BIOCHEMISTRY

THE EFFECT OF A HIGH-CALORIE DIET ON THE TOTAL CONTENT OF CHEMICAL ELEMENTS AND METAL-LIGAND FORMS OF ZINC IN THE BLOOD SERUM AND LIVER OF WISTAR RATS

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ABSTRACT

Background. *Worldwide, there is a rapid increase in the number of people suffering from various forms of carbohydrate and lipid metabolism disorders. Modern studies show that the transport, distribution, excretion and accumulation of chemical elements in these types of metabolic disorders change in different ways and affect the further functional state of the body differently.*

The aim. *To evaluate the level of macro- and microelements in the blood serum and liver, as well as the content of metal-ligand forms of zinc in the blood serum of a Wistar rat in a high-calorie diet.*

Materials and methods. *Thirty male rats were selected for the experiment, from which two groups were formed: control (n = 15) and experimental (n = 15). The animals of the control group received the basic diet (270 kcal/100 g), and the animals of the experimental group received a high-calorie diet. During the experiment, the caloric content of the diet of the experimental group gradually increased from the caloric content of the total diet. During the study, body weight, biochemical parameters of blood and urine were evaluated. The analysis of macro- and microelements in the samples was carried out using inductively coupled plasma mass spectrometry. Determination of the content of individual zinc compounds in blood serum was carried out using a combination of a chromatograph and a mass spectrometer.*

Results. *It was found that a high-calorie diet led to a decrease in the level of iron, chromium, iodine, zinc, potassium, calcium, and an increase in vanadium in blood serum. In the liver, there was a decrease in the level of lithium and an increase in the level of calcium, vanadium, chromium, iron, zinc, cobalt. When assessing the chemical forms of zinc in the blood serum, a percentage increase in the albumin fraction was recorded against the background of a decrease in amino acid complexes and low-molecular-weight forms of zinc.*

Conclusion. *The data obtained suggest that a high-calorie diet leads to an imbalance of chemical elements, which can serve as one of the triggers for dysregulation of a number of physiological functions of the body.*

Key words: *trace elements, zinc, high-calorie diet, overweight, obesity, speciation analysis*

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ВЛИЯНИЕ ВЫСОКОКАЛОРИЙНОЙ ДИЕТЫ НА СОДЕРЖАНИЕ ХИМИЧЕСКИХ ЭЛЕМЕНТОВ И МЕТАЛЛО-ЛИГАНДНЫЕ ФОРМЫ ЦИНКА В СЫВОРОТКЕ КРОВИ И ПЕЧЕНИ КРЫС ЛИНИИ WISTAR

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РЕЗЮМЕ

Обоснование. *Во всём мире отмечается стремительный рост числа людей, страдающих различными формами нарушения углеводного и липидного обмена. Современные исследования показывают, что транспорт, распределение, экскреция и накопление химических элементов при данных видах нарушения обмена изменяются по-разному и неодинаково влияют на дальнейшее состояние организма.*
Цель исследования. *Оценить уровень макро- и микроэлементов в сыворотке крови и печени, а также содержание металло-лигандных форм цинка в сыворотке крови у крыс линии Wistar в условиях высококалорийной диеты.*
Материалы и методы. *Для проведения эксперимента было отобрано 30 крыс-самцов, из которых были сформированы две группы: контрольная (n = 15) и опытная (n = 15). Животные контрольной группы получали основной рацион (270 ккал/100 г), а животные опытной группы – высококалорийную диету. В ходе эксперимента калорийность диеты опытной группы ступенчато увеличивалась от калорийности общего рациона. В ходе исследования оценивали массу тела, биохимические параметры крови и мочи. Анализ макро- и микроэлементов в образцах проводился с помощью метода масс-спектрометрии с индуктивно-связанной плазмой. Определение содержания индивидуальных соединений цинка в сыворотке крови проводился на комбинации хроматографа и масс-спектрометра.*
Результаты. *Установлено, что высококалорийная диета приводила к снижению уровня железа, хрома, йода, цинка, калия, кальция и увеличению содержания ванадия в сыворотке крови. В печени отмечалось снижение уровня лития и увеличение уровня кальция, ванадия, хрома, железа, цинка, кобальта. При оценке химических форм цинка в сыворотке крови фиксировалось процентное увеличение альбуминовой фракции на фоне снижения аминокислотных комплексов и низкомолекулярных форм цинка.*
Заключение. *Полученные данные позволяют предположить, что высококалорийная диета приводит к дисбалансу химических элементов, что может служить одним из пусковых механизмом дизрегуляции ряда физиологических функций организма.*

