su, torpaq, hava və canlılar, antropogen maddələr, əşyalar və qurğular nəzərdə tutulur. İnsan özü də ətraf mühitin ayrılmaz və çox güclü təsirə malik olan hissəsidir. Ətraf mühiti təbii mühit və süni mühit olaraq iki hissəyə ayırmışlar. İnsanların həmişə asılı olduqları mühit təbiidir. Süni mühit isə cəmiyyətin inkişafı ilə əlaqədər insanların fəaliyyəti nəticəsində yaradılmışdır. Müasir elmin köməyi ilə yaradılmış yeni çoxsaylı bitki və heyvan növləri, süni dəryalar, göllər, qoruqlar və s. süni mühitin obyektləridir.

Artıq XX əsrin ortalarında ekoloji böhran özünü bildirməyə başladı. Bu dövrü, ətraf mühitin nəzarətsiz istismarının get-gedə artması dövrü kimi qiymətləndirmək olar. Bitki və heyvan növlərinin, eləcə də meydana gələn ekosistemlərin hamısı özlərinə aid olan coğrafi və ya məkan aralıqlarına malikdir. Bu səbəbdən də, ekoloji çirkləndiricilərin Yer kürəsində yayılması bərabər miqyasda deyildir. Bu kimi müxtəlifliklərin anlaşılması və çirkləndirici mənbələrin aşkar olunmasında CİS-in istifadəsinin xüsusi rolu vardır.

CİS-atmosfer çirklənmələrində, torpaq eroziyasında, müxtəlif miqyasda iqlim modifikasiyalarının yaradılmasında, müxtəlif ekoloji layihələrin hazırlanmasında, şəhər ekologiyasının həllində, bioloji müxtəliflik məsələlərində və ətraf mühitin mühafizəsində, həmçinin ətraf mühitə təsirlərin qiymətləndirilməsi sahəsində müstəsna əhəmiyyətə malikdir. CİS ətraf mühitin təbii və texnogen meyarlara əsasən modelləşdirilməsində effektiv bir vasitə kimi qiymətləndirilir.

Bu gün təbiət-cəmiyyət münasibətlərinin kəskinləşərək pik həddə çatması bütün beynəlxalq təşkilatların və dünya ölkələrinin ciddi narahatlığına səbəb olub. Çünki təbiətə göstərilən antropogen təsirlər, ona vurulan ağır zərbələr ekosistemlərin, biosferin normal ahəngini ağlasığmaz dərəcədə pozur, bəşəriyyətin həyatını ciddi təhlükə qarşısında qoyur. Bu baxımdan, davamlı inkişafla bağlı dünya ölkələri tərəfindən 2030-cu ilədək həyata keçirilməsi nəzərdə tutulan 17 məqsəddən biri də iqlim dəyişmələrinə qarşı mübarizədir.

Ekoloji vəziyyətin yaxşılaşdırılması, ətraf mühitin mühafizəsi, yaşıllıq sahələrinin artırılması, su ehtiyatlarından və dayanıqlı enerji mənbələrindən səmərəli istifadə dövlətimizin siyasətində

prioritet təşkil edir və bu istiqamətdə böyük işlər görülür. Neftlə çirklənmiş torpaqların təmizlənməsi, dünya standartlarına uyğun yeni sənaye müəssisələrinin yaradılması prosesin ardıcıl olaraq həyata keçirildiyini sübut edir və öz müsbət nəticəsini verir. Bu baxımdan, dünyada ən mötəbər beynəlxalq tədbirlərdən biri olan BMT-nin İqlim Dəyişmələri üzrə Tərəflər Konfransının 29-cu sessiyasının (COP29) bu il ölkəmizdə keçirilməsi Azərbaycanın iqlim dəyişmələrinin fəsadlarının aradan qaldırılmasında fəal iştirak etdiyini, neft-qaz hasil edən ölkə olmasına baxmayaraq, "yaşıl enerji"yə keçidə üstünlük verdiyini, iqlim böhranını həll etmək üçün ardıcıl addımlar atdığını təsdiq edir. Həmçinin ölkəmizin ətraf mühitin mühafizəsi sahəsində gördüyü işlər, bu istiqamətdə qlobal problemlərin qarşısının alınmasına verdiyi töhfələr beynəlxalq aləmdə yüksək qiymətləndirilir.

BMT-nin İqlim Dəyişmələri üzrə Çərçivə Konvensiyasına üzv ölkələrin 21-ci konfransında qəbul olunan Paris sazişinə əsasən COP tədbirlərinin keçirilməsində məqsəd karbon qazının miqdarını azaltmaq, inkişaf etməkdə olan ölkələrə iqlim dəyişmələrinin təsirini minimuma endirmək üçün maliyyə yardımı etməkdir. Əks halda, inkişaf etməkdə olan ölkələr təmiz enerji mənbələrinə keçid edə, qlobal karbon qazının həcmini azalda bilməzlər. Yüzdən çox ölkənin dövlət və hökumət rəhbərləri, xarici işlər, ətraf mühit nazirləri tərəfindən imzalanan Paris sazişi 2016-cı ildə qüvvəyə minib və dünyanın 190-dan çox ölkəsi, o cümlədən Azərbaycan da bu razılaşmaya qoşulub.

