

DOI: 10.31393/reports-vnmedical-2018-22(1)-38

UDC: 616.36-003.826

## EFFICIENCY OF TREATMENT OF PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS COMBINED WITH DIABETES MELLITUS TYPE 2 USING THE S-ADENOSYLMETHIONIN

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Received 15 December 2017; Accepted 2 February 2018

**Annotation.** *Non-alcoholic fatty liver disease is an important cause of chronic liver damage in many countries and is growing rapidly in both adults and children due to obesity and diabetes type 2. Aim - investigate the effectiveness of complex treatment of patients for the course of NASH using S-adenosylmethionin on the background of basic therapy. The study included 25 patients with non-alcoholic steatohepatitis against type 2 diabetes, age on average ( $58.69 \pm 1.25$ ) years. The control group comprised 15 healthy individuals. In order to identify the diagnosis, data from clinical and laboratory, biochemical and instrumental studies were fully integrated into account. Statistical processing of the results was carried out using Statistica 6. 1. In the group of patients with NASH before treatment, the stage I of hepatosis was observed in 15% of cases, the second - in 50%, the third in 35%. Lipid blood spectrum revealed high levels of low and very low density lipoprotein and low levels of high density lipoprotein. High levels of triglycerides among men and high thyroid test among women were determined. The results of the complex (with the inclusion of S-adenosylmethionine) treatment for patients with NASH showed a significant improvement in the subjective state of patients: reduced complaints of discomfort in the right hypochondrium, general weakness, nausea and dizziness. In the ultrasound study in the group of NASH, the redistribution of the number of patients in the side with the reduction of heavier stages of hepatosis was observed: the number of patients with stage I hepatosis was determined in 52.9% of cases (an increase of 3.5 times), stage II - in 24.9% (reduction in 2 times), the third stage - in 22.2% (reduction by 1.5 times). Among all patients, the cytolysis, mesenchymal-inflammatory syndrome, cytology, hemograms improved, and lipid and metabolic parameters were stabilized, confirming the positive membranotropic effect of S-adenosylmethionin on the membrane structures of hepatocytes and indicating anti-inflammatory, hepatoprotective and regenerative effects of the drug in the treatment of patients with steatohepatitis combined diabetes mellitus type 2.*

**Keywords:** *non-alcoholic steatohepatitis, diabetes mellitus type 2, S-adenosylmethionin, treatment.*

### Introduction

Non-alcoholic fatty liver disease (NAFLD) is an important cause of chronic liver damage in many countries and a rapidly growing public health crisis [11]. The frequency of NAFLD increases in both adults and children due to current obesity and type 2 diabetes epidemics [12]. Histologic fibrosis of the liver is recognized as the main predictor of the overall long-term outcome of NAFLD, including cardiovascular disease and mortality from liver disease [13]. The definition of prognosis and optimal treatment of patients with NAFLD and directed monitoring of the development of hepatocellular carcinoma is important here. Treatment of NASH in Ukraine is recommended in accordance with the "Unified Clinical Protocol for primary, secondary (specialized) medical care. Non-alcoholic steatohepatitis" (Order of the Ministry of Health of Ukraine dated November 06, 2014, No. 826). The diagnosis of NASH is based on the symptoms, the results of visualization (ultrasound of the liver), the results of laboratory and physical examination, with the fulfillment of all compulsory actions [10]. Researchers offer complex therapy taking into account the main pathogenic factors of NASH, which is increasingly combined with type 2 diabetes.

*The aim* is to study the effectiveness of complex treatment for patients with NASH combined with type 2 diabetes.

### Materials and methods

The study included 25 patients with steatohepatitis associated with type 2 diabetes (group 1). Patients belonged to middle-aged people - ( $58.69 \pm 1.25$ ) years. All patients had normal body mass. The control group comprised 15 healthy individuals (group 2).

