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THE POSSIBILITIES TO REDUCE CARDIOMETABOLIC RISK OF PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE. ARE DRUGS ALWAYS ESEENTIAL?

Abstract. *The efficacy of internal administration of various mineral waters and bischofite water solution has been examined in patients with non-alcoholic fatty liver disease (NAFLD). Administration of Poltava bischofite water solution improves clinical course of the underlying disease (p<0,05), comorbid pathology of the biliary tract (p<0,02) and irritable bowel syndrome (IBS) with constipations (p<0,003), improves liver functional state and lipid spectrum of the blood (p<0,02), reduces insulin resistance considerably (p<0,01), first of all, at the expense of decreased hyperinsulinemia (p<0,01), produces a positive effect on diurnal profile of blood pressure (BP) at the expense of reduced average values of systolic and diastolic arterial blood pressure. The use of mineral waters with prevailing sulfates in their content enables to improve clinical course of liver pathology (p<0,01), biliary tract (p<0,01) and intestines (p<0,003), normalize the liver functional state including those patients with non-alcoholic steatohepatitis (NASH) (p<0,05), improve considerably the values of lipid blood spectrum (p<0,02) against the ground of reliable decrease of insulin resistance (p<0,05). The use of mineral waters with prevailing hydrocarbonate content improves the course of NAFLD with comorbid esophageal-gastroduodenal pathology (p<0,001), enables to decrease the rate of insulin resistance (p<0,05) at the expense of leveling hyperinsulinemia, promotes restoration of lipid blood spectrum, first of all, at the expense of reduced level of general cholesterol (p<0,05) and low density lipoproteins (p<0,02). The possibility of differentiated use of mineral waters and Poltava bischofite water solution depending on the stage of the disease, determination of metabolic disorders, comorbid pathology of the digestive organs, arterial hypertension has been demonstrated. A positive effect on the atherogenic lipid profile, level of the arterial blood pressure, body weight, and insulin resistance defines the possibility of decreased cardiometabolic risk in this category of patients.*
Key words*: non-alcoholic fatty liver disease, mineral water, Poltava bischofite.*

Introduction. Non-alcoholic fatty liver disease (NAFLD) is considered to be one of the most spread diffuse liver diseases [4,11]. Thus, even 7-10 years ago NAFLD was considered to be detected in 20-30% of Western Europe and the USA, 15% of the population in Asian countries, 27% of able-to-work population in Russia. Nowadays this pathology is increasing: in the USA non-alcoholic steatosis is diagnosed in 40% of the adult population, including 25% of cases with more severe form – non-alcoholic steatohepatitis (NASH) [7].

According to contemporary opinion NAFLD is associated with an increased risk of cardio-

vascular diseases [3,7] irrespective of other risk factors such as age, sex, cholesterol level, low density lipoproteins (LDLP), diabetes mellitus (DM), increasing the risk of their development in 3,5-7 times and determining the course of cardio-vascular diseases more than the course of liver diseases [8].

The term "cardiometabolic risk" is used to indicate those factors which promote the development of both cardiovascular diseases and type 2 diabetes mellitus. In addition to age, sex, and family anamnesis the factors of cardiometabolic risk include also dyslipidemia, obesity, insulin resistance, smoking, arterial hypertension, hypercoagulation and increased level of pro-inflammatory markers. Nowadays cardiometabolic comorbid conditions produce a serious effect on clinical consequences and prognosis in different populations of patients, and identification of individual development is assumed as one of the main components in conducting the strategy of prevention and treatment of cardiovascular diseases [3].

The frequency of NAFLD in patients with arterial hypertension without obesity and diabetes mellitus is approximately 3 times as high than those of healthy individuals compared by their age and sex. Moreover, these diseases develop according to the principle of interrelation and inter-complication [6, 9]. Thus, arterial hypertension available either intensifies or provokes development of non-alcoholic steatohepatitis. In > 50% of cases of patients with arterial hypertension NAFLD is found without other risk factors of liver disease. The biggest number of NAFLD cases (≈ 80 %) is diagnosed in the non-dippers group – individuals with insufficient lower decrease of arterial blood pressure (diurnal index< 10%) which is associated with a high level of insulin and adiponectin [6,12].

Arterial hypertension is found 2,9 times as frequent in obese people than those with normal body weight. In 80 % of men and 61 % of women included in Framingham examination arterial hypertension was caused by increasing body weight. 5% increase of the body weight during 4 years promotes the possibility of arterial hypertension development 30% as much. Every extra 4,5 kg of the body weight is responsible for increased systolic arterial pressure to 4,4 mm Mercury among men and to 4,2 mm Mercury among women [2].

