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CHANGES IN THE ANTIOXIDANT SYSTEM AND HEMATOLOGICAL PARAMETERS DURING THE DEVELOPMENT OF OXIDATIVE STRESS IN HYPOTHYROIDISM.

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Abstract In our country, special attention is being paid to developing and implementing medications with positive effects for treating diseases associated with thyroid insufficiency. Thyroid diseases are the most widespread non-communicable endocrine disorders in the world, second only to diabetes in prevalence. Their occurrence depends on age, gender, and iodine consumption. A distinctive feature of hypothyroidism is the diversity and specificity of its clinical manifestations and symptoms. This makes diagnosing the disease challenging, potentially leading to misdiagnosis and subsequent iodine deficiency. There are three main types of hypothyroidism: primary, secondary, and peripheral. Primary hypothyroidism arises from damage to the thyroid gland itself. Secondary hypothyroidism develops as a result of damage to the pituitary gland (due to trauma, radiation, hemorrhage, or neuroinfection) and is significantly less prevalent than the primary form. Peripheral hypothyroidism is very rare and is caused by a disruption in tissue sensitivity to thyroid hormones. In this study, we are creating a model of hypothyroidism and investigating the changes in CAT, GGT, SOD, and MDA enzymes in the blood, as well as ALT and AST enzymes in the blood.

Keywords: CAT, GGT, SOD, MDA, ALT and AST, antioxidant system, hypothyroidism, mercazalil.

ИЗМЕНЕНИЯ В АНТИОКСИДАНТНОЙ СИСТЕМЕ И ГЕМАТОЛОГИЧЕСКИХ ПАРАМЕТРАХ В ПРОЦЕССЕ РАЗВИТИЯ ОКСИДАТИВНОГО СТРЕССА ПРИ ГИПОТИРЕОЗЕ

Аннотация В нашей стране особое внимание уделяется разработке и внедрению препаратов с положительным эффектом для лечения заболеваний, связанных с недостаточностью функции щитовидной железы. Заболевания щитовидной железы являются наиболее распространенными неинфекционными эндокринными нарушениями в мире, уступая по частоте только диабету. Их возникновение зависит от возраста, пола и потребления йода. Отличительной особенностью гипотиреоза является разнообразие и специфичность его клинических проявлений и симптомов. Это затрудняет диагностику заболевания, что может привести к ошибочному диагнозу и последующему дефициту йода. Существует три основных типа гипотиреоза: первичный, вторичный и периферический. Первичный гипотиреоз возникает в результате повреждения самой щитовидной железы. Вторичный гипотиреоз развивается вследствие повреждения гипофиза (из-за травмы, облучения, кровоизлияния или нейроинфекции) и встречается значительно реже, чем первичная форма. Периферический гипотиреоз встречается крайне редко и вызывается нарушением чувствительности тканей к гормонам щитовидной железы. В данном исследовании мы разрабатываем модель гипотиреоза и изучаем изменения активности ферментов каталазы (CAT), гамма-глутамилтрансферазы (ГГТ), супероксиддисмутазы (СОД) и уровня малонового диальдегида (МДА) в крови, а также активности ферментов аланинаминотрансферазы (АЛТ) и аспартатаминотрансферазы (АСТ) в крови.

Ключевые слова: КАТ, ГГТ, СОД, МДА, АЛТ и АСТ, антиоксидантная система, гипотиреоз, мерказолил.

GIPOTIREOZDA OKSIDATIV STRESS RIVOJLANISHI JARAYONIDA ANTIOKSIDANT TIZIM VA GEMATOLOGIK KO‘RSATKICHLARDAGI O‘ZGARISHLARI

Annotatsiya Mamlakatimizda qalqonsimon bez yetishmovchiligi bilan bog‘liq kasalliklarni davolashda ijobiy ta’sir ko‘rsatadigan dori vositalarini ishlab chiqish va amaliyotga tatbiq etishga alohida e’tibor qaratilmoqda. Qalqonsimon bez kasalliklari dunyoda eng keng tarqalgan yuqumsiz endokrin kasalliklar hisoblanib, tarqalishi bo‘yicha qandli diabetdan keyin ikkinchi o‘rinda turadi. Ularning yuzaga kelishi yosh, jins va yod iste’moliga bog‘liq.Gipotireozning o‘ziga xos xususiyati uning klinik ko‘rinishlari va alomatlarining xilma-xilligi va o‘ziga xosligidir. Bu esa kasallikka tashxis qo‘yishni murakkablashtiradi, noto‘g‘ri tashxis qo‘yilishiga va keyinchalik yod tanqisligiga olib kelishi mumkin. Gipotireozning uchta asosiy turi mavjud: birlamchi, ikkilamchi va periferik. Birlamchi gipotireoz qalqonsimon bezning o‘zidagi shikastlanishdan kelib chiqadi. Ikkilamchi gipotireoz gipofizning

