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Therapeutic potential of sodium selenite in patients with non-alcoholic fatty liver disease and hypertension disease

Liver parenchyma damage is associated with significant activation of oxidative stress. Correction of oxidative stress can be a promising direction in the treatment of arterial hypertension. It has been established that in patients with hepatopathies, lower concentrations of selenium are found in blood and erythrocytes, which gives reason to consider selenium as a potential therapeutic agent in patients with liver pathology.

Objective — to determine the therapeutic potential of sodium selenite in patients with non-alcoholic fatty liver disease in combination with hypertension.

Materials and methods. 100 patients with nonalcoholic fatty liver disease (NAFLD) were included in the study: the main group — 49 patients (67.3% women, median age is 51.0 years) with concomitant NAFLD and arterial hypertension (HTN), the comparison group — 51 patients (58.8% women, median age is 52.0 years) with NAFLD isolated course. The control group included 20 practically healthy people (55.0% women, median age is 51.0 years). Among the patients of the main group, the first degree of HTN was diagnosed in 28.6% of patients (14 people), the second degree — 71.4% (35 people). Among these patients, 32.7% (16 people) had the first stage of HTN, 67.3% (33 people) had the second stage. In the main group, 55.1% of patients had steatosis, 44.9% had steatohepatitis. In the comparison group, 58.8% had steatosis, 41.2% had steatohepatitis ($\chi^2=0.141$, $p=0.707$). The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured according to the standard method (kinetic method). Gamma-glutamine transpeptidase (GGTP) was measured by the enzymatic colorimetric method, alkaline phosphatase (AP) by the colorimetric method. Selenium and selenoprotein P (Sel P) levels were determined using the immunofluorescence method. Ultrasound examination of the liver was performed according to the standard method on an empty stomach.

Results. Body mass index corresponded to normal or increased body weight: in the main group — 27.8 [26.6; 28.5] kg/m^2 and 27.3 [24.2; 28.3] kg/m^2 in the comparison group, in the control group — 24.3 [21.9; 26.0] kg/m^2. In patients of the main group was determined a significant ($p<0.001$) predominance of ALT levels (45 [43.0; 47.5] U/L), AST levels (53 [51.0; 56.0] U/L), AP levels (285.7 [217.6; 321.1] U/L) and GGTP levels (96.2 [75.0; 108.9] U/L) opposite to comparison group (respectively 36 [34.0; 39.0] U/L, 41 [40.0; 45.0] U/L, 215.5 [183.2; 246.7] U/L and 65.5 [51.5; 76.8] U/L) and control group levels (respectively 25.5 [24.0; 30.8] U/L, 23 [19.3; 26.0] U/L, 129.2 [116.9; 140.6] U/L and 22.6 [16.1; 31.7] U/L). A two-fold decrease in selenoprotein P levels was obtained in patients with NAFLD and HTN compared to patients with NAFLD (19.7 [8.0; 26.7] ng/mL and 43.1 [41.3; 45.4] ng/mL respectively, $p<0.001$), and selenium in one and a half times compared to patients with NAFLD (43.5 [39.9; 49.1] μg/L and 67.2 [61.5; 77.4] μg/L respectively, $p<0.001$). The highest Sel P median levels (71.0 [54.3; 76.1] ng/ml and selenium levels (108.0 [96.9; 118.8] μg/L) registered in the control group ($p<0.001$). Evaluating the data on selenium metabolism and liver tests depending on the intake of sodium selenite, a significant increase in the levels of Sel P (53.6 [43.1; 60.4] ng/ml, $p<0.001$) and selenium (89.1 [63, 4; 99.5] μg/L, $p<0.009$), as well as a decrease in AST levels (41.7 [32.6; 43.2] U/l, $p<0.001$) in the group with isolated NAFLD, while in the group with NAFLD and HTN comorbid course, no significant changes in the studied parameters were detected.

Conclusions. The obtained results provide a basis for sodium selenite use in the therapy of patients with NAFLD. Further research on the duration of such therapy and sodium selenite dosing regimen in patients with a comorbid course of NAFLD and HTN is a promising and relevant direction.

Keywords: non-alcoholic fatty liver disease, arterial hypertension, selenium, selenoprotein P.

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Liver parenchyma damage is associated with significant activation of oxidative stress, which intensifies fibrosis processes through free oxygen radicals production and subsequent peroxidation of cell wall lipids [21]. It has been established that patients with hepatopathies have lower selenium concentrations in the blood and erythrocytes [21]. Reduced selenium content is also associated with cirrhosis development and a higher risk of mortality, suggesting selenium as a potential therapeutic agent in patients with liver disease [21].