Development of arterial hypertension with obesity is caused by the activation of a number of mechanisms regulating arterial blood pressure rate including those cases with hyperinsulinemia and insulin resistance [2,6].

Arterial hypertension and NAFLD occurring against the ground of obesity influence upon the prognosis and development of cardiovascular diseases and progressing liver lesions. In case of obesity liver steatosis is 2,6 times higher, and NASH – 7,7 times as much than that of the patients with normal body mass index (BMI) [3,12].

The fact of an accelerated development of type 2 diabetes mellitus in patients with NAFLD is evidenced to be 2,5-3 times as much as compared to the patients without NAFLD due to intensified syndrome of insulin resistance [4]. At the same time, insulin resistance and compensatory hyperinsulinemia caused by it play an important role in the development of cardiovascular diseases including those developed due to disorders of lipid metabolism [3, 6, 9, 13].

Another substantial risk factor in the development of cardiovascular diseases is lipid metabolism disorder which can be manifested by an increased level of triglycerides, cholesterol, LDLP, general cholesterol, decreased cholesterol content of high density lipoproteins (HDLP), and practically in all the cases associated with NAFLD.

An active struggle against the modified components of the total cardiometabolic risk enables to reduce morbidity and mortality of patients.

Modern therapeutic tactics of NAFLD treatment including those cases with obesity and arterial hypertension assumes modification of life style and pharmacological effect. At the same time, such kind of treatment requires long and active therapeutic tactics using several classes of medicines [7].

Unfortunately, the possibilities of administration of natural and preformed physical factors in the treatment of this category of patients has not been practically studied irrespective of a great Ukrainian experience to use mineral waters, therapeutic peloids, physiotherapeutic measures in the treatment of

various digestive diseases and metabolic disorders. Side effects and certain refraction are characteristic for pharmacological therapy which makes a search of new non-pharmacological technologies of treatment and prevention of different diseases including non-alcoholic fatty liver disease rather topical.

At the same time, different natural and preformed physical factors are known to produce a modifying effect on the processes of hormonal regulation of carbohydrate and lipid metabolism [11], which a priori assumes the perspective scientific investigations dealing with the correction of certain factors of cardiometabolic risk, and in case of NAFLD in particular. In addition, natural and preformed physical factors are characterized by sanogenic, preventive and pleiotropic direction of the effect, when one therapeutic factor is able to influence upon several pathogenic links of formation and progress of pathologic process simultaneously [11].

Objective of our investigation was to study the efficacy of internal use of mineral waters of different balneological kinds and bischofite solution from Poltava deposit in patients suffering from non-alcoholic fatty liver disease.

Materials and methods. Chemical formulas of mineral waters used and bischofite water solution are presented lower:

1. Poltava bischofite by its content ("Ltd Group" TM "Doctor Pirogov Laboratory") is a hydrous magnesium chloride mineral containing magnesium, potassium and calcium chloride, with a high content of iodine, bromine, zinc, manganese, iron, molybdenum, copper, chromium and other trace elements. According to certain studies [5,10], the efficacy of bischofite is first of all caused by a high content of magnesium (to 99 g/l), as well as the complex itself and biological interaction of all its minerals. According to its content Poltava bischofite is characterized by boron, iodine-bromine chloride magnesium very concentrated brine (general mineralization is 339,88 g/l). Its chemical formula is the following:

H_3BO_3 - 0,065 mg/l M - 339,88 g/l $\underline{Cl\ 97\ SO_4\ 3}$
Br - 3,04 mg/l Mg 95 (Na+K) 5
I - 0,068 mg/l

To prepare the solution with mineralization 5,0 g/l the brine of Poltava bischofite was diluted with low mineralized water. The obtained solution is characterized as bromine-chloride-magnesium one with low mineralization (5 g/l), and the following is its formula:

H_3BO_3 - 0,040 mg/l M - 5,11 g/l $\underline{Cl\ 95\ SO_4\ 4\ HCO_3\ 1}$
Mg 95 (Na+K) 3 Ca 2

The content of sanitary-chemical indices, standardized components and compounds in water solution with the concentration 5 g/l is not higher than that of alarm level of concentrations for mineral waters.

