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USE OF MINERAL WATER WITH HIGH ORGANIC SUBSTANCES IN EXPERIMENTAL METABOLIC SYNDROME

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Introduction. Metabolic syndrome (MS) is considered a combination of several pathological processes – obesity, high blood pressure, dyslipidemia, carbohydrate metabolism disorder, and diabetes mellitus (DM), which determines the involvement of many functional systems of the body. One method for correcting metabolic disorders is crenotherapy, i.e., drinking various mineral waters (MW).

The research **aims** to determine experimentally the possibility of using MW with a high content of organic substances to restore the morpho-functional parameters of the body of a rat with a model of metabolic syndrome.

Materials and methods. Twenty-four rats were reproduced in the MS model using a high-glycemic load diet. After reaching the MS model, all rats were randomly divided into two groups of 12 animals each. All rats continued to receive the diet described above; however, the second (experimental) group also received intragastric MW with a high content of organic substances at a dose of 1% of body weight.

Results. The establishment of the MS model in rats is a crucial step, as it leads to significant functional disorders of the liver and kidneys. A comprehensive study of the histological structure of the liver and kidneys in rats with a model of MS revealed the dystrophic changes in hepatocytes and nephrons, underscoring the relevance of our research. MW treatment significantly improved the structural characteristics of the liver and kidney parenchyma of experiment rats. The level of endogenous intoxication normalized, and the water-electrolyte balance was restored.

Conclusions. Using a course of MW with an increased content of organic substances in rats with a metabolic syndrome model promotes the restoration of the structural organization of liver and kidney tissue, which leads to the normalization of the corresponding functional indicators. The obtained experimental results allow us to recommend the use of mineral waters with increased organic content for clinical studies in the rehabilitation of patients with metabolic syndrome.

Key words: metabolic syndrome, natural mineral water, liver, kidneys.

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ВИКОРИСТАННЯ МІНЕРАЛЬНОЇ ВОДИ З ВИСОКИМ ВМІСТОМ ОРГАНІКИ ПРИ ЕКСПЕРИМЕНТАЛЬНОМУ МЕТАБОЛІЧНОМУ СИНДРОМІ

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Мета роботи – експериментально визначити можливість використання МВ із високим вмістом органічних речовин для відновлення морфофункціональних показників організму щура з моделлю метаболічного синдрому. На 24 щурах була відтворена модель МС із використанням дієти з високим глікемічним навантаженням. Дослідна група отримувала внутрішньошлунково МВ з високим вмістом органічних речовин у дозі 1% від маси тіла. Комплексне вивчення гістологічної структури печінки та нирок у щурів з моделлю МС виявило дистрофічні зміни гепатоцитів та нефронів. На фоні прийому МВ відбувалися значні позитивні зміни структурних характеристик паренхіми печінки та нирок дослідних щурів; нормалізація рівня ендогенної інтоксикації та відновлення водно-електролітного балансу. Отримані експериментальні результати дозволяють рекомендувати використання мінеральних вод із підвищеним вмістом органічних речовин для клінічних досліджень у реабілітації хворих на метаболічний синдром.

Ключові слова: метаболічний синдром, природна мінеральна вода, печінка, нирки.

Introduction. Metabolic syndrome (MS) is one of the most pressing problems of modern medicine. Today, there is a steady trend of increasing disease cases among the population of most world countries [1]. MS is considered a combination of several pathological processes – obesity, high blood pressure, dyslipidemia, carbohydrate metabolism disorder, and diabetes mellitus (DM), which determines the involvement of many functional systems of the body [2]. There is no single method for treating MS, and existing pharmacotherapy requires the constant use of a large number of drugs, which can cause unwanted side effects [3]. Therefore, an essential task for researchers dealing with MS is searching for new non-drug correction agents with optimal metabolic, physiological, and organoprotective effects [4].

One method for correcting metabolic disorders is crenotherapy, i.e., drinking various mineral waters (MW). This treatment affects metabolic processes and activates protective and adaptive mechanisms by modulating the activity of the body's functional systems [5]. The use of MW has several advantages compared to medications: they do not cause negative side effects, have great polyvalent biological activity, have a long-term therapeutic effect, and can be used in complex treatment [6].