Oxidative stress correction can be a promising direction in the treatment of arterial hypertension. Endothelium function in the cascade of cardiovascular system working is realized by vasoactive compounds. It was noted that oxidative stress can significantly affects endothelial function, disrupting its vasomotor function [21]. For example, data were obtained regarding about connection between low selenium concentrations and glutathione peroxidase (GP) reduced activity in the development of cardiovascular pathology [28].

Selenium performs its biological functions by including it in human selenoproteins composition as selenocysteine form [17]. Hepatokine selenoprotein P (Sel P) is the main selenium-containing compound in human plasma [2, 10, 11], which contains almost 60 % of selenium, while almost 40 % of selenium is contained in GP-1 [5, 19]. Selenoproteins perform various biological roles, ranging from catalyzing enzymatic redox reactions, thyroid hormone metabolism, and protection against oxidative DNA damage caused by hydrogen peroxide (H_2O_2) and lipid hydroperoxide, to inflammation regulation [19].

Sel P production progresses mainly in the liver, although it is determined in other tissues, from where it enters the extracellular fluid. Sel P function consists primarily in selenium transport to ensure mostly antioxidant action [17]. Structurally, Sel P includes 10 selenocysteine residues [11, 13], which distinguishes it from other members of the selenoproteins family, which have mainly one or two residues [23]. Therefore, Sel P is also a selenium concentration indicator in the body [12]. In addition, its determination in plasma is fast and effective, unlike the determination of tissue selenoproteins, which requires a biopsy [21].

It is known that selenium enters the food chain through plants that absorb it from the soil [24]. Selenium amount absorbed by plants depends not only on selenium concentration in the soil, but also on the soil pH, organic substances presence in the soil, and climatic conditions. Selenium resources are also found in fish and shellfish, which are particularly nutrition important sources in some communities [24]. In plants, selenium is represented by the compound selenomethionine (SeMet), in meat in the form of selenomethionine and selenocysteine, and in fish it is represented by selenomethionine and selenonine [24]. Dietary supplements contain selenomethionine, selenite, or sodium selenite [24].

Dietary selenium supplementation is necessary in the case of very low intake levels, from 55 to 75 g/day [24]. However, it is defined as toxic above 800 μg/day, and the safe upper limit is 400 μg/day [24].

Objective — to determine the therapeutic potential of sodium selenite in patients with nonalcoholic fatty liver disease with concomitant arterial hypertension.

Materials and methods

The study included 100 patients with nonalcoholic fatty liver disease (NAFLD): the main group consisted of 49 patients with concomitant NAFLD and arterial hypertension (HTN), and the comparison group was represented by 51 patients with isolated NAFLD. The control group included 20 practically healthy people. The gender ratio of the subjects was as follows: 67.3 % (33) women and 32.7 % (16) men in the main group, 58.8 % (30) women and 41.2 % (21) men in the comparison group, 55.0 % (11) of women and 45.0 % (9) of men in the comparison group ($\chi^2 = 1.219$; $p = 0.544$).

The median age of patients in the main group was 51.0 years [45.0; 56.0], in the comparison group — 52.0 years [47.0; 54.0] and in the control group — 51.0 years [45.0; 55.5].

Among patients of the main group, the first degree of hypertension was diagnosed in 28.6 % of patients (14 people), and the second degree in 71.4 % (35 people). Among these patients, 32.7 % (16 people) had the first stage of hypertension, and 67.3 % (33 people) had the second stage.

Among the main group, liver steatosis was found in 27 (55.1 %) patients, steatohepatitis in 22 (44.9 %) patients; in the comparison group there were 30 (58.8 %) patients and 21 (41.2 %) patients, respectively ($\chi^2 = 0.141$, $p = 0.707$).

The diagnosis of non-alcoholic fatty liver disease was established according to local protocols (Unified clinical protocol of primary, secondary (specialized) medical care «Non-alcoholic steatohepatitis» (2014) and Adapted evidence-based clinical guideline «Non-alcoholic fatty liver disease») and practical recommendations of the European Association for the study of liver diseases, European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity «Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease», 2016), of the American Association for the

Study of Liver Diseases (American Association for the Study of Liver Diseases «The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease», 2018).

The diagnosis of hypertension was established according to local recommendations (Unified clinical protocol of primary, secondary (specialized) medical care «Arterial hypertension» (2012)) and according to the criteria of the European Society of Cardiology and the European Society of Hypertension (European Society of Cardiology and European Society of Hypertension Clinical Practice Guidelines for the Management of Arterial Hypertension, 2018).