In order to identify the diagnosis of NAFLD complex the data of clinical, laboratory, biochemical and instrumental studies were taken into consideration, according to the standards of examination of patients with pathology of organs of the gastrointestinal tract. By the time of the examination, the patients did not receive treatment for NAFLD according to standard procedures. A mandatory diagnostic method was the implementation of an ultrasound study to determine the size of the particles of the liver.

The biochemical blood test included: determination of protein (total protein content, thymol test), lipid (total cholesterol, triglycerides, high, low and very low density lipoprotein), pigmentary metabolism (total bilirubin), enzyme (aspartate aminotransferase, AST), alanine aminotransferase, ALT), alkaline phosphatase, gamma-glutamyltranspeptidase (GGTP) and glucose levels in the onset blood; general blood test.

Treatment of NASH was carried out in accordance with the "Unified clinical protocol of primary, secondary

(specialized) medical aid. Non-alcoholic steatohepatitis" (Order of the Ministry of Health of Ukraine dated November 06, 2014, No. 826) [10]. The diagnosis of NASH was based on the symptoms, the results of visualization (ultrasound of the liver), the results of laboratory and physical examination. All required actions were completed.

Since diabetes type 2 is a risk factor for NASH treatment, these patients were aimed at preventing the development of fibrosis and cirrhosis. Patients with NAFLD are given appropriate recommendations for changing lifestyle and eating behavior. First of all, for the correction of NAFLD, a balanced diet is recommended: the number of proteins within the physiological norm (on average 1 g/kg of body weight); reducing the daily amount of fats to 70 g and carbohydrates, limiting the amount of calories (1200 kcal - for women and 1500 kcal - for men). In order to achieve efficiency, diet therapy was recommended to be strengthened by regular exercises, smoking and alcohol cessation [4].

According to a unified clinical protocol, the base therapy was administered with the inclusion of a metabolic drug with proven efficacy of one million, which contains active ingredients - vitamins B1, B6, B12 for 1 month. Since the opinion of scientists about the use of medicines is ambiguous, it is decided to adjust the treatment of patients with NASH complex of drugs that act on the pathogenetic factors of the disease. In order to influence the course of NASH, S-adenosylmethionine (heptal) was used for 8 weeks. S-adenosylmethionine is a lipotropic compound that is necessary for the formation of new cells in the body as a donor of labile methyl groups. It participates in the synthesis of mediators, promotes the utilization of neutral fat from the liver cells, normalizes lipid metabolism, prevents fibrosis and cirrhosis, positively affects the function of detoxification. At the same time, it improves the deposition of glucose in the form of glycogen and in the case of diabetes, it lowers blood levels, supporting the liver cells. In order to correct the glucose content in the blood, patients were prescribed diabetic (gliclazid) - an oral hypoglycaemic agent, a sulfonylureasic derivative that reduces blood glucose levels by stimulating insulin secretion by the B-cells of pancreatic Langerhans islets.

Statistical processing of the results was carried out using Statistica 6.1.

## Results. Discussions

The results of the treatment were evaluated according to the dynamics of the subjective and objective status of the patients. Typical complaints in patients before the treatment were general weakness, urination, fatigue, headaches, more than half of patients had high blood pressure, which was on average ( $144.91 \pm 1.99$  /  $89.84 \pm 1.50$ ) mm Hg. Art. With the duration of the disease up to 5 years, common complaints were associated with bitterness in the mouth, abdominal discomfort, periodic pain in the right upper quadrant of the abdomen, associated with an increase in the liver that protruded from under the edges of the arc, averaged over

( $2.45 \pm 0.24$  cm). Among these patients, fluctuations of hyperglycemia were more frequent, with the incidence of 1-12 years (12 patients) these complaints were more pronounced. With an increase in the duration of the disease, complaints among patients became more.

The ultrasound investigation revealed signs of fatty liver dystrophy - steatohepatitis (distal contraction of the signal, diffuse hyperhegogenicity of the liver tissue, compared with the kidneys, and uncertainty of the contour of the vascular picture). The dimensions of the right lobe of the liver before treatment were ( $15.45 \pm 0.19$ ) cm, left - ( $9.20 \pm 0.03$ ) cm. When refining the ultrasonographic picture of the liver in group 1, by a combination of features (slight increase echogenicity, wall visualization veins of medium and large caliber) at NASH. In the stage of hepatosis, 15% of cases were observed, II - 50%, and the third - 35%.

