# MICROELEMENT STATUS IN RATS UNDER IODINE DEFICIENCY AND INSULIN RESISTANCE

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S u m m a r y. Macro- and micronutrient status in animals with insulin resistance was studied and referred to proper and limited iodine supply. The analysis involved the reduction of magnesium, chromium content and the increase in iron and calcium content in the liver, reduction of copper, calcium and the increase in iron level in the erythrocyte mass in animals with insulin resistance and respective reference values in intact animals. The findings of the study carried out in rats with insulin resistance with underlying iodine deficiency included: reduced liver magnesium concentration compared to initial increase in iron and calcium, in the red blood cell mass - the decrease in the concentration of copper, magnesium, zinc, and increased iron level compared to the initial values.

K e y w o r d s: insulin resistance, iodine deficiency, macro-, microelement status, liver, erythrocyte mass.

### INTRODUCTION

The content of macro- and microelements in a healthy body, its organs and tissues is determined by certain reference limits. Balance in macro- and microelements is very important for vital processes [8, 16]. As part of the common homeostatic system, it plays an important role in the regulation of the body functioning, and the biological significance of sustainability of biochemical elements is revealed at the molecular, cellular, tissue, and systemic level [4, 6]. Essential microelements stimulate the processes of tissue respiration, energy metabolism, blood formation, immune reactions, the synthesis of biologically active substances, hormones, metabolism of proteins, carbohydrates, lipids, nucleic acids, activate most enzyme systems of the body, and also correct the level of free radicals in the body [15]. Upset trace element balance leads to the development of common pathological processes, including iodine deficiency conditions, insulin resistance, anemia. Considering the etiology of thyroid dysfunction, more attention is focused on the elucidation of the role of trace element imbalance (deficiency of essential microelements and their potential toxicity). Selenium, iron, zinc play important role in the synthesis of thyroid hormones. Insulin resistance, which is a pathophysiological defect, triggers a cascade of pathological reactions and leads to the formation of a complex of disorders and diseases. At the cellular level, prerequisites for its development are deviations in the functioning of any of the components of the insulin signaling cascade, in addition to micronutrients. Despite the fact, that the breach of insulin-stimulated glucose uptake is quite common in cardiovascular diseases, the activation of kinase different signaling pathways occurs [7, 17]. It is interesting to clarify the pathophysiological role of insulin resistance in diseases of the hepato-biliary system, because the liver plays an important role in the metabolism of metal cations. Macro- and microelements are involved in all vital processes of hepatocytes. The role of the liver in the metabolism of bioelements is associated with bile formation and biliary functions, with its participation in the formation of metal-enzyme complexes, deposition of macro-

and microelements and their maintenance in the blood. The participation of bioelements in metabolic process depends on the transport function of plasma proteins metabolism, which in most cases also depends on the liver. In case of insulin resistance, the processes of pathogenesis and nature of the lesions in the liver remain obscure. Pathological processes occurring in the liver and disordered metabolism can significantly alter macronutrient and micronutrient content in the blood and hepatocytes. To reduce the risk of all sorts of complications, it is not only necessary to compensate carbohydrate metabolism, but also comprehensively correct other metabolic disorders [2, 13]. Therefore, the study of pathogenesis of insulin resistance in the context of macro and trace-element supply, understanding of pathogenic and therapeutic significance of trace element imbalance may suggest new methods of prevention and treatment of comorbid pathologies. Topicality of the research is caused by the prevalence and projected growth of both iodine deficiency conditions and metabolic syndromes, a combination of highly probability, especially in the residents of iodine-deprivated regions.

#### AIM OF THE STUDY

The aim of this study was to determine the characteristics of macro- and trace element status in animals with insulin resistance with reference to proper and limited iodine supply.