Ключевые слова: *микроэлементы, цинк, высококалорийная диета, избыточный вес, анализ содержания химических форм элементов*

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INTRODUCTION

Worldwide, there is a rapid increase in the number of people suffering from various forms of carbohydrate and lipid metabolism disorders [1, 2]. This group of population has an increased risk of developing obesity, type 2 diabetes mellitus, as well as a number of other diseases [3]. The ability of the body to effectively adapt metabolism depending on the needs and intake of nutrients is known as metabolic flexibility [4]. The basis for maintaining a normal metabolism of the body is a full diet. However, the diet of modern man is characterized by an unprecedented high level of consumption of high-calorie food [5]. Despite the increased caloric content of the diet, such a diet does not meet the recommended dietary requirements for the consumption of nutrients [6]. Improper nutrition in combination with physical inactivity reduces the metabolic flexibility of the body [7].

Fundamental and clinical studies show that the transport, distribution, excretion and accumulation of chemical elements in various forms of carbohydrate and lipid metabolism disorders change differently and affect the further state of the body differently [8, 9]. This is due to the fact that elemental homeostasis is a particular form of the general homeostatic system of the body, changes in which lead to a disorder of the molecular mechanisms of adaptation [10]. Until recently, elemental homeostasis was assessed by the total content of chemical elements in various bio substrates. However, recent studies have shown that changes in the level of trace elements, even in the range of normal values, are accompanied by their redistribution in different fractions [11]. Thus, metabolic disorders can occur not only as a result of a deficiency or excess of a certain element, but also due to the interaction between various metal ions and the presence of metal-binding (chelating) agents [12, 13]. Modern studies confirm that the change in the ratios of the forms of chemical elements in biological systems is the main trigger mechanism for the regulation or dysregulation of many physiological functions of living organisms [14, 15]. Zinc deficiency is known to be a risk factor for obesity and diabetes. The study of zinc content is important because various forms of this trace element are involved in a variety of biochemical and physiological processes, including the transport of Zn^{2+} to the liver and other organs; participation in the processes of cytotoxicity and inflammation, deactivation of free radicals, etc. However, the vast majority of works are focused only on determining the total level of chemical elements in individual bio substrates, which does not allow for a detailed assessment of metabolism.

THE AIM OF THE STUDY

To evaluate the level of macro- and microelements in the blood serum and liver, as well as the content of metal-ligand forms of zinc in the blood serum of a Wistar rat in a high-calorie diet.

MATERIALS AND METHODS

The study was carried out on the basis of the experimental biological clinic (vivarium) of the Federal Research Center for Biological Systems and Agrotechnologies of the Russian Academy of Sciences. The experiment was performed on Wistar rats in accordance with the protocols of the Geneva Convention and the principles of good laboratory practice (National Standard of the Russian Federation GOST 33044-2014: Principles of Good Laboratory Practice). The design of the experiment was approved by the local Ethics Committee of the Federal Research Center for Biological Systems and Agrotechnologies of the Russian Academy of Sciences.