During the study, all conditions of Ukrainian legislation on clinical research involving human subjects, the Helsinki Declaration of Human Rights (1964) and the Council of Europe Convention on the Protection of Human Rights and Dignity (Convention on Human Rights and Biomedicine, ETS-164 of April 4, 1997) were observed with additions in the protocols dated 12.01.1998, dated 24.01.2002 and dated 25.01.2005), including the additional protocol to the Convention on Biomedical Research dated 25.01.2005 and the Integrated Annex on Harmonization of Good Clinical Practice (ICH GCP dated 09.11.2016).

The patients of the study groups and individuals of the control group underwent a questionnaire to determine alcohol dependence and differential diagnosis of NAFLD with alcoholic fatty liver disease — the AUDIT test (Alcohol Use Disorders Identification Test).

Body mass index was calculated by the formula for the ratio of body weight in kilograms to height in meters squared:

$$\text{BMI} = \text{Body weight, kg} / (\text{Height, cm})^2.$$

Levels of alanine transaminase (ALT), aspartate transaminase (AST), and total and fractional bilirubin was conducted by standard methods (kinetic method). Gamma-glutamyl transferase (GGT) was measured by enzymatic colorimetric method, and alkaline phosphatase (AP) — by colorimetric method. De Ritis index was calculated according to the standard formula of the ratio of AST to ALT.

Selenium and Selenoprotein P levels were measured by immunoassays (ELISA Kit) using Elab-Science reagents (USA).

Liver ultrasound examination was performed according to standard methods using the Samsung (Medison) SonoAce X8 ultrasound device.

Statistical processing. Statistical calculation of the obtained data was performed using the application package IBM SPSS 25.0 (trial version) for Windows. The distribution of quantitative and qualitative features was carried out visually graphically and using Kolmogorov-Smirnov & Lilliefors test for normality and Shapiro-Wilk's test of normality. The assessment revealed differences from the normal nature of the distribution, so the calculations were performed using non-parametric statistics.

Thus, to characterize the central tendency and variability of quantitative (continuous or interval) variables, the median (Me), lower (LQ) and upper (UQ) quarters were determined. Data were presented as Me [LQ; UQ]. The significance of differences in the obtained quantitative traits in the two independent groups was determined using the Mann-Whitney U-test. Qualitative (binomial, ordinal, nominal) characteristics were presented in absolute (absolute) and relative (percentage) values. Comparisons of groups by qualitative characteristics were performed using Pearson's chi-squared test.

The threshold value of the probability level of all calculated features was taken as 0.05 ($p = 0.05$) with an indication of the exact value of the level of reliability «p» with three decimal places.

Results

Median BMI in all study groups corresponded to normal or increased body weight. The lowest indicator was in the control group — 24.3 [21.9; 26.0] kg/cm^2 ($p_{1-3} = 0.004$), and the largest median was determined in patients of the main group — 27.8 [26.6; 28.5] kg/cm^2 ($p_{1-2} < 0.001$). Patients with an isolated NAFLD course had a slightly lower median BMI — 27.3 [24.2; 28.3] kg/cm^2 than patients with NAFLD and HTN, but the indicators differed significantly ($p_{2-3} = 0.031$).

In patients of the main group, systolic (SBP) and diastolic blood pressure (DBP) were higher (150.0 [145.0; 158.0] and 90.0 [85.0; 90.0] mm Hg, respectively) in comparison with the indicators of the comparison group (125.0 [115.0; 130.0] and 80.0 [70.0; 80.0] mm Hg, respectively, $p < 0.001$) and control group (120.0 [110.0; 120.0] and 80.0 [70.0; 80.0] mm Hg, respectively, $p < 0.001$), while the median SBP value in patients of the comparison group was significantly higher than in patients of the control group ($p_{2-3} = 0.012$). The median values of DBP in the comparison and control groups were the same ($p_{1-3} = 0.918$).

Analyzing liver parenchyma biochemical activity results (Table 1), a significant ($p < 0.001$) predominance of ALT and AST median levels in patients with NAFLD and HTN combined course was found in comparison with the indicators of patients with an isolated NAFLD. A similar trend is also observed in relation to AF and GGTP median levels. AF and GGTP levels significantly exceeded similar levels in the control group by 2 times ($p < 0.001$)

