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DISTRIBUTION OF ZINC IN MUSCLE, ADIPOSE TISSUE AND BLOOD SERUM OF RATS UNDER CONDITIONS OF ZINC-DEFICIENT, IODINE-DEFICIENT, HIGH-CARBOHYDRATE AND HIGH-FAT DIETS

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Abstract. The relevance of the study is due to the prevalence of hypothyroid dysfunction, type II diabetes mellitus, and metabolic syndrome. The study was carried out on sexually mature male rats that were on a standard vivarium diet (control group), zinc-deficient, iodine-deficient, high-carbohydrate and high-fat diets. Under the experimental conditions, the distribution of zinc in blood serum, adipose (visceral fat) and muscle (femoral and tibial muscles) tissues was studied. The study showed a decrease in serum zinc content by 13.79-30.89 % ($p<0.05$) compared to the control group, regardless of diet. The concentration of the trace element in adipose tissue was significantly reduced relative to the control under conditions of zinc deprivation (by 18.37 %, $p<0.05$), and especially high-fat feeding (by 74.74 %, $p<0.001$). The increase in the content of the trace element in muscles under conditions of zinc deficiency (by 36.84 %, $p<0.001$) compared to the same indicator in animals fed a standard diet) is noteworthy. Taking into account the role of the bioelement in the maintenance of thyroid homeostasis, carbohydrate metabolism, and antioxidant potential, the detected changes involving zinc may act as a trigger for changes in the hormonal profile, metabolic and oxidative disorders.

Key words: zinc deficiency, iodine deficiency, hypothyroidism, insulin resistance, obesity, blood serum, muscle and adipose tissue.

Introduction. Among the current medical and social problems, there is a prevalence of such diseases as thyroid pathology, diabetes mellitus, obesity, hypertension, coronary heart and vascular diseases. Unfortunately, they lead to disability and shorten life expectancy, and are among the leading causes of mortality. Numerous scientific studies have proven the significant role of trace elements in the development of these pathologies. Among them is the essential trace element zinc, which participates in complex cascades of biochemical reactions of the body, affects the incremental activity of secretory organs; it is a part of a number of enzymatic substances and transporter proteins, which allows us to assert its significant importance in the functioning of multicomponent regulatory systems [1-3]. According to the literature, about 17% of the world's population has a reduced concentration of zinc in the body [3]. The average daily requirement of this trace element for an adult is about 11 mg for men, 8-10 mg for women, and 12-15 mg for pregnant women, breastfeeding mothers, children and adolescents [3, 4]. Zinc enters the human body with food (it is abundant in whole grain cereals, meat products, pumpkin seeds, pine nuts) and is absorbed by gastrointestinal organs. Zinc deficiency in the body is affected not only by its insufficient content in the diet, but also by gastrointestinal diseases accompanied by impaired absorption and assimilation of substances, as well as by the competitive interaction of trace elements during resorption [4]. After entering the cells, thanks to a complex of proteins regulating the metabolism of the trace element, zinc is accumulated as part of specific cysteine-rich proteins – metallothioneins. Metalothioneins maintain zinc homeostasis, protect cells from the harmful effects of excess cations of the trace element and highly toxic chemical elements, in particular, cadmium, mercury, arsenic. Metalothioneins have antioxidant properties, as they inactivate free radicals [2, 3]. Due to the large number of transporter proteins, zinc is involved in the signalling function that regulates cell differentiation, proliferation and growth [3, 5].

Among the endocrine pathologies, in the genesis of which zinc plays a significant role, hypothyroidism deserves special attention, as zinc is involved in the metabolism of thyroid hormones [7, 8]. It is important that the prevalence of thyroid pathology is almost 50 % of endocrine gland dysfunction, which tends to increase [4]. Over the past five years, the prevalence of thyroid hypofunction has increased by more than 20 %, hyperfunction – by 9 %, and autoimmune thyroiditis – by 17 % [7, 8].

Zinc also plays an important role in the metabolic activity of insulin, which has led to the study of new ways to prevent the development of diabetes. However, according to experimental studies, the correction of carbohydrate profile indicators by the trace element in animals is not significant. At the same time, the number of people with diabetes mellitus in Ukraine is almost 2.5 million, and the incidence continues to grow [9-13].

Therefore, an in-depth study of the role of zinc in the development of endocrinopathies remains relevant, which will supplement the data on the pathogenesis of multiorgan disorders, expand the mechanisms of their prevention and correction under conditions of trace element imbalance.

The purpose of the study: to investigate the peculiarities of zinc distribution in blood serum, adipose and muscle tissue under conditions of zinc- and iodine-deficient, high-carbohydrate and high-fat diets in the experiment.