Thirty male rats were selected for the experiment, from which two groups were formed: control (n = 15) and experimental (n = 15). At the beginning of the experiment, all laboratory animals were of the same age (12 weeks). The animals of the control group received the basal ration, and the animals of the experimental group received a high-calorie diet. The basal ration included a full-grain granular feed in accordance with GOST-R 50258-92 (full-grain feed for laboratory animals). The total caloric content of the ration was 270 kcal/100 g (20 % protein, 10 % fat and 70 % carbohydrates). A high-calorie diet was used to simulate the state of disorders of carbohydrate and lipid metabolism. The combination of a large amount of carbohydrates and fats of different origins more accurately mimics the human diet [16], in this regard, the diet is based on the addition of lard, coconut and sunflower oils to the overall balanced diet, a 10 % solution of fructose was used as a drink. All components of the diet were crushed into a homogeneous mixture, then granules were formed, which were subsequently dried in an oven at 25 °C. During the experiment, the caloric content of the diet gradually increased by 30 % (1–4 weeks), 60 % (5–8 weeks) and 90 % (9–12 weeks) of the caloric content of the total diet (Table 1). A step-by-step diet was used to gradually increase body weight in order to reduce the stress response of the body with an increase in caloric intake. The amount of feed consumed was 30 g per rat, which corresponds to the daily food requirement for this type of laboratory animals. Throughout the experiment, both in the experimental and control groups, complete feed consumption was recorded.

Every 4 weeks, an examination of animals was conducted, including an assessment of body weight, biochemical parameters of blood and urine, which made it possible to assess the disorder development degree of carbohydrate and lipid metabolism in the experiment. At the end of the test period, the animals were excluded from the experiment to collect biomaterial in order to assess the effect of a high-calorie diet on the body of laboratory animals.

Screening studies to assess the disorder development degree of carbohydrate and lipid metabolism were carried out by determining the level of glucose in an oral glucose tolerance test, total cholesterol, HDL, triglycerides and atherogenic index using a biochemical express analyzer Car-

TABLE 1

THE COMPOSITION OF A HIGH-CALORIE DIET (PER 100 G OF FEED)

Parameters	1–4 weeks	5–8 weeks	9–12 weeks
Caloric content, kcal	351	430	506
Proteins, %	17.2	14.5	12.1
Fats, %	20.8	32	42.3
Carbohydrates, %	62	53.5	45.6

dioChek (Polymer Technology System, USA). Urine analysis was performed using a semi-automatic analyzer Combilyzer 13 (Human, Germany) using Combina 13 test strips for the following indicators: color, volume, transparency, pH, specific gravity, erythrocytes, leukocytes, glucose, urobilinogen, protein, ketones, creatinine.

The analysis of macro- and microelements in blood serum and liver samples of laboratory animals was carried out using inductively coupled plasma mass spectrometry on an Elan 9000 (ICP-MS, PerkinElmer, USA). Determination of the content of individual zinc compounds in blood serum with high and low molecular weight biological ligands was carried out by high-performance liquid chromatography with inductively coupled plasma mass spectrometry (HPLC-ICP-DRC-MS) on a combination of PerkinElmer S200 chromatograph (PerkinElmer, USA) and Elan 9000 mass spectrometer (PerkinElmer, USA).

The data obtained were processed by variation statistics methods using Statistica 10 statistical package (StatSoft Inc., USA). The hypothesis that the data belonged to a normal distribution was rejected in all cases with a probability of 95 %, which justified the use of non-parametric Mann – Whitney U test. The relationships between the parameters were evaluated using Spearman's Rank Correlation Coefficient. The correlation coefficients were estimated as follows: less than 0.3 – weak relationship, from 0.3 to 0.5 – moderate, from 0.5 to 0.7 – significant, from 0.7 to 0.9 – strong and more than 0.9 – very strong relationship. In all statistical analysis procedures, the achieved significance level (p) was calculated, while the critical significance level was assumed to be $p \leq 0.05$.

RESULTS

The results of the studies showed that with a step-by-step increase in the caloric content of the diet, the body weight of laboratory animals of the experimental group significantly increased relative to the control group (Fig. 1). By the 4th week of the experiment, the body weight of the animals of the experimental group increased by 9.8 %, by the 8th week – by 30 % and by the 12th week – by 44.6 %.