MW are characterized by high bioavailability of macro- and microelements, biologically active compounds, and components, which, in some cases, makes them more effective in achieving a therapeutic effect at a dose significantly lower than in pharmaceutical preparations [7]. In this regard, our attention was drawn to low-mineralized minerals with a high content of organic substances (OS). These minerals, with low total mineralization (the content of HCO_3^-, CI^-, SO_4^{2-}, Na^+, K^+, Mg^{2+}, Ca^{2+} does not exceed 1 g/l), are distinguished by proven corrective and therapeutic properties [8]. The high biological activity of this type of MW is associated precisely with OS, which include low molecular weight fatty acids, amine-like substances, volatile and non-volatile organic acids, phenols, bitumens, humins, and estrogen-like compounds similar to natural hormones. At the same time, these OS do not influence independently but in combination with a complex of basic salts and MW gases as a single bioactive complex [9]. Considering their specific composition, these MW can exert a systemic effect on the mechanisms regulating the body's vital activity as a whole, not just on individual organs.

This hypothesis was the basis for the **aim of the present work** – to determine experimentally the possibility of using MW with a high content of organic substances to restore the morpho-functional parameters of the body of a rat with a model of metabolic syndrome.

Materials and methods of research. The experiment was carried out on female white rats of the Wistar line, herd breeding, 12 months old, obtained from the nursery of the private enterprise "Biomodelservis", Kyiv. Experimental studies were carried out in the vivarium of the State Institution "Ukrainian Research Institute of Medical Rehabilitation and Resort Therapy of the Ministry of Health of Ukraine". The keeping of rats and research were carried out by regulatory documents – Directive of the European Parliament and Council (2010/63/EU), and the order of the Ministry of Education and Science, Youth and Sports of Ukraine dated 01.03.2012 No. 249 "On approval of the Procedure for conducting research by scientific institutions experiments, experiments on animals" and Protocol No. 3 of 05/03/2024 from the Bioethics Commission of the State Institution "Ukrainian Research Institute of Medical Rehabilitation and Resort Therapy of the Ministry of Health of Ukraine". The animals were kept under standard conditions, at a temperature of 19–24°C, in plastic cages (6 animals in each), under natural day-night light conditions.

The study design was as follows: the MS model was reproduced in 24 animals by daily adding 30 g of white bread and 10% fructose solution in distilled water as a drink to the standard diet [10].

After 60 days, all rats were randomly divided into two groups of 12 animals each, 1st – "Control", and 2nd – "Experimental". All rats continued to receive the diet described above, but the second (experimental) group also received intragastric MW at a dose of 1% of body weight. The study used natural, low-mineralized sodium bicarbonate water with a high organic content. The organic content in the water in terms of total organic carbon (Corg) was 12.00 mg/l (with the balneological norm for waters with a high Corg content over 5.00 mg/l). The composition of the MW complied with the requirements according to the Industry Standard of Ukraine 42.10-02-96. Kyiv: Ministry of Health of Ukraine, 1996. 30 p. and the Order of the Ministry of Health of Ukraine dated 06/09/2003 No. 243 "On approval of the Procedure for carrying out medico-biological assessment of the quality and value of natural medicinal resources, determination of methods of their use." The total mineralization of MW was 81.00 mg/l. The formula of the chemical composition of water has the following form:

$$C_{org}\ 0.012\ M_{0,81}\ \frac{(HCO_3 + CO_2)\ 94}{(Na+K)99}$$

MW was injected into the esophagus of rats with a soft probe once a day, at a dose of 1% of the animal's body weight, in the evening (at approximately 17.00), taking into account the peculiarities of rats' daily biorhythm. The course of taking MW was 12 days. One day before the end of the experiment, the animals were placed in special container cages, and daily urine was collected to assess kidney function.

The functional state of the kidneys was assessed by the effect on urine formation function (glomerular filtration rate, tubular reabsorption, daily diuresis), excretory function (by creatinine and urea excretion), and ion-regulatory function (by concentration and daily excretion of ions). The acid-base reaction of 24-hour urine was also determined based on the concentration of hydrogen ions (a pH-meter pH-150 MI was used). The CI^-, Na^+, and K^+ concentrations in urine were determined using an AEK-01 "Kver" analyzer for the concentration of electrolytes in biological fluids.

In the blood serum, the glucose content, the content of triglycerides and cholesterol, and the content of molecules of average weight (MAW_{254} and MAW_{280}) were determined by biochemical methods: urea, creatinine, and uric acid content. The studies of the above indicators were carried out using generally accepted procedures [11].

Animals were removed from the experiment by decapitation under ether anesthesia. Three ml of blood was

taken from the animals for biochemical studies, and parts of the kidney and liver for morphological studies.

During the autopsy, pieces of kidneys and liver measuring ten mm^2 were selected. Material for histological examination was prepared according to generally accepted methods [12].