2. The mineral water from the well № 3-K of Nynivske deposit, Morshyn health resort, Lviv region (Ukraine) is moderately mineralized sulfate, chloride-sulfate-sodium mineral water. General mineralization of the water is 7,00 g/l.

M - 7,00 g/l $\underline{SO_4\ 97\ Cl\ 18}$
(Na+K) 82 Mg 14

3. The mineral water from the well № 9-P in the village of Solochyn, Svaliava district, Zakarpatska region (Ukraine) is of moderately mineralized carbonic boric hydrocarbonate-sodium one. Its general mineralization is 7,19 g/l.

H_3BO_3 - 0,177 mg/l M - 7,19 g/l $\underline{HCO_3\ 97\ Cl\ 3}$
CO_2 - 1,90 mg/l (Na+K) 91 Ca 7 Mg 2

The diagnosis was verified on the basis of a comprehensive examination including anamnesis and clinical methods; general clinical and vital signs, biochemical blood parameters were examined including the indices of lipid metabolism; insulin resistance was assessed

according to HOMA index, ultrasonographic examination of the digestive organs and esophagogastroscopy were performed, arterial blood pressure was monitored during 24 hours. The results obtained were processed by means of general statistical methods, mean values and their errors were calculated, Fisher-Student reliability index was evaluated.

Chronic viral hepatitis and type 2 diabetes mellitus were exclusive criteria.

Results of the study. 80 patients aged from 48 to 64 (54,53±3,41) with NAFLD were examined including 32 men and 48 women. Non-alcoholic liver steatosis was diagnosed in 54 patients, steatohepatitis of a minimal degree of activity – in 26 patients. Comorbid pathology was the following: pathology of the biliary system (chronic acalculous cholecystitis, dysfunction of the gallbladder and/ or Oddi's sphincter) – 81,25% of patients, diseases of the esophagogastroduodenal system (gastroesophageal reflux disease, chronic non-atrophic gastritis and ulcerous disease of the stomach and duodenum) – 40,00% of patients, chronic pancreatitis - 48,75%, irritable bowel syndrome with constipations - 32,5%. Comorbid arterial hypertension I-II stage, 1-2 degree was found in 57,5 % of patients.

Clinical manifestation of NAFLD in patients involved into the study differed by oligosymptomatic course. Thus, only one third of the patients suffered from pain syndrome (severity or pain in the right subcostal area, painful palpation in this area), the majority of patients (77,5 %) complained of the signs characterizing the syndrome of gastric and/or intestinal dyspepsia (bitter taste in the mouth, nausea, heartburn, belching, bloating, constipation), mostly associated with comorbid pathology of the digestive organs.

Patients with comorbid arterial hypertension complained of periodical headache, dizziness, ear noise, unstable arterial pressure. While measuring "office" arterial pressure the following average values of systolic arterial pressure (154±3,8) mm Mercury and diastolic arterial pressure (98±3,4) mm Mercury were found.

In the majority of patients (68,75 %) an excessive body weight or obesity I-II degree (average BMI (32,67±1,14 kg/ m2) were determined.

According to biochemical examination an elevated level of general bilirubin was found at the expense of its indirect fraction in 32,5 % of patients, level of alkali phosphatase and GGTP to1,5 N - in 40,0 % of patients.

Lipid metabolism disorders were characterized by increased levels of general cholesterol in an average to (6,83±0,19) µmol/L, ß-lipoproteins - (68,18±2,15) units, triglycerides - (2,14±0,14) µmol/L, LDLP in an average to (4,05±0,28) µmol/L, reduced level of HDLP in an average to (1,32±0,16) µmol/L. Atherogenic coefficient was in an average (4,58±0,32) units.

Examination of carbohydrate metabolism determined excessive reference values of blood glucose level which was in an average (6,50±0,39) µmol/L. Insulin concentration was a little accelerated and was in an average (18,54±0,97) mcUN/ml. Hyperinsulinemia was determined in one third of patients and in an average (22,96±1,69) mcUN/ml. HOMA index was (4,12±0,43) units which is indicative of pronounced insulin resistance among the examined patients.

Discussion. According to the results of US examination sonographic signs of liver steatosis was found in 100% of individuals (diffuse enlargement of "brightness" of the liver parenchyma, distal extinction of echo signal, indistinct vascular outline, its "blur"), hepatomegaly was determined in 67,5 % of patients, the signs of biliary system pathology in the form of enlargement of the gallbladder, thickening of its walls, gallbladder sediment available were determined in 60,0 % of patients.