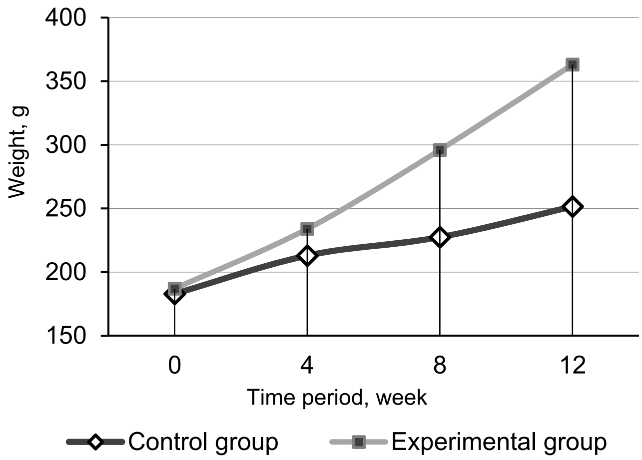

FIG. 1.

*The effect of a high-calorie diet on the dynamics of body weight of rats: ** – statistically significant difference between the experimental group and the control (p ≤ 0.01)*

The results of a biochemical analysis of blood by the end of the study showed a statistically significant ($p \leq 0.01$) increase in glucose levels by 52.5 %, total cholesterol by 40.6 %, triglycerides by 127 %, an increase in the atherogenic index by 239 % and a decrease in HDL levels by 26.5 % in animals of the experimental group relative to the control group (Table 2). These changes were not spontaneous, but tended to change gradually, starting from the 4th week of the experiment.

The results of the oral glucose tolerance test by 12 weeks of the experiment showed significant differences between the experimental and control groups. Post-load glucose levels in the control group began to decrease after the 30th minute and by the 120th minute returned to near baseline values; while in the experimental group the decrease started only after the 60th minute (Fig. 2).

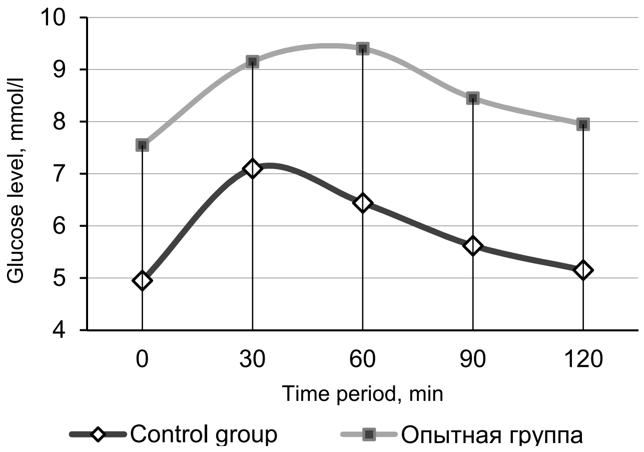

FIG. 2.
*The effect of a high-calorie diet on glucose levels in an oral glucose tolerance test (12 weeks of experiment): ** – statistically significant difference between the experimental group and the control (p ≤ 0.01)*

The results of clinical and biochemical urinalysis did not undergo significant statistical changes at all stages of the experiment and were within normal values (Table 3).

Macro- and microelements are known to play an important role in the normal functioning of carbohydrate and lipid metabolism [17], so the content of chemical elements in the blood serum of laboratory animals was studied. In the experimental group relative to control, there was a statistically significant decrease in the level of iron (Fe) by 30 %, chromium (Cr) – by 20 %, iodine (I) – by 18 %, zinc (Zn) – by 11 %, potassium (K) – by 8.3 %, calcium (Ca) – by 6.3 % and an increase in vanadium (V) by 5.3 % (Fig. 3).

The liver is a key organ of homeostasis, the metabolic role of which consists in the metabolism of a number of nutrients, including chemical elements [18]. In this regard, the content of chemical elements in liver tissues was also evaluated. In the experimental group of rats, there was a statistically significant decrease in the level of lithium (Li) by 39.7 % and an increase in the level of Zn by 4.3 %, Ca by 32.4 %, V by 33.3 %, Cr by 45.2 %, Fe by 53.4 %, and cobalt (Co) by 74.4 % (Fig. 4).