Table 1. **Biochemical blood analysis depending on the group, Me [LQ; UQ]**

Index	Control (n = 20)	NAFLD + HTN (n = 49)	NAFLD (n = 51)
Total protein, g/L	66.5 [62.8; 71.8]	63.0 [57.0; 69.0]	65.0 [59.0; 71.0]
Albumin, g/L	41.5 [37.5; 44.5]	42.0 [37.5; 46.0]	39.0 [36.0; 43.0]
ALT, U/L	25.5 [24.0; 30.8]	45.0 [43.0; 47.5]*	36.0 [34.0; 39.0]*#
AST, U/L	23.0 [19.3; 26.0]	53.0 [51.0; 56.0]*	41.0 [40.0; 45.0] *#
AST/ALT	0.87 [0.76; 0.99]	1.16 [1.11; 1.24]*	1.14 [1.08; 1.21]*
AP, U/L	129.2 [116.9; 140.6]	285.7 [217.6; 321.1]*	215.5 [183.2; 246;7]*#
GGTP, U/L	22.6 [16.1; 31.7]	96.2 [75.0; 108.9]*	65.5 [51.5; 76.8]*#
Total bilirubin, μmol/L	13.0 [11.9; 17.8]	13.4 [12.1; 15.2]	13.2 [12.0; 16.6]
Conjugated bilirubin, μmol/L	4.1 [3.6; 5.5]	4.0 [3.2; 4.9]	4.1 [3.6; 5.2]
Unconjugated bilirubin, μmol/L	8.7 [6.8; 12.6]	9.3 [8.4; 11.4]	9.0 [7.8; 11.1]

Note. * The difference from the control group is statistically significant ($p < 0.001$).
The difference from the NAFLD + HTN group is statistically significant ($p < 0.001$).

and by 1.5 times ($p < 0.001$) in the isolated NAFLD group. The median de Ritis index was significantly ($p < 0.001$) lowest in patients of the control group; in the main and comparison groups, the indicators were at the same level ($p_{2-3} = 0.167$) with a slight predominance in patients of the main group. There were no differences in the indicators of total protein, albumin, bilirubin and its fractions.

Comparing the indicators of selenium metabolism, a two-fold decrease in Sel P levels were obtained in patients with NAFLD and HTN in comparison with patients with isolated NAFLD ($p < 0.001$), and selenium — one and a half times in comparison with patients with NAFLD ($p < 0.001$) (Table 2). The highest median levels of Sel P and selenium were registered in the control group ($p < 0.001$).

All patients were given recommendations on eating behavior correction and diet, appropriate caloric content and diet assortment, as well as systematic physical exercises.

Antihypertensive therapy in patients of the main group involved the use of angiotensin-converting enzyme inhibitors (ramipril at a dose of 5—10 mg/day or 2—8 mg/day of perindopril tert-butylamine) and, according to the indications, calcium channel blockers were additionally prescribed (amlodipine 5—10 mg/day) or non-thiazide diuretics (indapamide 2.5 mg/day).

In order to correct the selenium metabolism, 22 patients of the main group and 29 patients of the comparison group were prescribed 300 μg/day of sodium selenite during the first 14 days, followed by a maintenance dose of 100 μg/day for the next 2 months.

According to the analysis, Sel P and selenium levels significantly increased in the patients of the main group after complex treatment (Table 3), and the median AST, de Ritis index, GGTP and AP levels were significantly reduced relative to the corresponding levels before treatment. In the patients of the comparison group, there is also a tendency to changes in selenium metabolism and liver parenchyma activity, a significant increase in Sel P levels and a decrease in ALT, de Ritis index and GGTP levels were also observed.

Evaluating the data on selenium metabolism and liver tests depending on sodium selenite intake

Table 2. **Selenium and selenoprotein P metabolism depending on the group, Me [LQ; UQ]**

Index	Control (n = 20)	NAFLD + HTN (n = 49)	NAFLD (n = 51)
Sel P, ng/ml	71.0 [54.3; 76.1]	19.7 [8.0; 26.7]*	43.1 [41.3; 45.4]*#
Selenium, μg/L	108.0 [96.9; 118.8]	43.5 [39.9; 49.1]*	67.2 [61.5; 77.4]*#

Note. * The difference from the control group is statistically significant ($p < 0.001$).
The difference from the NAFLD + HTN group is statistically significant ($p < 0.001$).

Table 3. **Liver function tests, selenium and selenoprotein P levels before and after treatment, Me [LQ; UQ]**

Index	NAFLD + HTN (n = 49)		NAFLD (n = 51)	
	Before	After	Before	After
Sel P, ng/ml	19.7 [8.0; 26.7]	43.5 [39.3; 51.9]*	43.1 [41.3; 45.4]	46.0 [40.7; 57.1]***
Selenium, μg/L	43.5 [39.9; 49.1]	72.3 [61.3; 84.0]*	67.2 [61.5; 77.4]	72.5 [61.2; 91.6]
ALT, U/L	45.0 [43.0; 47.5]	42.9 [38.7; 48.5]	36.0 [34.0; 39.0]	41.2 [33.1; 46.8]*
AST, U/L	53.0 [51.0; 56.0]	42.6 [38.7; 47.8]*	41.0 [40.0; 45.0]	42.4 [37.0; 47.0]
AST/ALT	1.16 [1.12; 1.22]	0.99 [0.90; 1.18]*	1.13 [1.11; 1.20]	1.03 [0.87; 1.19]**
AP, U/L	96.2 [75.0; 109.0]	62.1 [54.8; 71.2]*	65.5 [51.5; 76.8]	60.7 [53.7; 69.4]
GGTP, U/L	285.7 [217.6; 321.1]	173.9 [147.9; 183.7]*	215.5 [183.2; 246.7]*	168.5 [144.5; 192.2]*

Note. The difference from the control group is statistically significant: * $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$.
The differences between groups at the post-treatment stage is statistically insignificant for all indexes.