At the beginning of the study 4 groups of patients were randomized. Patients of I group (20 individuals, control group) received a standard complex of treatment (dietary cure and regimen of graduated physical activity). Patients of II group (20 individuals) in addition to the standard therapy received internal administration of bischofite water solution taken from Poltava deposit with mineralization of 5 g/L (dilution 1:39 - 1:72) 40 minutes before meals three times a day during 21-24 days. III group of patients in addition to a standard complex of therapy received moderately mineralized sulfate mineral water from Nynivske deposit, Morshyn health resort. IV group included patients who received moderately

mineralized carbonic boric hydrocarbonate-sodium mineral water from the well № 9-P, Zakarpatska region.

The mineral waters were indicated traditionally – on the basis of acid-formation function of the stomach, 150 - 200 ml (1% from the body weight), 3 times a day during 21 - 24 days.

Administration of different mineral waters by their content as well as bischofite solution enabled to examine the action of every factor on the course of NAFLD and possibilities of the effect on certain modifying factors of cardiometabolic risk.

Discussion of the results.

In the group of patients who received bischofite the findings were obtained indicative of the improvement of the clinical course of the underlying disease ($p<0,05$), comorbid pathology of the biliary tract ($p<0,02$), elimination of obstipation syndrome ($p<0,003$) in patients suffering from IBS even on the 3-5th day of intake.

From the side of biochemical indices normalization of pigment metabolism ($p<0,05$), and the tendency to decrease of cholestasis signs were observed ($p>0,05$). At the same time, bischofite intake did not influence considerably upon the values of hypertransferasemia.

Improvement of lipid blood spectrum was characterized by a reliable decrease of general cholesterol concentration ($p<0,02$), ß-liporpoteins ($p<0,001$) and triglycerides ($p<0,05$), and the tendency to decrease of low density lipoproteins ($p>0,05$). HDLP were not substantially affected.

Special attention should be drawn to a considerable ($p<0,01$) decrease of insulin resistance according to HOMA index, first of all due to decreased basic hyperinsulinemia which level at the end of treatment became twice as less and corresponded to reference values.

Since bischofite is first of all magnesium-containing substance, its effect on the course of comorbid arterial hypertension was of certain interest to examine (planned pharmacotherapy included hypotensive drugs from the group of angiotensin converting enzymes (ACE) inhibitors or angiotensin receptor blockers. Thus, patients with comorbid arterial hypertension at the end of treatment experienced improvement of diurnal profile of the arterial blood pressure at the expense of decreased indices of an average and maximal systolic ($p<0,01$) and diastolic pressure ($p<0,02$), improvement of nocturnal decrease of arterial blood pressure ($p<0,01$), which was accompanied by reduced variability of arterial blood pressure during 24 hours and decreased pharmacotherapy. Patients from the control group did not experience the above changes, although changes in the diurnal profile of arterial blood pressure were reliable but were less pronounced ($p<0,05$).

The use of moderately mineralized sulfate mineral water from Nynivske deposit was characterized by a considerable positive dynamics of the clinical course of NAFLD ($p<0,01$), comorbid pathology of the biliary tract ($p<0,01$) and functional intestinal diseases associated with constipations ($p<0,003$).

Biochemical examination demonstrated pronounced positive effect concerning normalization of general bilirubin level ($p<0,02$) and markers of cholestasis ($p<0,05$). The use of this mineral water promoted leveling of hypertransferasemia in patients with minimal steatohepatitis ($p<0,05$), which was not found in other groups. Thus, before treatment in patients with steatohepatitis the level of ALT and AST was (1,21±0,12) and (0,76±0,08) µmol/(hour : L) respectively, and after a course of internal use of mineral water it became (0,82±0,11) and (0,34±0,05) µmol/ (hour · L), ($p<0,05$), respectively.

Simultaneously a considerable decrease of general cholesterol concentration ($p<0,02$), triglycerides ($p<0,02$), ß-lipoproteins ($p<0,01$), LDLP ($p<0,01$), and the tendency to increase of HDLP ($p>0,05$) were determined.

The obtained results concerning blood lipid spectrum changes can be compared with the effect after statins administration, and even exceed them. Thus, in the study [1] administration of rosuvastatin in the dose of 10 mg/day during 1 month enabled to achieve 23% decrease of cholesterol LDLP and 8.7% increase of HDLP. In our study the level of cholesterol LDLP during treatment became 42,59% decreased, and the level of cholesterol HDLP became 20,53% increased, although a reliable change in the level of cholesterol HDLP was not achieved ($p>0,05$).