The biochemical functional state of the liver remained satisfactory. Protein exchange was characterized by indicators in the reference limits of the indicator of healthy individuals: the protein content was ( $69.00 \pm 1.39$ ) g/l. The patients showed the expressed signs of mesenchymal-inflammatory syndrome: on average, thymol index - ( $3.42 \pm 0.32$ ) units. Timol index - ( $3.42 \pm 0.32$ ) units; among men, on average - ( $1.70 \pm 0.32$ ) units, among women - ( $3.89 \pm 0.64$ ) units, so that women exhibit more pronounced signs of mesenchymal-inflammatory syndrome. The level of total cholesterol was ( $5.51 \pm 0.41$ ) mmol/l, in men - ( $5.33 \pm 0.28$ ) units, in women - ( $5.66 \pm 0.19$ ) units, that is, near the upper limit of norm and these indicators differed little from each other.

The presence of cytolytic syndrome was confirmed by a significant increase in ALT activity - up to ( $1.41 \pm 0.05$ ) mmol/hl and AST - up to ( $1.63 \pm 0.06$ ) mmol/hl. The level of alkaline phosphatase increased to ( $198.15 \pm 9.1$ ) units/l, gammaglutamyltranspeptidase - to ( $97.18 \pm 3.56$ ) units/l, as compared with the control group ( $p < 0.05$ ). That is, among patients with combined nonalcoholic fatty liver disease combined with diabetes type 2, deterioration of the functional state of the liver was observed, which is indicated by an increase in the activity of the indicator enzymes of transaminases and excretory enzymes [3].

The content of triglycerides, on average, exceeded the upper reference limit - ( $3.70 \pm 0.61$ ) mmol/l. At the same time, the content of very low density lipoproteins was ( $1.38 \pm 0.11$ ) mmol/l. The low density cholesterol content among these patients reached ( $3.14 \pm 0.23$ ) mmol/L, and high density - ( $2.86 \pm 0.57$ ) mmol/L, indicating the presence of dyslipidemia. The liver becomes the target organ and, according to many authors, hypertriglyceridemia is the first impetus to the development of non-alcoholic fatty liver disease [7, 6, 5].

With the application of integrated therapy with lipotropic drug, the results of treatment showed a significant improvement in the subjective state of patients. Thus, complaints of feeling discomfort in the right hypochondrium, general weakness, bitterness in the mouth, nausea and dizziness have diminished. The liver, acting from the edge of the arch, on the average, was ( $2.02 \pm 0.16$ ) cm, which is

probably less than that of the treatment ( $p < 0.05$ ). In the ultrasound study in group 1, the number of patients with stage I hepatosis was determined in 52.9% of patients (an increase of 3.5 times), stage II - in 24.9% (decrease by 2 times), stage III - at 22.2% (reduction by 1.5 times), that is, there was a redistribution of the number of patients in the side with a decrease in heavier hepatoses, compared with the state of treatment. Blood pressure indicators decreased to ( $139.61 \pm 3.77 / 83.65 \pm 2.13$ ) mm Hg. compared with the state of treatment ( $p < 0.05$ ).

Among all patients, the cytolysis, mesenchymal-inflammatory syndrome, cytology, hemogram, hemogram improved, lipid metabolism and lipid metabolism, which confirms the positive membranotropic effect of adenosine metionine on the membrane structures of hepatocytes and confirms the anti-inflammatory, hepatoprotective and regenerative effects of the drug.