Table 4. **Liver function tests, selenium and selenoprotein P levels depending on selenium supplementation, Me [LQ; UQ]**

Index	NAFLD + HTN (n = 49)		NAFLD (n = 51)	
	Without selenium supplementation (n = 27)	Selenium supplementation (n = 22)	Without selenium supplementation (n = 22)	Selenium supplementation (n = 29)
Sel P, ng/ml	43.3 [40.8; 50.1]	46.3 [34.1; 54.4]	42.1 [37.5; 46.1]	53.6 [43.1; 60.4]*
Selenium, μg/L	72.3 [54.3; 85.9]	71.5 [64.2; 82.9]	65.3 [59.5; 75.9]	89.1 [63.4; 99.5]**
ALT, U/L	42.9 [39.7; 49.9]	43.0 [38.0; 47.8]	43.2 [39.4; 49.3]	40.0 [32.5; 45.6]
AST, U/L	41.7 [36.6; 47.7]	44.6 [39.9; 48.4]	43.1 [40.2; 53.1]	41.7 [32.6; 43.2]***
AST/ALT	0.96 [0.89; 1.18]	1.05 [0.93; 1.24]	0.97 [0.86; 1.28]	1.05 [0.87; 1.16]
AP, U/L	64.2 [55.3; 73.5]	59.8 [54.3; 69.0]	64.7 [56.3; 71.3]	60.2 [51.9; 65.0]
GGTP, U/L	170.4 [146.7; 180.1]	175.0 [162.3; 187.8]	178.9 [151.2; 193.4]	157.6 [134.4; 188.8]

Note. The difference from the control group is statistically significant: * $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$.
The differences between groups at the post-treatment stage is statistically insignificant for all indexes.

(Table 4), it is noteworthy that a significant increase in Sel P and selenium levels, as well as a decrease in AST levels, is observed in the group with isolated NAFLD course, while in no significant changes in the studied parameters were found in the group with comorbid NAFLD and HTN course. In the comparison group, there was also a trend toward a decrease in ALT and GGTP levels in individuals that take selenium compound.

Discussion

Dietary habits and their influence on NAFLD pathophysiology and treatment are widely studied [8]. One of the most common is Dietary Approaches to Stop Hypertension (DASH). This dietary pattern includes a diet rich in fruits, vegetables, whole grains, lean foods, and foods low in saturated fat, sodium, and sugar [8]. DASH was primarily developed to reduce blood pressure, but has been shown to be effective for other cardiovascular diseases. Its benefit relative to NAFLD patients may have a direction of risk factors effect, including dyslipidemia and insulin resistance [8].

Since there is currently no standardized and effective treatment for NAFLD or NASH, the effectiveness of the lifestyle modification approach is determined [1]. It emphasizes the Mediterranean diet effectiveness in patients with NAFLD, which combines both changes in dietary habits and physical activity intensity. The nutritional component consists of products combination with antioxidant and anti-inflammatory properties, which are more effective

in combination than taking individual products or nutrients with similar properties. This approach use in NAFLD patients can lead to changes disease's clinical course and its biochemical parameters, including improving weight indicators, liver fat accumulation, correcting transaminase and cholesterol metabolism indicators, and reducing inflammatory activity by affecting adhesion molecules, cytokines and atherosclerotic stability plaques indicators [1].

Selenium deficiency can activate the inflammatory process in liver parenchyma by certain metabolic pathways. In an experiment by Tang C. et al. in pigs, a global picture of changes in the liver with Se deficiency was developed. The data showed that Se deficiency induces a redox imbalance by regulating selenoproteins at both mRNA and protein levels, blocking glutathione system metabolism in combination with enhanced synthesis and catabolism of GP. At the same time, lipid metabolism suppression was found on the background of carbon metabolism disturbance due to the increase number of glycolysis intermediate products, which increases toxic lipid units, and as a result, intensification of oxidative stress [27].

In addition, selenium supplementation in liver disease treatment can reduce pro-inflammatory cytokines and expression of clearance-related proteins in the liver, and increase regulate heme oxygenase-1 to reduce an inflammatory response [27].