The dynamics of insulin resistance in this group of patients was less pronounced, although

reduced HOMA index under the effect of treatment was reliable (p<0,05).

The use of moderately mineralized alkali mineral water enabled to improve clinical course of the underlying disease (p<0,05), as well as comorbid esophagogastroduodenal pathology (p<0,001) and pancreatic pathology (p<0,02).

Analysis of biochemical indices was characterized by reliable improvement of pigment metabolism (p<0,05), reduced signs of cholestasis (p>0,05), but unfortunately it did not influence upon the signs of hypertransferasemia in patients with NASH substantially.

Changes of blood lipid "mirror" were less pronounced than those in III group, but were characterized by reduced level of general cholesterol (p<0,05), a tendency to decrease of triglycerides (p>0,05) and ß-lipoproteins (p>0,05). The level of cholesterol LDLP experienced considerable positive dynamics (p<0,02), and considering the fact that LDLP is a lipid fraction ensuring pro-atherogenic profile, their reduced level to 24,76 % is important due to intake of the mineral water. Although, the effect of sulfate mineral water prevails this index.

Analysis of the dynamics of carbohydrate metabolism demonstrated reduced insulin resistance including that one at the expense of hyperinsulinemia. Thus, a tendency to decrease serum glucose level (p>0,05), and reliable decrease of insulin concentration (p<0,05) was determined, first of all at the expense of hyperinsulinemia which became 1,4-1,6 times reduced, and due to this fact reduced HOMA-IR index was found (p<0,02).

It should be noted that most frequently for the correction of insulin resistance metmorfin is indicated in the world. At the same time, it produces a positive effect on lipid metabolism in patients with NAFLD [4,12]. Although metmorfin is able to realize its positive effect in 3-6 months [7,14], while the use of natural factors – mineral waters, bischofite water solution – is able to accelerate this effect considerably, especially it refers to the phenomena of compensatory hyperinsulinemia, producing a positive effect on lipid metabolism and body weight.

The dynamics of body mass decrease was observed in all the groups of the study. At the same time, it was the least in the control group (1,88±0,46) kg. On the contrary, the use of mineral waters or bischofite water solution intensified this effect which was manifested by decreased body weight in an average (2,18±0,38) kg in the main groups of the study and did not differ between them.

The obtained results prove reasonability and perspective to use natural and preformed physical factors in a comprehensive treatment of patients with NAFLD, enable to differentiate the use of bischofite water solution and mineral waters of different balneological kinds depending on the stage of the disease (steatosis or steatohepatitis), prevailing of metabolic disorders, comorbid pathology of the digestive organs and arterial hypertension. And a positive effect of the examined therapeutic factors on the atherogenic lipid profile, BP level, body mass, insulin resistance and hyperinsulinemia determine the possibility of reduced cardiometabolic risk in this category of patients.

Conclusions. 1. Administration of Poltava bischofite water solution improves clinical course of the underlying disease, comorbid pathology of the biliary tract and irritable bowel syndrome with constipations, improves liver functional state and lipid spectrum of the blood, reduces insulin resistance considerably, first of all, at the expense of decreased hyperinsulinemia, promotes reduction of the body weight and regulates the level of arterial blood pressure with comorbid arterial hypertension.

2. The use of moderately mineralized sulfate, chloride-sulfate mineral water by patients with NAFLD enables to improve clinical course of liver, biliary tract and intestinal pathology, normalizes functional state of the hepatobiliary system including patients with NASH of a minimal degree of activity, improve considerably the indices of blood lipid spectrum, reduce the level of cholesterol LDLP and increase the level of cholesterol HDLP against the ground of reliable decrease of insulin resistance and body weight.

3. The use of moderately mineralized carbonic boric hydrocarbonate-sodium mineral water improves the course of NAFLD with comorbid esophagogastroduodenal pathology, enables to improve considerably the indices of carbohydrate metabolism, that is, reduce the level of insulin resistance, renew blood "lipid mirror", first of all,

at the expense of reduced levels of general cholesterol and cholesterol LDLP, promotes reduction of body weight.

Prospects of further studies assume the investigation of efficacy of other kinds of mineral waters (chloride-sodium, mineral waters with increased content of organic substances) and various methods of peloidotherapy in the treatment of non-alcoholic fatty liver disease depending on the stage of the disease, metabolic disorders, comorbid pathology of the digestive organs and cardiovascular system.

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