Materials and methods

The study was conducted on 60 white outbred mature rats (males, 150-180 g) for 8 weeks. The animals were

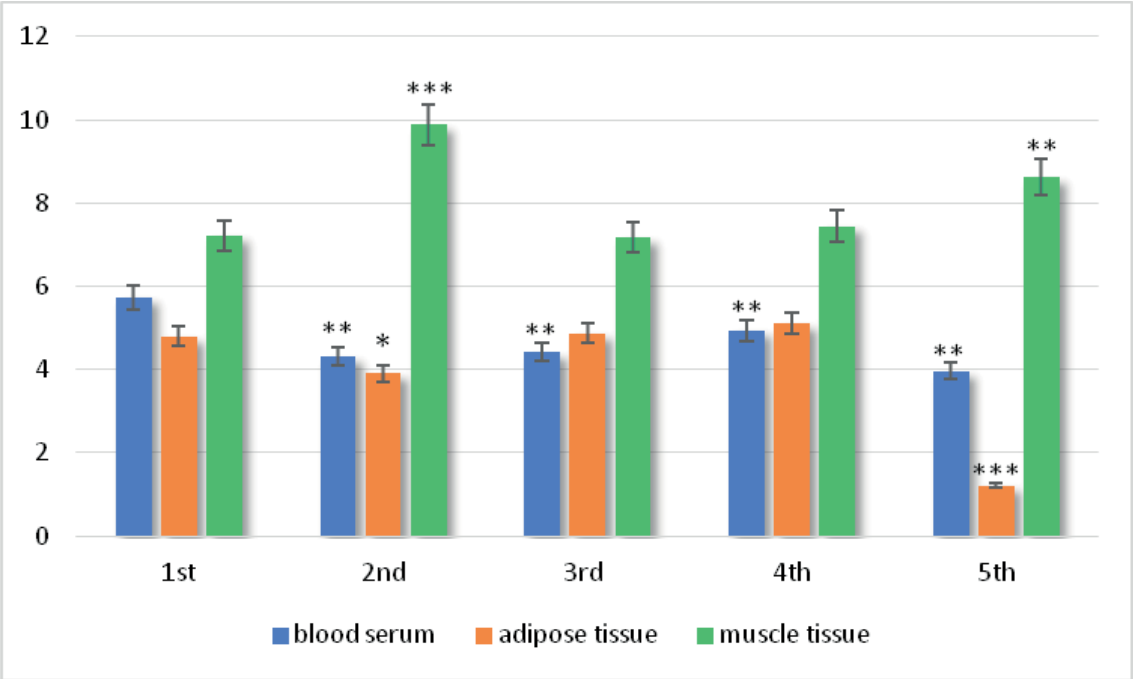

Fig. 1. Zinc content (μg/g) in blood serum, adipose and muscle tissues of rats that were on zinc-deficient, iodine-deficient, high-carbohydrate and high-fat diets (M±m)

Notes: p – reliable difference to the indexes of animals of control group (p<0.05*, p<0.01**, p<0.001***)

divided into five experimental groups: group 1 (n=12) – intact animals on the usual vivarium diet, group 2 (n=12) – animals on a diet with a limited zinc content (cereals, soybeans, vegetables, etc.) [1], group 3 (n=12) – animals on an iodine-deficient diet (corn flour and oil, wheat gluten, brewer's yeast, etc.) [12], group 4 (n=12) – animals on a high-carbohydrate diet (received a 10% fructose solution instead of drinking water) [9], group 5 (n=12) – animals on a high-fat diet (food high in fat and cholesterol, in particular, pork fat, brain, etc.) [13]. Rats were withdrawn from the experiment by decapitation under ketamine anaesthesia (100 mg/kg body weight). Zinc content was determined in blood serum, muscle (femoral and tibial muscles) and adipose (visceral fat) tissues.

Statistical analysis was performed with standard mathematical software using Student's t-test. The difference was considered statistically significant at p<0.05.

Research results and their discussion

The study revealed multidirectional changes in the distribution of zinc in blood serum, muscle and adipose tissue under the studied conditions (Fig. 1).

In particular, in rats with zinc-deficient and iodine-deficient diets, a decrease in serum zinc content by 24.78% (p<0.01) and 23.04 % (p<0.01) was observed, respectively, compared to the control. It is important that a significant decrease in the trace element in the blood serum was observed in the high-fat diet (by 30.89 %, p<0.001), while the high-carbohydrate diet was accompanied by a decrease in zinc content by only 13.79 % (p<0.01) compared with similar values in intact rats. In the animals of experimental group 2 (on a zinc-deficient diet), the zinc content in adipose tissue decreased by 18.37 % (p<0.05), while in muscle tissue it increased by 36.84 % (p<0.001) compared to the baseline values. Unidirectional changes were observed in animals kept on a high-fat diet: the zinc content significantly decreased in adipose tissue (by 74.74%, p<0.001), while in muscle tissue it increased by 19.39% (p<0.01). No significant changes were observed in the adipose and muscle tissue of rats in experimental groups 3 and 4 compared to the control.

Discussion of results

It is known that most of the zinc in the mammalian body is concentrated in the muscles (up to 57 %) [2, 4]. The effect of zinc accumulation in the muscles observed in animals on a zinc-deficient diet, against the background of a decrease in blood serum and adipose tissue, can be explained by the involvement of compensatory mechanisms for the accumulation of zinc reserves under conditions of severe deprivation of the trace element, and the inclusion of feedback mechanisms to maintain homeostasis.