During the correlation analysis between the chemical elements of blood serum and liver, the following pattern was established: in animals of the experimental group, as a result of high-calorie diet, a decrease in a number of chemical elements in blood serum was recorded, which led to their increase in the liver (iron, chromium, iodine, sodium, zinc, calcium) and vice versa (manganese). Strong negative correlation was observed for iron ($r = -0.728$), significant correlation – for chromium ($r = -0.654$) and calcium ($r = -0.679$), moderate correlation – for iodine ($r = -0.456$), weak correlation – for sodium ($r = -0.227$), zinc ($r = -0.171$) and manganese ($r = 0.116$). Lithium, selenium, boron, magnesium, potassium, phosphorus, copper, vanadium, and cobalt had the same tendency to change, both in blood serum and in the liver.

Zinc deficiency is known to be a risk factor for obesity and diabetes [19]. In this regard, the metal-ligand fractions of zinc in the blood serum of laboratory animals were evaluated. Four zinc-containing fractions were identified: α2-macroglobulin, albumin, amino acid complexes (AMC complexes) and low molecular weight forms of zinc. Figure 5 shows the results of the analysis of the percentage distribution of zinc by fractions when exposed to a high-calorie diet.

A statistically significant percentage increase in the albumin fraction from 45 to 66 % ($p < 0.05$) occurred in the experimental group of rats relative to the control affected by a decrease in AMC complexes and low molecular weight

TABLE 2

THE EFFECT OF A HIGH-CALORIE DIET ON THE BIOCHEMICAL ANALYSIS OF RAT BLOOD (12 WEEKS OF EXPERIMENT)

Parameters	Control group	Experimental group
Glucose, mmol/L	4.95 (4.83–5.15)	7.55 (7.43–7.68)**
Cholesterol, mmol/L	1.6 (1.56–1.64)	2.25 (2.13–2.45)**
HDL, mmol/L	0.98 (0.97–0.99)	0.72 (0.69–0.74)**
Triglycerides, mmol/L	0.59 (0.48–0.69)	1.34 (1.28–1.4)**
Atherogenic index	0.64 (0.61–0.71)	2.17 (1.97–2.35)**

Note. ** – statistically significant difference between the experimental group and the control ($p \leq 0.01$).

TABLE 3

THE EFFECT OF A HIGH-CALORIE DIET ON CLINICAL AND BIOCHEMICAL URINALYSIS OF LABORATORY ANIMALS (12 WEEKS OF EXPERIMENT)

Parameters	Control group	Experimental group
Color	yellow	yellow
Volume, ml	2.1 (1.8–2.1)	2 (1.9–2.1)
Transparency	transparent	transparent
pH	7.4 (7.3–7.5)	7.4 (7.3–7.5)
Specific gravity, rel.units	1.05	1.07
Erythrocytes, u/ml	0	0
Leukocytes, u/ml	0	0
Glucose, mmol/L	0	0
Urobilinogen, mmol/L	0.2 (0.18–0.24)	0.22 (0.19–0.27)
Protein, g/L	0	0
Ketones, µmol/l	0	0
Creatinine, mmol/L	13.2 (8.4–17.7)	12.4 (8.8–16.9)