Microscopic studies of structural changes were carried out on the resulting preparations. The methodological techniques involved in the research were approved by Order of the Ministry of Health of Ukraine No. 692, dated September 28, 2009, "On approval of methodological recommendations on methods for studying the biological effects of natural medicinal resources and preformed medicinal products".

The statistical processing of the obtained data was carried out using the statistical package Statistica 10.0. All data were tested for normality using the Kolmogorov-Smirnov test. The significance of differences was determined using Student's t-test. Data were presented as mean ± standard deviation.

Results and discussion. The proposed nutritional methodology led to evidence-based reproduction of the MS model on the 60th day of the experiment, which is consistent with the data of other authors [13]. Table 1 shows changes in metabolic parameters upon reaching the MS model.

According to the data in Table 1, in rats with the MS model, all studied metabolic parameters change significantly, which are unidirectional negative. The content of cholesterol ($p<0.01$), triglycerides ($p<0.01$), and glucose ($p<0.01$) increases significantly, which indicates a violation of lipid and carbohydrate metabolism.

Similar changes are observed with the urea level, indicating a protein metabolism violation. The uric acid content also significantly increases ($p<0.05$), indicating negative changes in purine metabolism, increased catabolic processes, and the risk of developing cardio-renal disorders [14]. The combination of the above changes in metabolic parameters leads to an increase in endogenous intoxication, confirmed by a significant rise in MAW_{280} [15].

Table 2 shows data on the configuration of the filtration characteristics and excretory functions of the kidneys of rats during the development of MS.

According to Table 2, the development of MS in rats leads to impaired renal function in addition to changes in metabolism. This primarily concerns indicators of electrolyte metabolism: against the background of a practically unchanged level of potassium ion excretion,

Table 1

Metabolic parameters of rats before the experiment and after reaching the metabolic syndrome model, (M ± m)

Indexes	Before the experiment (norm) n=24	After reaching the MS model n=24	P
Glucose, mmol/l	5.11 ± 0.22	7.42 ± 0.33	< 0.001
Cholesterol, mmol/l	1.63 ± 0.10	2.04 ± 0.11	< 0.001
Triglycerides, mmol/l	1.10 ± 0.06	2.48 ± 0.27	< 0.001
Urea, mmol/l	2.80 ± 0.27	3.52 ± 0.21	< 0.01
MAW_{254}, c. u	0.34 ± 0.02	0.33 ± 0.01	> 0.05
MAW_{280}, c. u	0.22 ± 0.01	0.29 ± 0.02	< 0.01

Note: P is the reliability of the differences between indicators before the experiment and after reaching the MS model

Table 2

The state of functional activity of the kidneys of rats before the experiment and upon reaching the metabolic syndrome model, (M ± m)

Indexes	Before the experiment (norm) n=24	After reaching the MS model n=24	P
Daily diuresis, ml/dm2 of body surface	0.98 ± 0.07	1.25 ± 0.11	< 0.05
Glomerular filtration rate, ml/(dm2×min)	0.16 ± 0.01	0.18 ± 0.02	> 0.05
Tubular reabsorption percentage of filtration, %	99.54 ± 0.04	97.37±0.16	> 0.05
Creatinine excretion, mmol	0.016 ± 0.001	0.017±0.002	> 0.05
Urea excretion, mmol	0.74 ± 0.09	0.79 ± 0.13	> 0.05
Daily urine pH, units. pH	7.21 ± 0.16	8.13 ± 0.11	< 0.001
Concentration of potassium ions in daily urine, mmol/l	108.00 ± 5.60	111.27 ± 8.44	> 0.05
Daily excretion of potassium ions, mmol.	0.11 ± 0.01	0.12 ± 0.01	> 0.05
Concentration of sodium ions in daily urine, mmol/l	152.64 ± 10.87	102.78 ± 8.25	< 0.001
Daily excretion of sodium ions, mmol	0.13 ± 0.01	0.07 ± 0.02	< 0.05
Concentration of chloride ions in daily urine, mmol/l	231.09 ± 17.64	227.16 ± 16.35	> 0.05
Daily excretion of chloride ions, mmol	0.22 ± 0.02	0.21 ± 0.05	> 0.05
Uric acid, mkmol/l	122.98 ± 8.43	185.23 ± 11.16	< 0.01
Creatinine, mkmol/l	48.36 ± 1.13	54.02 ± 2.17	< 0.05

Note: P is the reliability of the differences between indicators before the experiment and after reaching the MS model

sodium excretion sharply decreases, which is a sign of the formation of disturbances in water-electrolyte metabolism.