shikastlanishi (jarohat, nurlanish, qon quyilishi yoki neyroinfeksiya) natijasida rivojlanadi va birlamchi shaklga nisbatan ancha kam uchraydi. Periferik gipotireoz juda kam uchraydi va to‘qimalarning qalqonsimon bez gormonlariga sezgirligi buzilishi natijasida yuzaga keladi. Ushbu tadqiqotda biz gipotireoz modelini yaratamiz va qondagi CAT, GGT, SOD va MDA fermentlari, shuningdek, qondagi ALT va AST fermentlaridagi o‘zgarishlarni o‘rganamiz.

Kalit so‘zlar : KAT, GGT, SOD, MDA, ALT va AST, antioksidant tizim, gipotireoz, merkazalil.

INTRODUCTION

Typically, our body has an antioxidant system that produces dangerous radicals and maintains a normal balance throughout our entire life. However, after the age of 40, a person can no longer perform this function independently. If a person is exposed to high levels of radiation or chemical toxins in the environment, this process needs to work twice as hard. The body cannot handle this on its own, so it becomes necessary to assist the organism [1]. Under the influence of unfavorable environmental factors, in various pathological conditions of the body, as well as during the aging process, the process of free radical formation is activated.

The antioxidant system of the organism functions as a regulator of peroxidation processes. In biochemical reactions, this system performs its role perfectly, neutralizing endogenously formed free radicals without causing any harm to the body. The organism's antioxidant system includes enzymes such as superoxide dismutase, catalase, enzymes of the glutathione system, as well as various vitamins and coenzymes.

The proliferation of free radicals leads to disruptions in mitochondrial function, resulting from the suppression of endogenous antioxidant systems that neutralize free radicals. The reactive oxygen species produced at this stage oxidize fatty acids, leading to the formation of their free radical forms. The integrity of cellular structures is compromised, potentially leading to cell death. Under such conditions, the therapeutic use of both natural and synthetic antiradical agents may be advisable [2].

Antioxidants act on mitochondrial dysfunction by reducing the formation of free radicals in respiratory chains through participation in the antiradical mechanism. Additionally, there are prooxidant substances. Such substances lead to an increase in free radicals in mitochondria, resulting in the initiation of lipid peroxidation processes in membrane lipids. For our organism, an excess of oxygen beyond the normal level does not lead to positive outcomes either. When this situation occurs, cellular structures begin to deteriorate due to the formation of free radicals [3].

Most patients with goiter unrelated to Hashimoto's thyroiditis are in a euthyroid or hyperthyroid state. However, hypothyroidism with endemic goiter can also occur as a result of iodine deficiency. Iodine deficiency disrupts the uniform structure of the thyroid gland. In response, TSH is produced, which increases the size of the thyroid gland and its ability to absorb

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iodine, leading to the development of goiter. In cases of acute iodine deficiency, patients develop symptoms of hypothyroidism.

In primary hypothyroidism of the thyroid gland, ultrasound examination often reveals increased blood flow intensity. This phenomenon is characteristic of hyperthyroidism and is observed with increased thyroid activity under the influence of the nervous system. Only as a result of prolonged disease progression does the thyroid tissue significantly decrease; moreover, blood flow weakens due to the suppression of regenerative processes by large doses of hormones (which is less common).