M. H. Al-Dossari et al. found that treatment with selenium (0.1 mg/kg/day) for 7 days reduced liver damage caused by lipopolysaccharide and diclofenac toxicity. Selenium inhibited inflammation of TLR4 signaling pathway induced by lipopolysaccharide and contributed to antioxidant defense enhancement to reduce oxidative stress in rats [3].

In J. A. Del Campo et al. work it has been proven that influencing various pathways of inflammatory processes in NAFLD, such as, for example, inhibition of the TLR4 signaling pathway, in which Se plays an important role, can prevent the development of nonalcoholic steatohepatitis and liver fibrosis [6, 30].

Selenium addition to the diet can have a direct effect on antioxidant system activity. So, according to an experiment with rats conducted by B. Ruseva et al. [22], the activity of GP-1 in the blood was 409 ± 40 U/g Hb for Wistar-Kyoto rats with normal selenium amount in the diet, and 546 ± 35 U/g Hb in rats with an increased selenium amount in the diet. For Okamoto-Aoki rats, corresponding values were 430 ± 24 and 506 ± 24 U/g Hb. Further regression analysis revealed a positive relationship between medium strength GP-1 activity and serum selenium concentration in Wistar rats: GP-1 = 114.243 ± 0.5356 [Selenium]; r = 0.652 ($p < 0.001$). Similar dynamics were determined in Okamoto-Aoki rats: GP-1 = 259.824 ± 0.3341 [Selenium]; r = 0.615 ($p = 0.007$).

Some studies have been conducted on the relationship between selenium and NAFLD development [16, 31], but the lack of data about selenium intake levels among the population in study countries makes it difficult to provide large-scale randomized trials.

National Health and Nutrition Examination Survey (NHANES) trial examined an association of serum selenium with serum ALT activity and NAFLD prevalence between 2011 and 2016 [5, 29]. It involved 3,827 adults aged 20 years or older who did not have positive hepatitis B surface antigen or positive serum hepatitis C antibodies, elevated transferrin saturation (> 60 % for men and > 50 % for women), and with high alcohol consumption ≥ 20 g/day for men and ≥ 10 g/day for women). The average age was 47.5 (0.5) years, 53.1 % of the participants were women. Out of 3,827 participants, 1,319 had cases of suspected NAFLD (weighted prevalence in the sample = 35.7 %). Participants with NAFLD were more likely to be female, Lationos, and had a higher BMI. Median serum selenium concentrations were 127.9 (117.9, 139.4) μg/L in the general population, 127.2 (117.7, 138.9) μg/L in participants without NAFLD, and 129.4 (118.3; 140.5) in participants with NAFLD, respectively. The results showed nonlinear associations of serum selenium with ALT activity and NAFLD stage. It is interesting to note that a positive relationship between selenium level, ALT and NAFLD stage was observed at a serum selenium level > 130 μg/L [29].

Another NHANES study examined the relationship between serum selenium levels and fibrosis development in patients with NAFLD (2017—2018) [14]. In this study, 3336 participants were registered, who were divided into 4 groups according to selenium concentration in blood: group Q1 > 89.8 ≤ 174.91 μg/L (n = 833), group Q2 > 174.91 ≤ 189.005 μg/L (n = 835), group Q3 > 189.005 ≤ 205.32 μg/L (n = 835), group Q4 > 205.32 ≤ 453.62 μg/L (n = 835). As a result, in multiple logistic regression models, higher blood selenium levels (> 205.32, ≤ 453.62 μg/L) had a significant positive association with NAFLD (β = 1.31). However, the presence of widespread fibrotic liver parenchyma damage is an important pathological manifestation of late-stage NAFLD and has a serious impact on prognosis in patients with NAFLD. Therefore, in logistic models, high blood selenium levels (groups Q3 and Q4) were significantly inversely associated with progressive liver fibrosis (β = 95 % CI

0.46—0.93, P for trend = 04) even after accounting for age, sex, race/ethnicity, BMI, waist circumference, smoking status, physical activity, dietary selenium intake, and presence of diabetes (0.59; 95% CI 0.40—0.88 and 0.61 95% CI, 0.41—0.90, P for trend = 01). Interestingly, compared with women, men had a strong inverse correlation between blood selenium levels and progressive liver fibrosis in the Q2 group (0.41; 95% CI, 0.25—0.68 against 1.20; 95% CI, 0.72—2.01), group Q3 (0.43, 95). % CI, 0.27—0.70 against 1.01; 95% CI, 0.59—1.74) and Q4 group (0.47; 95% CI, 0.29—0.75 against 1.07; 95% CI, 0.62—1.84) [14].

Regarding associations between selenium concentration and cardiovascular diseases development, there are various studies with conflicting results.