Other authors also note negative changes in water-electrolyte balance in rats with a model of MS induced by prolonged use of a 10% fructose drinking solution [16].

Such a disturbance of electrolyte metabolism may be caused by a significant increase ($p<0.001$) in the glomerular filtration rate (GFR), which leads to an increase in the volume of daily diuresis. The effect of glomerular hyperfiltration against the background of MS development that we have established is confirmed in the works of other researchers [17]. Its further progression creates prerequisites for the development of nephropathy.

At the same time, it should be noted that the excretory function of the kidneys in terms of urea excretion is practically no different from the control.

Therefore, it can be concluded that the development of the MS model in rats, which leads to pronounced functional disorders of the liver and kidneys, opens up new avenues for future research.

Table 3 presents data showing how consumption of mineral water with a high organic content affects the above-described disorders.

Unlike rats of Control group, where negative dynamics continued, rats of Experimental group experienced significant improvements in almost all recorded metabolic parameters (Table 3). Compared to animals with uncorrected MS, a substantial decrease in the content of glucose, triglycerides, cholesterol, creatinine, and MAW_{280} was observed. As a result, all of the above indicators are normalized except glucose levels, which indicates a complete restoration of lipid metabolism and a significant improvement in protein metabolism.

The glucose level in rats of the Experimental group decreased significantly compared to the control, but complete recovery did not occur. Given this trend, a longer course of MW is required. In general, the metabolic structure

Table 3

Changes in metabolic parameters of rats with the MS model during course use of MW, (M ± m)

Indexes	Before the experiment (norm) n=24	Control Group n=12	Experimental Group n=12	P
Glucose, mmol/l	5.11 ± 0.22	8.06 ±0.33***	6.01 ± 0.14**	< 0.001
Cholesterol, mmol/l	1.63 ± 0.10	2.15 ± 0.11**	1.61 ± 0.07	< 0.01
Triglycerides, mmol/l	1.10 ± 0.06	2.80 ± 0.27***	1.07 ± 0.06	< 0.001
Urea, mmol/l	0.34 ± 0.02	0.30 ± 0.01	0.31 ± 0.01	> 0.05
MAW_{280}, ум. од.	0.22 ± 0.01	0.31 ± 0.01***	0.24 ± 0.01	< 0.001
Creatinine, mkmol/l	48.36 ± 1.13	59.04 ± 2.58**	52.04 ± 1.45*	< 0.05

Note: * – reliability of comparison of indicators of groups 1 and 2 with the norm:
* – (< 0.05), ** – (< 0.01), *** – (< 0.001);
P – the reliability of the comparison between the indicators of 1 and 2 groups.

Table 4

Changes in indicators of the functional state of the kidneys in rats with a model of MS during course use of MW, (M ± m)

Indexes	Before the experiment (norm) n=24	Control Group n=12	Experimental Group n=12	P
Diurnal diuresis, ml/dm2 of body surface	0.98 ± 0.07	1.29 ± 0.11*	1.94 ± 0.17**	< 0.05
Glomerular filtration rate, ml/(dm2×min)	0.16 ± 0.01	0.19 ± 0.08	0.14 ± 0.05	> 0.05
Tubular reabsorption percentage of filtration, %	99.54 ± 0.04	99.37±0.16	97.20 ± 0.26***	< 0.001
Creatinine excretion, mmol	0.016 ± 0.001	0.019±0.001*	0.014 ± 0.002	< 0.05
Urea excretion, mmol	0.74 ± 0.09	0.82 ± 0.13	0.99 ± 0.09*	> 0.05
Daily urine pH, units. pH	7.21 ± 0.16	8.31 ± 0.11**	8.35 ± 0.15**	> 0.05
Concentration of potassium ions in daily urine, mmol/l	108.00 ± 5.60	119.83 ± 8.44	71.00 ± 6.12**	< 0.01
Daily excretion of potassium ions, mmol.	0.11 ± 0.01	0.12 ± 0.01	0.07 ± 0.01**	< 0.001
Concentration of sodium ions in daily urine, mmol/l	152.64 ± 10.87	90.98 ± 8.25**	93.67 ± 7.56**	> 0.05
Daily excretion of sodium ions, mmol	0.13 ± 0.01	0.08 ± 0.02*	0.09 ± 0.03	> 0.05
Concentration of chloride ions in daily urine, mmol/l	231.09 ± 17.64	221.98 ± 16.35	138.07 ± 10.22**	< 0.05
Daily excretion of chloride ions, mmol	0.22 ± 0.02	0.21 ± 0.03	0.13 ± 0.04*	< 0.05
Urea, mmol/l	2.80 ± 0.23	3.71 ± 0.21*	3.46 ± 0.15*	> 0.05
Uric acid, mkmol/l	122.98 ± 8.43	196.77 ± 11.62**	142.71 ± 9.26	< 0.01