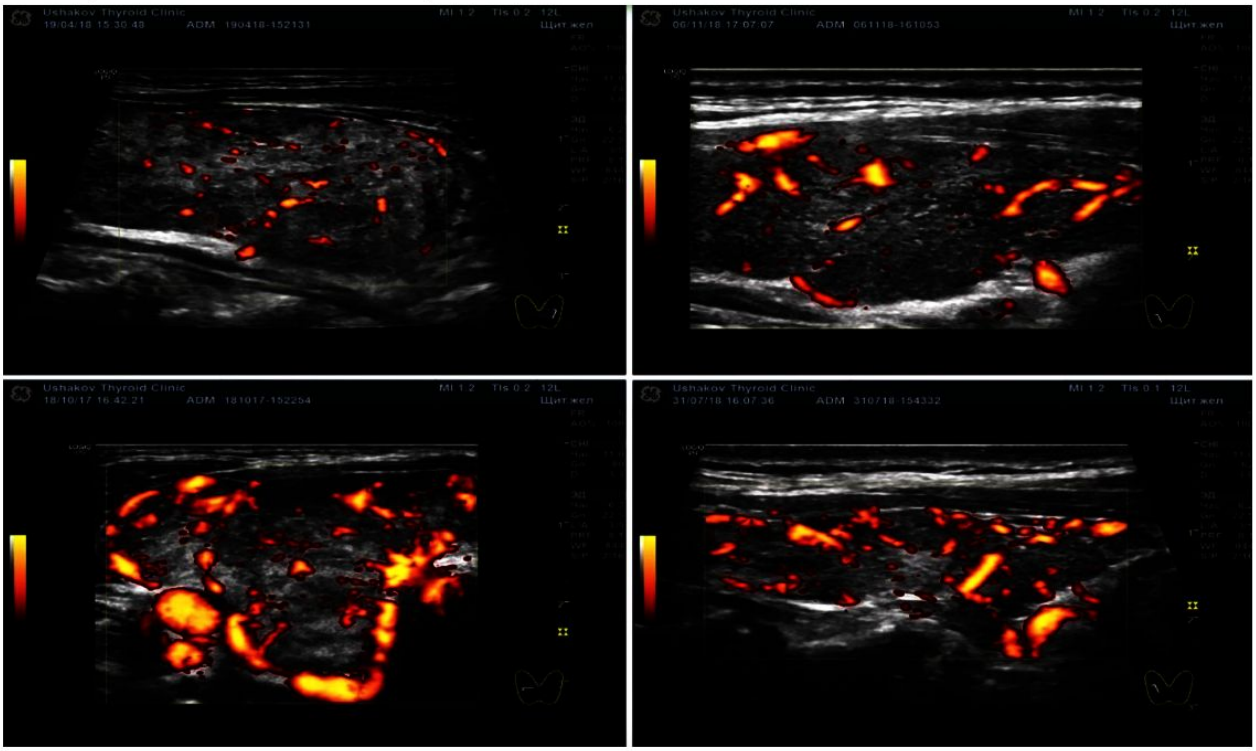


Figure 1. EDC mode: Strong Doppler ultrasound. Various options for enhancing blood flow in the thyroid gland lobes [9].

To date, no endocrinologist has explained the mechanism of increased blood flow in hypothyroidism! After all, antibodies to thyroid cells do not affect blood vessels. They are influenced by the peripheral nervous system. What is the main functional role of the thyroid gland? This question directly leads to the answer about the cause of hypothyroidism!

This role is to provide the body with energy (calories). Therefore, thyroid hormones are essential for all processes in the body. The thyroid gland is subject to excessive strain and fatigue and often fails to supply the body with the necessary amount of energy (through its T3 and T4 hormones). Any condition that increases energy expenditure leads to hypothyroidism - thyroid stimulation by TSH intensifies! TSH is the hormone that alerts the thyroid gland. Energy is expended excessively during pregnancy, illness, mental or physical exertion, prolonged lack of adequate rest, oxygen deficiency, living in a cold climate, and so on [4].

MATERIALS AND METHODS

The research was conducted on male white rats in the vivarium of the Human and Animal Physiology Laboratory at the National University of Uzbekistan and in the laboratory of the