# MATERIAL AND METHODS

The study was performed on 45 white mature outbred rats weighing 150-180g. The animals were divided into the following groups: group 1 (n=15) – animals with insulin resistance with adequate iodine supply, group 2 (n=15) – animals with insulin resistance against the backdrop of iodine deficiency. To simulate insulin resistance, the rats received 10% fructose solution with drinking water for 8 weeks [12]. Iodine deficiency status was induced by iodine-deficient diet [5]. Animals of the control group (n=15) were on a standard diet. Breeding, feeding and euthanasia complied with current international standards regarding the humane treatment of animals. The content of copper, iron, calcium, magnesium, zinc, manganese and chromium was determined in the red cellular mass and the liver by atomic-absorption spectrophotometry. All experiments were carried out according to the

National Institute of Health Guidelines for the care and use of laboratory animals, and the European Council directive of 24 November 1986 for Care and Use of Laboratory Animals (86/609/EEC), and approved by the Local Ethics Committee. Statistical analysis of the obtained data was performed by Student's t test using Statistic 7. A statistically significant difference was considered at p<0.05.

# **RESULTS OF THE STUDY**

In the group of animals with insulin resistance the results found a significant decrease in magnesium liver content to 19% (p<0.05), and chromium 52% (p<0.05) (Table 1). At the same time, an increase in iron content was found 34% (p<0.05) and calcium 24% (p<0.05) compared to the initial values. In the animals with a combined endocrine disorder (group 2) magnesium concentration in the liver decreased to 29% (p<0.05) compared to initial values, and iron and calcium 41% (p<0.05) and 22% (p<0.05) respectively in comparison to the group of intact animals.

In group 1, copper content in the red blood cell mass decreased to 26% (p<0.05) against the increase in calcium level 29% (p<0.05) and iron level 17% (p<0.05) with reference to control indexes. In the rats from group 2, the concentrations of copper decreased to 30% (p<0.05), magnesium 31% (p<0.05), zinc 39% (p<0.05) and increased iron level 24% (p<0.05) were found when referred to the control group of animals.

## DISCUSSION

Characterizing the role of studied micronutrients it is necessary to emphasize that copper in physiological concentration potentiates hypoglycemic effect of insulin, accelerates the processes of glucose oxidation, inhibits the breakdown of glycogen, and promotes its accumulation in the liver [3]. Reduction of copper content in the red cell mass in animals with insulin resistance can lead to reduced activity of metal-enzymes, copper-dependent including superoxide dismutase, ceruloplasmin, and as a result to the intensification of lipid peroxidation, oxidative modification of proteins, destruction of nucleic acids, cytokine release, and violations of functional status and the development of various pathological processes [9, 10]. The same trend of copper content in the red blood cell mass was observed in animals from the experimental group 2, while in the liver a slight increase in selenium content was detected in comparison to the controls. It is likely to be explained by the redistribution of this element between organs, in particular, its accumulation in the hepatocytes.

The content of iron and calcium in studied tissues of animals from both experimental groups was higher than in the control group. These changes in iron content may be due to disordered metabolism of this macroelement [15]. At the same time, calcium is another messenger, and an important component of the apoptosis in hepatocytes. It can be assumed that an increase in liver calcium content helps trigger mitochondrial apoptotic signaling cascade. Calcium cation causes the loss of cytochrome C, which also involved in the development of apoptosis. Dysregulation of Ca<sup>2+</sup> homeostasis plays an important role in the mechanisms of liver cell death [9]. Additional supply with calcium promotes normalization of fasting glucose level, and improves insulin sensitivity [8].

As it is known from the literature, the development of insulin resistance is associated primarily with magnesium deficiency. particular, there is a relationship between magnesium deficiency and the development of insulin resistance. Magnesium deficiency negatively affects the secretion and activity of insulin, which leads to the formation of insulin resistance [11]. In addition, according to clinical and basic research, magnesium reveals hepatoprotective effect. Insulin receptor molecule itself is an important magnesium-dependent protein in the cascade of intracellular signaling of the insulin receptor. In animals with insulin resistance this trace element content decreases both in the liver and in red cell mass. Combined endocrine pathology potentiates the reduction of trace element in all studied tissues. Removal of magnesium from the hepatocytes may be associated with a decrease in ATP content [14].