Thus, the activity of ALT significantly decreased to ( $0.58 \pm 0.03$ )  $\mu\text{mol/l}$ , AST ( $0.54 \pm 0.03$ )  $\mu\text{mol/l}$ , alkaline phosphatase - ( $87.23 \pm 4.21$ ) units/l, gammaglutamyl-transpeptidase - up to ( $56.12 \pm 2.06$ ), (the difference between pre and post treatment is probable,  $p < 0.05$ ). In previous studies, it was unequivocally proven that among the biochemical tests, the ALT index is a marker of NAFLD and can characterize the transformation of liver steatosis in NASH, and the combined increase in ALT and GGTP reflects the high activity of inflammation in the liver tissue [8] and can be used in non-invasive differential diagnosis steatohepatose and NASH [1].

The decrease in the manifestations of mesenchymal-inflammatory syndrome was demonstrated by a decrease in the thyme sample to ( $2.87 \pm 0.19$ ) units ( $p < 0.05$ ).

The biochemical functional state of the liver remained satisfactory. Protein exchange was characterized by indicators in the reference limits of the indicator of healthy individuals: the protein content was ( $71.76 \pm 1.52$ ) g/l. The level of total cholesterol reached ( $3.58 \pm 0.12$ )  $\mu\text{mol/l}$ . The content of total bilirubin after treatment was ( $16.11 \pm 0.65$ )  $\mu\text{mol/l}$ , before treatment ( $16.98 \pm 0.42$ ) mmol/l ( $p > 0.05$ ). Similar results (normalization of the lipid profile of the blood, decrease in the level of cytolysis) were obtained by O.Ya. Babak, E.A. Noodles [2] using a combination of ursodeoxycholic acid and ademetonine. To the same authors, there was a decrease in the level of the cytokine-18 in blood plasma, which testifies. in their opinion, about the reduction of apoptosis in the liver, the slowing down of the progression of the disease and its

transformation into NASH. Previously, I.M. Skrypnyk [9], based on the results of an open multicentre prospective study DIREG\_L\_04443, established the relationship between NASH, primarily lipid metabolism and diabetes mellitus, with factors that influence the choice of NASH treatment, including the appointment of hepatoprotectors - essential phospholipids.

Significant changes were not detected in the hemogram scores. Thus, the hemoglobin content remained within the reference limits of the norm ( $138.86 \pm 2.20$ ) g/l, before treatment ( $136.69 \pm 2.29$ ) g/l, color index 0.9-1.0; the content of erythrocytes to treatment ( $4.5 \pm 0.15$ )  $\times 10^{12}/\text{l}$ , after - ( $4.68 \pm 0.08$ )  $\times 10^{12}/\text{l}$ ; the content of leukocytes is up to ( $6.37 \pm 0.23$ )  $\times 10^9/\text{l}$  and ( $5.22 \pm 0.12$ )  $\times 10^9/\text{l}$  after treatment. Changes in the leukocyte formula were insignificant.

The level of glucose in the blood, on average, was after treatment ( $7.72 \pm 0.84$ ) mmol/l, against ( $9.95 \pm 0.91$ ) mmol/l before treatment ( $p < 0.05$ ).

## Conclusions and prospects for further developments

1. In the group of patients with NASH the I stage of hepatosis was observed in 15% of cases, II - in 50%, III in 35%. The lipid profile of the blood revealed high levels of low density lipoprotein and very low density and low levels of high density lipoprotein. High levels of triglycerides in men have been determined and high rates of thyme test in women.

2. Results of the complex (with the inclusion of S-adenosylmethionine) treatment for patients with NASH showed a significant improvement in the subjective state of patients, decreased complaints of a sense of discomfort in the right hypochondrium, general weakness, nausea and dizziness. In the ultrasound study in the NASH group there was a redistribution of the number of patients in the direction of reducing the heavier stages of hepatosis.

3. In all patients, the cytolysis, mesenchymal-inflammatory syndrome, cytology, hemograms improved, and lipid and metabolic parameters were stabilized, confirming the positive membranotropic effect of adenosine metionin on the membrane structures of hepatocytes and indicating anti-inflammatory, hepatoprotective and regenerative effects of the drug.

In the future, further studies are planned to study the indicators of the functional state of the liver and the possibility of its correction in patients with non-alcoholic fatty liver disease, combined with diabetes II type, with the use of integrated treatment regimens.