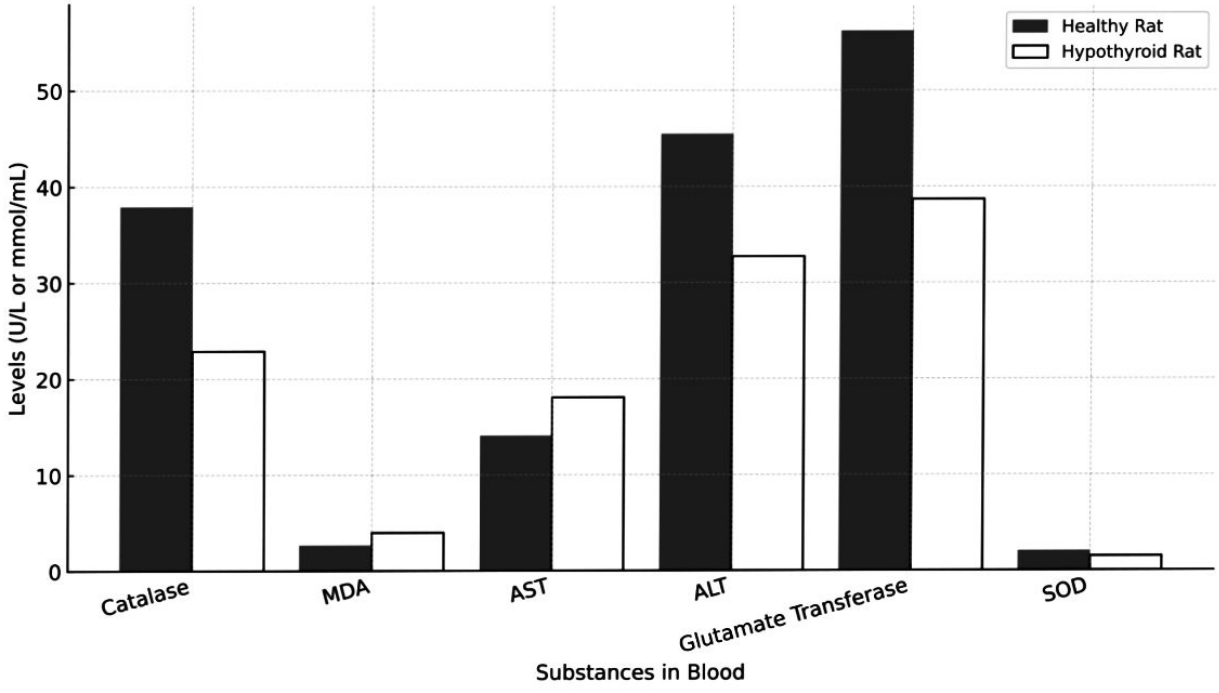
Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan. The experiments utilized rats weighing 100±20 g. The rats were housed in individual cages in clean rooms with natural lighting conditions. They had unrestricted access to food and water. The animals' diet comprised wheat, pistachios, milk and dairy products, meat products, wheat bread, herbs, vegetables, table salt, and feed. The rats were maintained in an environment with a room temperature of 22-24°C and humidity of 40-60%. Studies were conducted in vitro and in vivo on healthy animals, an experimental hypothyroidism model group, and a hypothyroidism group treated with antioxidant substances. Mercazolil was used to induce hypothyroidism in the animals. Each experimental group consisted of 5-10 animals. Cases of rat mortality were also observed in the hypothyroidism model groups. The experiments were repeated 4-5 times.

Creating a model of hypothyroidism: Mercazolil was used to induce hypothyroidism in the experimental animals. The rats used for the experiment were divided into 2 groups, and the levels of enzymes CAT, SOD, GGT, MDA, ALT, and AST were determined in the blood of both healthy and experimental rats.

RESULTS AND DISCUSSION

In the experimental hypothyroidism model, the activity of the catalase enzyme decreased significantly - down to 40% of the control level ($p \leq 0.001$). Such a substantial reduction in catalase activity may be attributed to the similar thyroid-like effect on the concentrations of both the apoenzyme and coenzyme [14]. Currently, the literature contains only a few indicators of changes in the body's antioxidant status in thyroid diseases. The available data on the involvement of thyroid hormones in the regulation of free radical oxidation (SRO) processes are highly controversial [8].

Changes in blood enzymes of healthy rats and those affected by hypothyroidism [6].



Catalase Activity (µKat/mg protein)

Healthy rats: 37.92 ± 0.74 Hypothyroid rats: 22.9 ± 1.10

Analysis: Catalase is an essential antioxidant enzyme that protects cells from oxidative stress by breaking down hydrogen peroxide (H_2O_2) into water and oxygen. The decrease in catalase activity indicates:

Increased oxidative stress, leading to cellular damage.

-A higher risk of apoptosis (programmed cell death) due to oxidative damage.

-Weakening of cell membranes and damage to proteins, lipids, and DNA.

Hypothyroidism slows down metabolism, reducing the efficiency of antioxidant defense systems and leaving cells more vulnerable to oxidative damage and premature aging

Superoxide Dismutase (SOD) Activity in Blood Plasma (U/L)

Healthy rats: 2.05 ± 0.78 Hypothyroid rats: 1.49 ± 0.42

Analysis: SOD is an essential antioxidant enzyme that neutralizes superoxide radicals. Its decline may result in: an increased accumulation of free radicals, leading to cell damage.

-Membrane and DNA damage, impairing cell growth and division.

-Weakened defense against oxidative stress in hypothyroidism.

This result indicates that hypothyroidism reduces the body's ability to combat oxidative stress [4,7]. Hypothyroidism significantly alters metabolic processes, impacting various organ systems, particularly the antioxidant defense mechanism. Our study revealed a marked decrease in catalase (CAT) and superoxide dismutase (SOD) activities in hypothyroid rats compared to healthy controls. These results suggest that hypothyroidism compromises the body's ability to neutralize oxidative stress, which aligns with findings from previous studies indicating a reduction in antioxidant enzyme activity under thyroid hormone deficiency [10].