An experiment on spontaneously hypertensive rats during 7 months increased selenium-dependent antioxidant activity and reduced oxidative heart damage. Other studies have shown a protective effect of 1 mg/kg of sodium selenite against cardiac tissue damage, a decrease in malonaldehyde plasma concentrations, and an increase in glutathione activity. It was also noted that lactate dehydrogenase and creatine kinase activity in plasma was reduced after treatment with selenium [20].

However, when adding selenium to treatment, one should not forget that exaggerating selenium concentration [28] can have negative consequences although clear recommendations with doses and treatment duration for NAFLD and HTN have not been developed yet.

A study by L. Su et al. [25] can confirm the hypothesis that the selenium level in blood serum of more than 400 μg/day [24, 28] has a negative effect and even worsens endothelial dysfunction in arterial hypertension. Thus, this study showed that systolic pressure reliably prevailed between the quantiles of selenium levels: 1st quantile (< 0.233 ng/g) — 133.8 ± 20.8 mm Hg; 2nd quantile (0.234—0.362) — 144.4 ± 23.0 mm Hg; 3rd quantile (0.363—0.442 ng/g) — 148.6 ± 25.8 mm Hg; 4th quantile (0.443—0.552 ng/g) — 150.1 ± 26.6 mm Hg and 5th quantile (< 0.552 ng/g) — 151.6 ± 24.4 mm Hg ($p < 0.001$). Diastolic pressure indicators also differed between the respective quantiles ($p < 0.001$), however, the lowest indicator was in the 1st quantile, and in the 2—5 quantiles DBP indicator was almost at the same level [25]. Further regression analysis revealed a significant and strong association between selenium levels and blood pressure, especially in the 5th quantile: odds ratio (OR) — 3.55 [95% CI 2.95—4.87] relative to the quantile of the lowest selenium levels [25]. Calculation of the risks of occurrence showed the occurrence of hypertension relative to groups by selenium levels. Thus, the highest risk of occurrence was relative to selenium levels of 0.443—0.552 ng/g: 2.35 [95% CI 1.69; 3.26] ($p < 0.0001$); and levels < 0.552 ng/g: 1.94 [95% CI 1.36; 22.77] ($p < 0.0002$).

M. M. Bastola et al. [4] study determined a significant positive association between high selenium levels and high blood pressure: OR for low concentration = 0.70 [95% CI 0.612—0.82] ($p < 0.01$); OR for high concentrations = 1.19 [95% CI 1.02; 1.39] ($p < 0.01$). After standardization for other sociodemographic, clinical, and biochemical parameters, high selenium concentrations (> 120 ng/L) were significantly associated with high BP: OR = 1.46 [95% CI 1.29—1.66]. Selenium levels influence on the increase in blood pressure was more due to the component of DBP than SBP [4].

Accordingly, results obtained in this study regarding the positive effect of selenium-containing compound addition on selenium, Sel P and AST concentration in the treatment of patients with isolated NAFLD and actualize the further study of selenium dose-dependent effects on liver metabolism in NAFLD. The absence of significant changes in liver biochemical profile and selenium metabolism in the group of patients with NAFLD and HTN indicates a constant oxidative stress that is difficult to correct and the possibility of certain biochemical processes irreversibility in liver parenchyma in the case of comorbid HTN.

Conclusions

NAFLD course is accompanied by a reliable suppression of selenium and selenoprotein P synthesis, while concomitant HTN presence is associated with a statistically more pronounced increase in these deviations.

The additional use of sodium selenite in the complex therapy of patients with isolated NAFLD is accompanied by significantly more pronounced positive selenium metabolism and AST dynamics compared to patients who followed only recommendations for lifestyle modification. At the same time, in patients with NAFLD and HTN comorbid course, positive changes in these indicators are only a trend and do not reach statistically significant levels, which may be the result of several factors influence: intensification of oxidative stress in the presence of concomitant HTN, insufficient duration of therapy, and inadequate sodium dosing regimen selenite.

The obtained results provide a basis for sodium selenite use in NAFLD therapy. Further research on the duration of such therapy and sodium selenite dosing regimen in patients with NAFLD and HTN is a promising and relevant direction.

Compliance with ethical requirements. Ethical approval was obtained by the Committee on Ethics and Bioethics of Kharkiv National Medical University. All procedures and experiments of this study adhere to the ethical standards of the 1975 Declaration of Helsinki, revised in 2008, as well as national legislation. Informed consent was obtained from all patients included in the study.

Conflicts of interest: none.
The authors have contributed equally to conception and design, acquisition and interpretation of data, drafting the article.