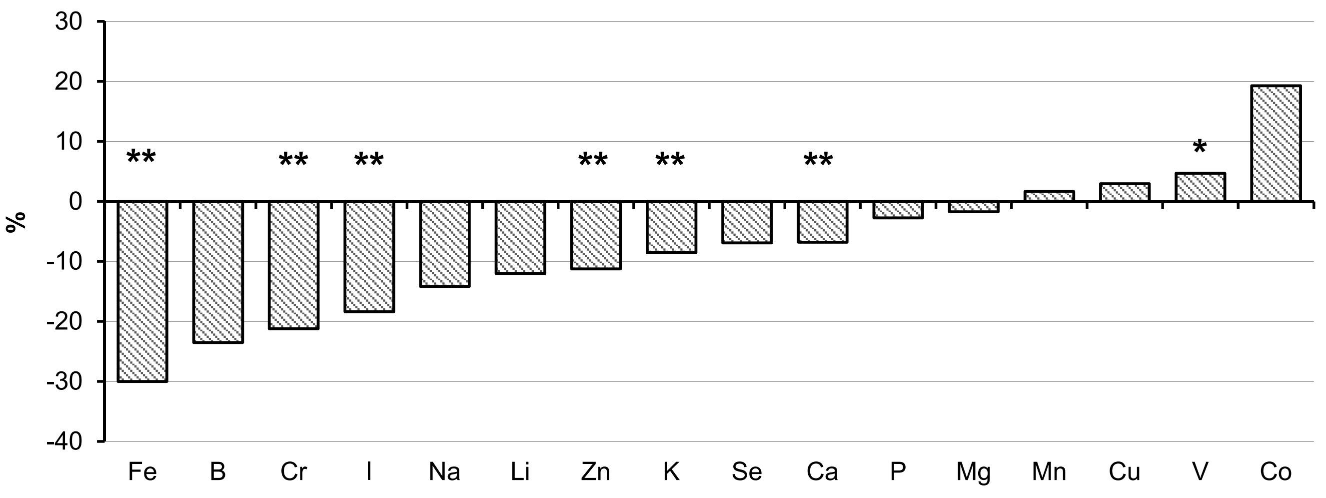

FIG. 3.
*Relative values of the content of chemical elements in the blood serum of the experimental group of rats (12 weeks of the experiment): X-axis (0) – the level of elements in the control group; * – statistically significant difference between the experimental group and the control (p ≤ 0.05); ** – statistically significant difference between the experimental group and the control (p ≤ 0.01)*

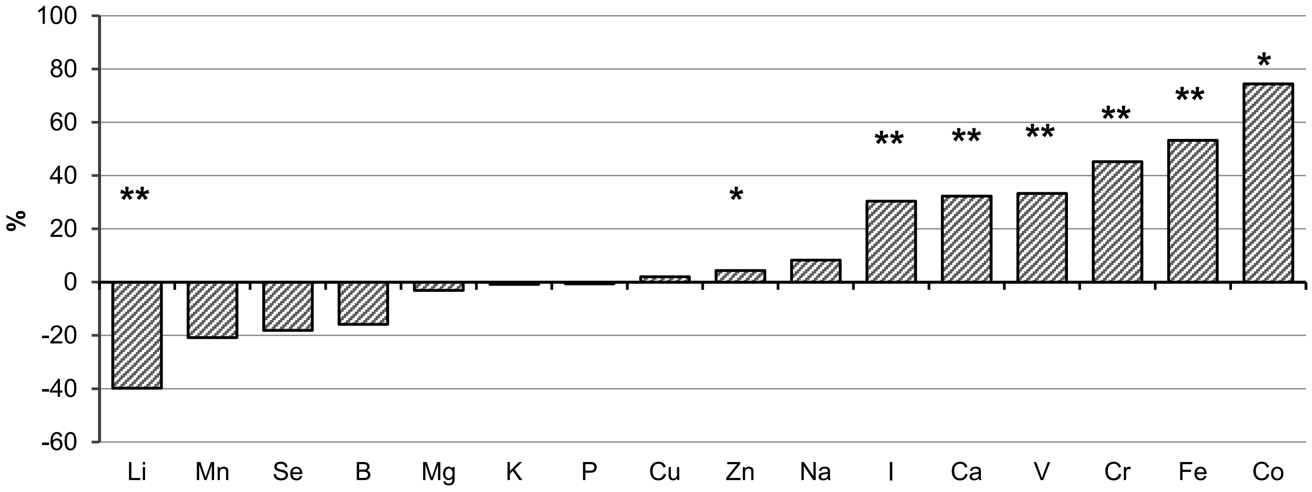

FIG. 4.