Attention is drawn to the decrease of the trace element in blood serum under the conditions of not only zinc-deficient, but also iodine-deficient diets. These data indicate an increased risk of thyroid homeostasis disorders under conditions of trace element imbalance. The mechanism of zinc participation in the functional activity of the thyroid gland is complex and multicomponent. It is known that the trace element is involved in the interaction of thyroid hormones with receptors in target tissues. In particular, zinc is a component of receptors that bind to T3. The following three functional sites are distinguished in their structures: 1) located at the C-terminal end of the receptor polypeptide chain and responsible for recognition and binding to the hormone; 2) the DNA binding domain containing two so-called "zinc fingers" (the central part of the receptor), one of which is involved in DNA binding and

another one is involved in receptor dimerisation; 3) the variable region of the receptor, which is key in interaction with proteins involved in transcriptional regulation. Zinc deficiency in the body can primarily cause impaired binding of T3 to the receptor, which blocks the development of the hormone's physiological effects [2, 5, 8]. In addition, biochemically active T3 is formed by deiodination of thyroxine (T4) under the influence of deiodinase enzymes. Zinc is a component of deiodinase D1, which is involved in the formation of the bulk of T3, mainly in the liver and kidneys, as well as in skeletal muscles. It should be noted that part of T3 is formed by deiodination of the inner and outer rings of T4 in tissues. At the same time, deiodinase D2 (active in the brain and pituitary gland) catalyses the conversion of T4 to T3, affecting only the outer ring of the hormone. And deiodinase D3 (present in the placenta) inactivates T3 and T4 by affecting the inner ring of the hormone [2, 5]. In addition, biochemically active T3 is formed by deiodination and the synthesis of thyrotropin-releasing hormone (TRH) in the hypothalamus involves a zinc-dependent carboxypeptidase. Therefore, zinc deficiency is a risk factor for the development of hypothyroid dysfunction, because it takes part in the functioning of the hypothalamic-pituitary-thyroid axis [5, 6]. However, thyroid hormones are also necessary for zinc metabolism. It has been proven that their deficiency leads to a decrease in the concentration of zinc in the blood [5, 14]. Such a mutual dependence is a risk factor for the progression of metabolic pathology involving the thyroid gland, which is especially dangerous in conditions of zinc deprivation.

Zinc plays a significant role in ensuring the endocrine function of the pancreas. In particular, the presence of ZIP-4 proteins on the membranes of β-cells of the organ was investigated. At the stages of insulin synthesis in the Golgi complex, proinsulin is saturated with zinc. The trace element is involved in the formation of hexameric insulin complexes in the secretory granules of β-cells of the islets of Langerhans [10, 12]. Zinc is known to be involved in the lipogenesis of rat adipocytes together with insulin, controlling the physiological effects of insulin in response to hyperglycaemia, stimulating glucose transport, activating phosphodiesterase and moving glucose transporter protein from the internal structures of adipocytes to the membranes, and inhibiting ritodrine-induced lipolysis in rat adipocytes [15, 16]. Zinc increases tyrosine phosphorylation of the IR-b subunit of the insulin receptor and potentiates glucose transport through the phosphoinositol 3-kinase pathway in insulin deprivation. This trace element is recognised as a tyrosine-1B-phosphatase inhibitor that slows down insulin signalling [3, 4]. This mechanism has been shown to alleviate insulin resistance and lipogenesis, in particular when rats are on a high-fat diet [13, 14]. In general, zinc plays the role of a secondary messenger in the transport of glucose to adipocytes, affects lipogenesis, has a mimetic effect on protein kinase, and activates glycogenesis by reducing the activity of glycogen synthase kinase-3. The zinc-dependent enzyme insulin-sensitive peptidase and GLUT-4 are absorbed by the cell membrane together during the physiological effects of insulin. The enzyme is localised on the membrane of muscle cells and adipocytes. Under conditions of insulin resistance, its activity decreases [3, 13, 15, 16]. As a result of this element deficiency, glucose tolerance is impaired.

The study showed a decrease in zinc concentration only in blood serum under high-fructose feeding conditions. At the same time, it is noteworthy that the content of the trace element in blood serum, and especially in adipose tissue, decreased against the background of the tendency to increase in muscles under conditions of high-fat feeding. These data confirm the growth of metabolic risks in animals of experimental groups 4 and 5. Taking into account the antioxidant potential of the trace element, we can assume an increase in the intensity of oxidative processes under the studied conditions.

Conclusions

In the experimental modelling of zinc and iodine deficiency, insulin resistance and obesity, a decrease in serum zinc levels was found regardless of diet. The concentration of the trace element in adipose tissue was significantly reduced under conditions of zinc deprivation, especially high-fat feeding. An increase in the content of the trace element in muscles under conditions of zinc deficiency is noteworthy. Given the role of the bioelement in the maintenance of thyroid homeostasis, carbohydrate metabolism, and antioxidant potential, the identified changes involving zinc may act as a trigger for changes in hormonal profile, metabolic and oxidative disorders.

Prospects for further research. Research into ways to prevent the development of hypothyroidism, insulin resistance and obesity by maintaining the balance of zinc in tissues remains relevant.

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