Cari ilin ölkə başçısı İlham Əliyevin sərəncamı ilə ölkəmizdə "Yaşıl dünya naminə həmrəylik ili" elan edilməsi dünyada əsasən neft-qaz ixrac edən ölkə kimi tanınan Azərbaycanın "yaşıl enerji" təchizatçısına çevrilməyi qarşıya əsas məqsəd kimi qoyulur. "Yaşıl iqtisadiyyat"a keçidi iqtisadi siyasətin əsas prioriteti kimi müəyyənləşdirən dövlətimiz, eyni zamanda 1990-cı illə müqayisədə 2030-cu ilə qədər istilik effekti yaradan qazların emissiyasının 35, 2050-ci ilə qədər isə 40 faiz azaldılmasını nəzərdə tutur. "Azərbaycan 2030: sosial-iqtisadi inkişafa dair Milli Prioritetlər"də iqtisadiyyatın bütün sahələrində bərpaolunan enerjinin tətbiqi, iqlim dəyişmələri ilə mübarizə məsələləri öz əksini tapmışdır. 2028-ci ilə qədər ölkəmizin enerjiyə olan tələbatının 30 faizinin bərpaolunan enerji mənbələrindən əldə edilməsinə nail olmaq qarşıya qoyulan ən mühüm vəzifələrdən biridir.

Qeyd edək ki, iqlim dəyişmələri bəşəriyyətin ümumi problemidir. Məhz bu dəyişmələrin ölkəmizdə meydana gələn təsirlərini göstərməkdəyik. Bu baxımdan CİS məlumarlarına əsaslanaraq, coğrafi hadisələri - hava proqnozunu, ətraf mühitdə baş verən dəyişikliklərin vaxtında aydınlaşdırılması, onların təsirinin yumşaldılması üçün tədbirlər həyata keçirilməli və ona uyğunlaşdırılması üçün zəruri addımlar atılmalıdır. Bu problemə səthi yanaşdıqda və onu ciddi qəbul etmədikdə artıq çox gec ola bilər.

Bunun üçün CİS iqlim dəyişikliyinin müxtəlif sahələr üzrə aşkarlanması və yaratdığı fəsadların aradan qaldırılması istiqamətində istifadəsi labüd olan ən dəqiq və mükəmməl sistemdir.

Bəyannamələr

Əlyazma başqa heç bir jurnala və ya konfransa təqdim edilməyib.

Təhsil Məhdudiyyətləri

Tədqiqatın nəticələrinə təsir göstərə biləcək məhdudiyyətlər mövcud deyil.

Təşəkkürlər

Müəllif bu tədqiqatda iştirak edən, öz dəyərli fikirlərini və təcrübələrini bölüşən qayğı göstərən işçilərə və yaşlı insanlara təşəkkürünü bildirir. Onların əməkdaşlığı və açıqlığı tədqiqat nəticələrinin dərinliyinə və zənginliyinə əhəmiyyətli dərəcədə kömək etmişdir.

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$$f(x) = a_0 + \sum_{n=1}^{\infty} \left(a_n \cos \frac{n\pi x}{L} + b_n \sin \frac{n\pi x}{L} \right) \quad (1)$$

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This section may each be divided by subheadings or may be combined. A combined Results and Discussion section is often appropriate. This should explore the significance of the results of the work, don't repeat them. Avoid extensive citations and discussion of published literature only, instead discuss recent literature for comparing your work to highlight novelty of the work in view of recent development and challenges in the field.

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Table 1: Summary of formatting requirement for submitting paper in this journal.
(Times New Roman, 12)

Layout	**Size**	**Margin (Normal)**	**Header**	**Footer**	
Single column	A4 (8.27" X 11.69")	Top=1" Bottom=1" Left=1" Right=1"	Do not add anything in the header	So not add anything in the footer	
Font	**Article Title**	**Headings**	**Subheadings**	**Reference list**	**Text**
	Times New Roman, 16 pt, Bold, centred	Times New Roman, 11 pt, Bold, Left aligned	Times New Roman, 10 pt, Bold, Left aligned	Times New Roman, 8 pt, Justified	Garamond, 11 pt, Justified
Line Spacing	1.15	1.15	1.15	1.15	1.15
Page number	We will format and assign page numbers				

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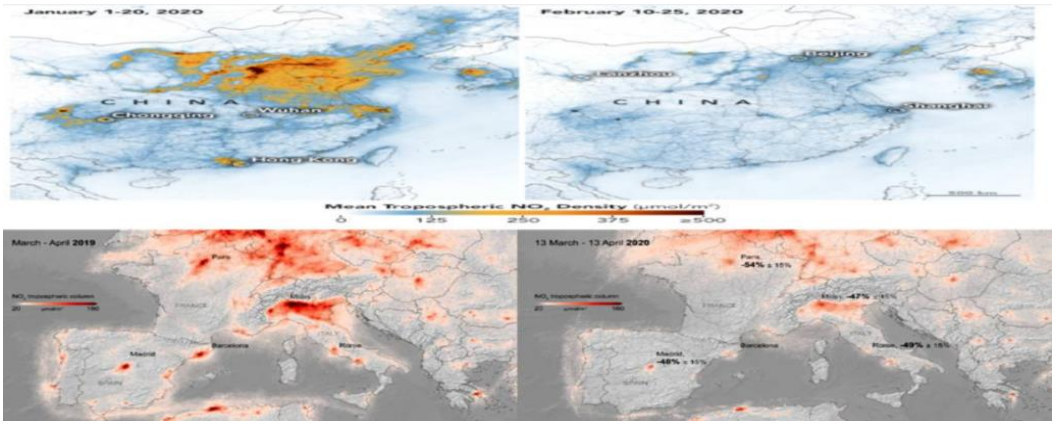

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2. Bahishti, “Peer Review; Critical Process of a Scholarly Publication”, J. Mod. Mater., vol. 2, no. 1, pp. 1.1-1.2, Oct. 2016. https://doi.org/10.21467/jmm.2.1.1.1-1.2
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