*Relative values of the content of chemical elements in the liver of the experimental group of rats (12 weeks of experiment): X-axis (0) – the level of elements in the control group; * – statistically significant difference between the experimental group and the control ($p \leq 0.05$); ** – statistically significant difference between the experimental group and the control ($p \leq 0.01$)*

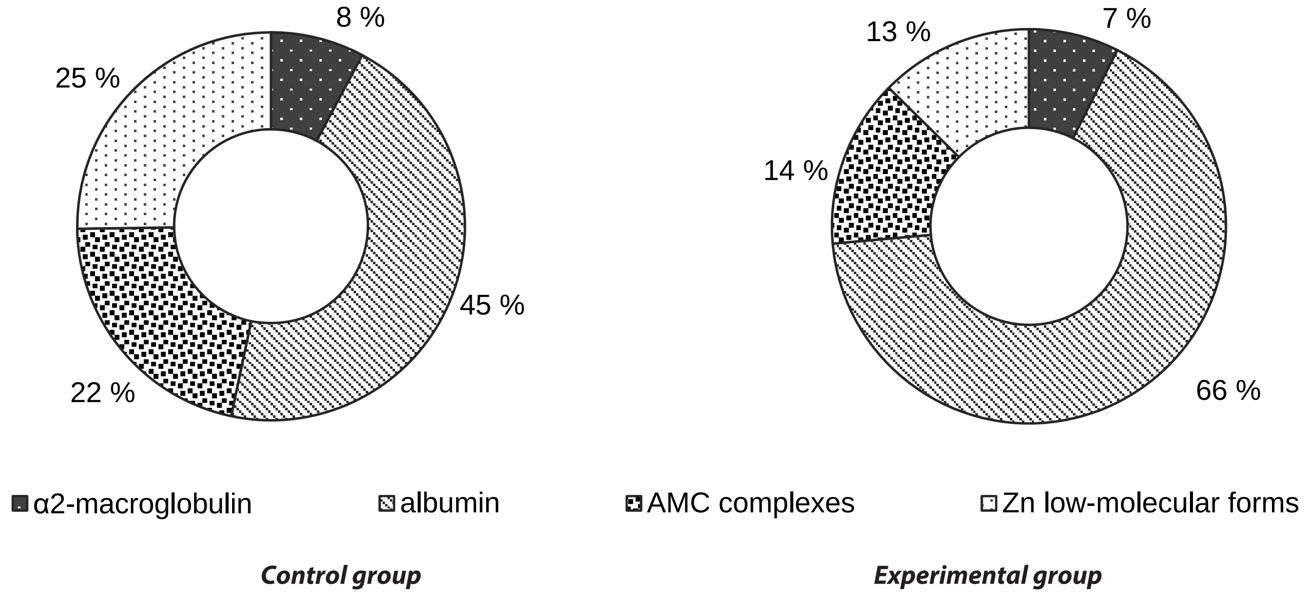

FIG. 5.

*Percentage distribution of zinc by fractions when exposed to a high-calorie diet (12 weeks of experiment): ** – statistically significant difference between the experimental group and the control ($p \leq 0.01$)*

forms of zinc. α2-macroglobulin level did not undergo significant changes throughout the study.

DISCUSSION

On average, the excess of the control body weight in animals of the experimental groups under the influence of the high-calorie diet by the end of the study was 44 %, which indicates the appearance of excess body weight. In the experimental group of animals, there was a statistically significant tendency for glucose, total cholesterol and triglyceride levels to increase while HDL levels decreased. The established impaired glucose tolerance as detected during the oral glucose tolerance test, as well as an increase in the atherogenic index, are predictors of diabetes and serve as risk factors for cardiovascular diseases [20]. The findings may indicate insulin resistance developing as a result of obesity, which in turn will aggravate the accumulation and retention of fat in the body. The revealed disorders of carbohydrate and lipid metabolism are among the first typical signs of metabolic syndrome and may be associated with pro-inflammatory processes that may partially occur in adipose tissue [21].