Malondialdehyde (MDA) Concentration (mmol/mL)

Healthy rats: 2.68 ± 0.03 Hypothyroid rats: 3.98 ± 0.03

Analysis: MDA is a marker of lipid peroxidation, and its increase suggests:

-Enhanced oxidative damage to cell membranes.

-Increased lipid peroxidation, leading to impaired cellular communication and function.

-Higher risk of cardiovascular diseases, as elevated MDA levels are linked to atherosclerosis.

-Accelerated apoptosis and inflammatory responses.

This indicates that hypothyroidism compromises the body's ability to neutralize free radicals, leading to extensive cellular damage. An increase in malondialdehyde (MDA) levels in hypothyroid rats further supports the hypothesis that oxidative stress is exacerbated in this condition. MDA is a well-known marker of lipid peroxidation, and its elevated levels indicate significant oxidative damage to cell membranes. Similar observations have been reported in other experimental models of hypothyroidism, reinforcing the role of oxidative stress in disease progression [11].

Aspartate Aminotransferase (AST) Activity (units/L)

Healthy rats: 14.11 ± 0.56 Hypothyroid rats: 18.07 ± 0.42
Analysis: AST is mainly found in the liver, heart, and skeletal muscles. Its increase suggests:
Liver tissue damage or inflammation. -
Slower tissue regeneration due to metabolic decline in hypothyroidism. -
Possible cardiac involvement, as hypothyroidism is associated with heart dysfunction. This result indicates potential pathological changes in liver and heart tissues due to hypothyroidism.

Alanine Aminotransferase (ALT) Activity (units/L)
Healthy rats: 45.47 ± 0.94 Hypothyroid rats: 32.72 ± 1.25
Analysis: ALT is a key enzyme for liver function assessment. Its reduction suggests:
-Decreased metabolic activity in liver cells. -
Impaired liver function and potential degenerative changes. -
Reduced ability of hepatocytes (liver cells) to regenerate. This suggests that hypothyroidism negatively impacts liver function, slowing down detoxification and metabolic processes. Hematological changes in our study also provide important insights. We observed a significant increase in AST and ALT enzyme activity in hypothyroid rats. Since these enzymes are commonly used markers of liver function, their elevation suggests that hypothyroidism may contribute to liver stress or dysfunction. Several studies have reported similar findings, linking hypothyroidism to impaired liver metabolism and enzyme dysregulation [12]. In contrast, the decrease in glutamate transferase levels in hypothyroid rats indicates a metabolic slowdown, which is expected given the overall reduction in cellular activity due to thyroid hormone deficiency.

Glutamate Transferase (GGT) Level in Blood Plasma (U/L)
Healthy rats: 56.14 ± 1.48 Hypothyroid rats: 38.68 ± 0.31
Analysis: GGT plays a role in detoxification and glutamate metabolism. Its decrease may indicate:

-Liver dysfunction and reduced enzyme production.

-Slowed metabolic detoxification due to hypothyroidism.

-Impaired glutamate metabolism, which may also affect nervous system function. This confirms that hypothyroidism weakens liver function and affects detoxification processes. Given the strong link between oxidative stress and hypothyroidism, the findings from our study highlight the potential benefits of antioxidant supplementation. Several studies have suggested that selenium, vitamin E, and other antioxidants can be protective by reducing oxidative damage in thyroid disorders [13]. Future research should investigate the long-term effects of antioxidant therapy on oxidative stress markers and metabolic function in hypothyroidism.

CONCLUSION

This study reveals that hypothyroidism leads to significant changes in enzyme activity and oxidative stress markers, affecting both liver function and metabolic balance. The decrease in catalase and superoxide dismutase (SOD) activity, along with an increase in malondialdehyde

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(MDA) levels, indicates a weakening of the body's antioxidant defense system. This suggests that hypothyroidism contributes to higher oxidative stress, which can lead to cellular damage and impaired physiological processes. Liver function is also noticeably affected, as reflected in the decreased alanine aminotransferase (ALT) and glutamate transferase (GGT) levels, suggesting reduced metabolic activity. At the same time, the increased aspartate aminotransferase (AST) levels may indicate tissue damage, particularly in the liver and possibly in the heart. These findings point to the broader systemic effects of hypothyroidism, extending beyond thyroid dysfunction itself. The results underscore the importance of early diagnosis and management to prevent further metabolic disturbances. Proper thyroid hormone therapy, along with antioxidant support and regular monitoring of liver and cardiovascular health, may help mitigate these effects. Further research is needed to explore additional therapeutic strategies that could help restore metabolic balance and reduce oxidative damage in hypothyroid conditions.

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