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Терапевтичний потенціал натрію селеніту у пацієнтів з неалкогольною жировою хворобою печінки та гіпертонічною хворобою

Ураження паренхіми печінки пов'язане з активацією оксидативного стресу. Корекція оксидативного стресу може бути перспективним напрямом лікування артеріальної гіпертензії. Установлено, що у пацієнтів із гепатопатіями в крові та еритроцитах нижча концентрація селену, що дає підставу розглядати селен як потенційний терапевтичний агент у пацієнтів з патологією печінки.

Мета — визначити терапевтичний потенціал натрію селеніту у хворих на неалкогольну жирову хворобу печінки у поєднанні із гіпертонічною хворобою.

Матеріали та методи. У дослідження було залучено 100 пацієнтів із неалкогольною жировою хворобою печінки (НАЖХП): основна група — 49 пацієнтів (з них 67,3 % жінок, медіана віку 51 рік) із супутнім перебігом НАЖХП та гіпертонічної хвороби (ГХ), група порівняння — 51 пацієнт (з них 58,8 % жінок, медіана віку 52 роки) з ізольованим перебігом НАЖХП. Контрольну групу утворено із 20 практично здорових осіб (з них 55,0 % жінок, медіана віку 51 рік). В основній групі 1-й ступінь ГХ діагностовано у 14 (28,6 %) пацієнтів, 2-й ступінь — у 35 (71,4 %), 1-шу стадію ГХ — у 16 (32,7 %), 2-гу стадію — у 33 (67,3 %). В основній групі стеатоз мали 55,1 % пацієнтів, стеатогепатит — 44,9 %, у групі порівняння — відповідно 58,8 та 41,2 %, (χ^2=0,141; p=0,707). Рівень аланінамінотрансферази (АЛТ) і аспартатамінотрансферази (АСТ) вимірювали за стандартною методикою (кінетичним методом), γ-глутамілтранспептидази (ГГТП) — ферментативно-колориметричним методом, лужної фосфатази (ЛФ) — колориметричним методом, селену та селенопротеїну Р — імунофлюоресцентним методом з використанням реактивів ElabScience (США). Діагноз НАЖХП та ГХ установлювали відповідно до локальних та міжнародних рекомендацій. Ультразвукове обстеження печінки проводили за стандартною методикою натще.

Результати. Індекс маси тіла відповідав нормальній або підвищеній масі тіла: в основній групі — 27,8 [26,6; 28,5] кг/м^2, у групі порівняння — 27,3 [24,2; 28,3] кг/м^2, у контрольній групі — 24,3 [21,9; 26,0] кг/м^2. У пацієнтів основної групи виявлено статистично значущо (p < 0,001) вищі показники АЛТ (45 [43,0; 47,5] Од/л), АСТ (53 [51,0; 56,0] Од/л), ЛФ (285,7 [217,6; 321,1] Од/л) та ГГТП (96,2 [75,0; 108,9] Од/л), ніж у групі порівняння (відповідно 36 [34,0; 39,0], 41 [40,0; 45,0], 215,5 [183,2; 246;7] і 65,5 [51,5; 76,8] Од/л) та контрольній групі (25,5 [24,0; 30,8], 23 [19,3; 26,0], 129,2 [116,9; 140,6] Од/л і 22,6 [16,1; 31,7] Од/л). У пацієнтів з НАЖХП та ГХ порівняно з пацієнтами із НАЖХП зареєстровано удвічі нижчий рівень селенопротеїну Р (19,7 [8,0; 26,7] та 43,1 [41,3; 45,4] нг/мл відповідно, p < 0,001), у 1,5 разу менший вміст селену (43,5 [39,9; 49,1] та 67,2 [61,5; 77,4] мкг/л, p < 0,001). Найвищу медіану рівня селенопротеїну Р (71,0 [54,3; 76,1] нг/мл) та селену (108,0 [96,9; 118,8] мкг/л) зафіксовано в контрольній групі (p < 0,001). Оцінювання показників метаболізму селену і активності печінкових проб залежно від прийому натрію селеніту виявило статистично значущо більший вміст селенопротеїну Р (53,6 [43,1; 60,4] нг/мл, p < 0,001) та селену (89,1 [63,4; 99,5] мкг/л, p < 0,009), а також менший рівень АСТ (41,7 [32,6; 43,2] Од/л, p < 0,001) у групі з ізольованим перебігом НАЖХП, тоді як у групі із коморбідним перебігом НАЖХП та ГХ статистично значущих змін досліджуваних параметрів не зареєстровано.

Висновки. Отримані результати дають підставу для застосування натрію селеніту в терапії хворих на НАЖХП. Перспективним і актуальним напрямом є дослідження тривалості такої терапії та режиму дозування натрію селеніту у пацієнтів з коморбідним перебігом НАЖХП та ГХ.

Ключові слова: неалкогольна жирова хвороба печінки, гіпертонічна хвороба, селен, селенопротеїн Р.

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