There are a number of studies investigating the possibility of using the content of macro- and microelements in various biosubstrates as biomarkers of various disorders of carbohydrate and lipid metabolism, as well as their use as dietary supplements for metabolic correction [22]. The data obtained during the study show that exposure to a high-calorie diet for 12 weeks led to a statistically significant decrease in the levels of iron, chromium, iodine, zinc, potassium, calcium and an increase in vanadium in blood serum. In the liver tissues of the experimental group animals, a statistically significant decrease in lithium levels and an increase in zinc, calcium, vanadium, chromium, iron, and cobalt levels were noted. It is possible that such a pattern, associated with the reverse redistribution of certain chemical elements from the blood serum to the liver, is due to a defense mechanism. One study has demonstrated that interleukins released from activated phagocytic cells reduce the concentration of certain trace elements in the blood of experimental animals by redistributing them from the blood to the liver [23]. The identified chemical elements play an essential role in the regulation of carbohydrate and lipid metabolism [24]. Any changes in calcium concentration can interfere with the normal release of insulin, especially in response to glucose load, which in turn will affect body fat accumulation [25]. Chromium increases insulin sensitivity and is a component of glucose tolerance factor, and its decrease in blood serum in obese individuals with impaired glucose tolerance is recorded in many studies [26]. The inflammatory component of obesity, which leads to excessive hepcidin production, is believed to be one of the potential mechanisms of iron deficiency (hypoferremia) in obesity [27]. Variations in iodine, potassium, vanadium and cobalt concentrations in various disorders of carbohydrate and lipid metabolism are found in the works of several researchers, but require more detailed study.

Zinc cannot freely cross cell membranes, so there are a number of special carriers [28]. In this regard, the study of zinc complexation is important since various forms of this trace element are involved in a variety of biochemical and physiological processes, including Zn^{2+} transport into the liver and other organs; participation in the cytotoxicity and inflammation processes, deactivation of free radicals, etc. [29]. In this study, a decrease in total blood zinc level and an increase in liver tissue zinc level were detected, while a statistically significant percentage increase in the albumin fraction was recorded, with a decrease in AMC complexes and low-molecular-weight forms of zinc. Studies conducted by K.T. Smith et al. on isolated perfused rat intestines have shown that albumin is responsible for Zn^{2+} transport into the liver [30], which may explain the findings. The observed statistically significant changes in zinc distribution by individual forms in blood serum indicate a change in zinc metabolism due to high-caloric diet consumption. Evaluation of zinc fractions in blood serum revealed the presence of dysmetabolism of this metal when exposed to a high-calorie diet at a more subtle level. It is possible that these changes served as the molecular basis for changes in the total concentration of zinc in blood serum.

CONCLUSION

1. In the course of the study, it was found that the use of the developed high-calorie diet by Wistar rats for 12 weeks led to overweight in animals, impaired lipid metabolism and impaired glucose tolerance. These findings show that this diet makes it possible to simulate metabolic disorders and prove the effectiveness of its further use in studies of disorders of carbohydrate and lipid metabolism in laboratory animals.
2. In the course of the study, it was found that a high-calorie diet led to a statistically significant decrease in the levels of iron, chromium, iodine, zinc, potassium, calcium and an increase in vanadium in blood serum. In turn, there was a statistically significant decrease in the level of lithium and an increase in the level of zinc, calcium, vanadium, chromium, iron, and cobalt in the liver.
3. Due to the evaluation of the chemical forms of zinc, it was found that the detected decrease in zinc in blood serum and an increase in its concentration in the liver when using a high-calorie diet is associated with an increase in the serum albumin fraction of zinc affected by a decrease in AMC complexes and low-molecular forms of zinc.

The evidence suggests that a high-calorie diet leads to an imbalance of chemical elements, which may be one of the triggering mechanisms for the dysregulation of a number of physiological functions in living organisms. The changes revealed in metabolism may be a direct cause of the development of various functional disorders responsible for the onset of metabolic disorders and associated diseases.

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Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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