Note: * – reliability of comparison of indicators of groups 1 and 2 with the norm:
* – (< 0.05), ** — (< 0.01), *** – (< 0.001);
P – the reliability of the comparison between the indicators of 1 and 2 groups.

approaches the state in intact rats, which is confirmed by the normalization of the level of endogenous intoxication (reduction of MAW_{280} content to control level).

As seen from Table 4, using a course of MW with increased OC in rats of an Experimental Group causes positive changes in kidney activity. Compared with the data of the Control group, this primarily concerns the function of urine formation due to the restoration of the glomerular filtration rate and a significant decrease in tubular reabsorption ($P<0.001$). As a result, the concentration of potassium, sodium and chloride ions in the urine decreases sharply, which leads to the restoration of the ionic balance of the blood and, as a consequence, the restoration of the water-electrolyte balance. We consider a reliable increase in the excretion of urea with daily urine (against the background of its decrease to the control level in the blood) as a positive phenomenon, which is due to the activation of the excretory function of the kidneys. These observed dynamics of functional indicators are of significant importance in understanding the physiological processes at play.

In the next stage of work, we investigated what morphological changes in the studied organs led to the observed dynamics of functional indicators.

A study of the histological structure of the liver in rats with a model of MS demonstrated the preservation of the lobular organization of the parenchyma and increased blood filling of the vessels, edema of Kupffer cells, and a corresponding narrowing of the interstitial spaces. Hepatocytes are mostly moderate in size, with a busty cytoplasm and small fat-containing vacuoles. There are structural manifestations of dystrophic changes – development of steatosis, which is confirmed by data from other authors [18].

During taking MW, significant positive changes occurred in the structural characteristics of the liver parenchyma of experiment rats. The vessels of the triads returned to moderate blood filling, the edema of Kupffer cells disappeared, and, as a consequence, an expansion of the interstitial space was observed. Hepatocytes in the beams are generally quite large, medium-sized nuclei are richly colored, and binucleate hepatocytes are found. The cytoplasm becomes homogeneous and darkly eosinophilic in color. That is, there is a restoration of the structural organization of the liver parenchyma and the disappearance of manifestations of dystrophy.

When studying the structural organization of the kidneys in rats with the MS model, the following was found: the placement and shape of the renal corpuscles did not change compared to the control, there are corpuscles with a swollen outer membrane, but the capillary glomeruli have a spherical shape. The epithelial cells are edematous, some with vacuoles in the cytoplasm. The interstitial spaces are also edematous and moderately infiltrated with lymphocytes. The twisting tubules are partly sharply dilated, partly with disordered epithelium, some of them contain cylinders in the lumen. The picture we observe corresponds to the morphological signs of dystrophic processes in the tissue other researchers observed [19].

A histological study of the kidneys of rats in Experimental Group determined that the nephron structure corresponded to the picture we observed in the intact animals. It can be concluded that the use of MW contributed to the disappearance of dystrophic changes and the complete restoration of the kidneys' morphological structure.

Natural MW are characterized by a high content of minerals and biologically active substances (microelements, gases, organic substances, etc.) [20]. Although to date the exact mechanism of the influence of natural minerals on the metabolic status 796 46 40 of the body has not yet been determined (or not studied, not established), a large number of substantiated evidence of their corrective and therapeutic properties are provided [21]. Natural MW are essentially non-specific modulators. They have a corrective effect on the state of numerous pathogenetic links that determine the course of the pathological process in the body. The results obtained by many researchers confirm this position [22; 23; 24].

Conclusions. Thus, the research findings showed that the development of metabolic syndrome in rats is accompanied by changes in the morphological structure and, accordingly, the function of the liver and kidneys. The progressing pathological process is caused by dystrophic changes in the parenchyma cells of these organs, which leads to disruption of carbohydrate, lipid, and protein metabolism and water-electrolyte balance. Using a course of MW with increased content of organic substances in rats with a metabolic syndrome model promotes the restoration of the structural organization of liver and kidney tissue, which leads to the normalization of the corresponding functional indicators.

The obtained experimental results allow us to recommend using mineral waters with increased organic content for clinical studies in rehabilitating patients with metabolic syndrome.

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