As for zinc, significant fluctuation of this trace element content in the liver was not observed, whereas in the red cell mass it was lower, especially under conditions of insulin resistance combined with iodine deficiency. Probably, disordered metabolism of hepatocytes leads to the generation of ROS, causing the release of zinc from proteins which results in their dysfunction [1]. Zinc deficiency disrupt the synthesis and secretion of normal physiological insulin molecules. If not enough convertible inactive hormone circulated in the blood, it initiates the development of tissue insulin resistance (on one hand). Zinc deficiency inhibits binding of the hepatocytes to insulin, which leads to the formation of hepatic insulin resistance (on the other) [1, 18].

Manganese is a component of many enzymes in the body and performs several important functions, one of which is to strengthen the hypoglycemic effect of insulin. The microelement activates enzymes of citric acid cycle, enhances the action of insulin required for its synthesis. However, significant changes in manganese content in tissues were not detected.

Another important trace mineral that provides implementation of insulin signal is chromium. Among the numerous biochemical effects of the microelement the most important one is its interaction with insulin molecule in the amplification of hormonal signal. The research revealed a significant decrease in the concentration of this trace element in animals regardless of iodine supply of the organism.

#### CONCLUSIONS

The obtained results suggest that under the conditions of insulin resistance, acquired trace elements imbalance occurs. In addition, the exchange of metal cations in the liver is broken. This may induce metabolic changes associated with functional activity of the intramolecular systems, which depends on the content of the studied cations. Further studies of metabolic bioelements peculiarities can contribute to better understanding of the biochemical mechanisms of several pathologies.

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Macro-,	Control group	1 <sup>st</sup> research group	2 <sup>nd</sup> research group
microelements		(insulin resistance)	(insulin resistance +
			iodine deficiency)
Cu, mg·kg	$3.27\pm0.52$	$2.39\pm0.50$	$3.60\pm0.65$
Fe, mg·kg	$55.12\pm3.60$	$73.70 \pm 10.89*$	77.62 ± 9.13*
Ca, mg·kg	$30.13 \pm 3.43$	37.36 ± 3.45*	36.73 ± 3.35*
Mg, mg·kg	$180.46 \pm 15.39$	146.17 ± 13.44*	128.18 ± 24.19*
Zn, mg·kg	$23.32\pm2.58$	$20.99 \pm 2.78$	$20.73 \pm 3.56$
Mn, mg·kg	$1.83\pm0.30$	$1.58 \pm 0.27$	$1.56\pm0.18$
Cr, mg·kg	$0.05\pm0.02$	$0.024 \pm 0.01*$	$0.029 \pm 0.01$

T a b l e 1. Macronutrient and micronutrient content in the liver of rats with insulin resistance against with reference to appropriate and limited iodine supply  $(M\pm m)$ 

\*p<0.05 - analogical indexes in intact animals;

p with Arabic numerals - reliable difference between the indexes of corresponding research groups

T a b l e 2. The content of macro- and micronutrients in the red cell mass in rats with insulin resistance with reference to proper and limited iodine supply (M+m)

Macro-, microelements	Control group	1 <sup>st</sup> research group (insulin resistance)	2 <sup>nd</sup> research group (insulin resistance +
Cu, mg·kg	1.25±0.11	0.93±0.09*	0.87±0.10*
Fe, mg·kg	3.75±0.44	4.51±0.18*	4.96±0.33*
Ca, mg·kg	0.80±0.16	1.13±0.02*	1.08±0.28
Mg, mg·kg	39.75±3.30	31.20 ±5.43	27.58±2.35*
Zn, mg·kg	3.16±0.54	2.02±0.60	1.92±0.27*
Mn, mg·kg	0.05±0.004	0.043±0.01	0.039±0.01
Cr, mg·kg	0.02±0.01	0.012±0.004	0.016±0.01

TEKA Archives of the Commission of Medical Sciences 2017. Vol.5, No 1.