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**ЕФЕКТИВНІСТЬ ЛІКУВАННЯ ХВОРИХ НА НЕАЛКОГОЛЬНИЙ СТЕАТОГЕПАТИТ, ПОЄДНАНИЙ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ S-АДЕНОЗИЛМЕТІОНІНОМ**

**Анотація.** Неалкогольна жирова хвороба печінки є важливою причиною хронічного пошкодження печінки в багатьох країнах і швидко зростає як у дорослих, так і у дітей, через фактори ожиріння та діабет 2 типу. Мета - вивчити ефективність комплексного лікування хворих на неалкогольний стеатогепатит (НАСГ) при використанні s-аденозилметіоніну на тлі базової терапії. У дослідження включено 25 хворих на неалкогольний стеатогепатит на тлі цукрового діабету 2 типу середнім віком  $58,69 \pm 1,25$  років. Група контролю становила 15 здорових осіб. Для ідентифікації діагнозу комплексно враховували дані клініко-лабораторних, біохімічних та інструментальних досліджень. Статистична обробка результатів була проведена за допомогою Statistica 6.1. У групі хворих на НАСГ до лікування I стадію гепатозу спостерігали в 15% випадків, II - у 50%, III - у 35%. Ліпідний спектр крові виявив високі показники рівня ліпопротеїдів низької і дуже низької щільності та низький рівень ліпопротеїдів високої щільності, визначено великий вміст тригліцеридів у чоловіків і високий показник тимолової проби у жінок. Результати комплексного (із включенням s-аденозилметіоніну) лікування хворих на НАСГ показали значне поліпшення суб'єктивного стану хворих: зменшилися скарги на відчуття дискомфорту в правій підреберній ділянці, загальна слабкість, нудота та запаморочення. За результатами ультразвукового дослідження встановлено, що у групі НАСГ зменшилась кількість хворих з більш важкими стадіями гепатозу: кількість хворих із I стадією гепатозу визначена в 52,9% хворих (збільшення в 3,5 рази), II стадія - у 24,9% (зменшення в 2 рази), III стадія - у 22,2% (зменшення в 1,5 рази). У всіх хворих достовірно зменшилися показники цитолізу, мезенхімно-запального синдрому, покращилися показники гемограми, стабілізувалися показники білкового та ліпідного обміну, що підтверджує позитивну мембранотропну дію аденозинметіоніну на мембранні структури гепатоцитів і засвідчує протизапальну, гепатопротекторну та регенераторну дію препарату в лікуванні хворих на стеатогепатит, поєднаний з цукровим діабетом 2 типу.

**Ключові слова:** неалкогольний стеатогепатит, цукровий діабет, аденозилметіонін, лікування.

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**ЭФФЕКТИВНОСТЬ ЛЕЧЕНИЯ БОЛЬНЫХ НЕАЛКОГОЛЬНЫМ СТЕАТОГЕПАТИТОМ, СОЧЕТАННЫХ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА S-АДЕНОЗИЛМЕТИОНИНОМ**

**Аннотация.** Неалкогольная жировая болезнь печени является важной причиной хронического повреждения печени во многих странах и быстро растет как у взрослых, так и у детей из-за факторов ожирения и диабета 2 типа. Цель - изучить эффективность комплексного лечения больных неалкогольным стеатогепатитом (НАСГ) при использовании s-аденозилметионина на фоне базовой терапии. В исследование включено 25 больных неалкогольным стеатогепатитом на фоне сахарного диабета 2 типа со средним возрастом  $58,69 \pm 1,25$  лет. Группа контроля составила 15 здоровых лиц. Для идентификации диагноза комплексно учитывали данные клинико-лабораторных, биохимических и инструментальных исследований. Статистическая обработка результатов проводилась с использованием Statistica 6.1. В группе больных НАСГ до лечения I стадию гепатоза наблюдали в 15% случаев, II - у 50%, III - у 35%. Липидный спектр крови обнаружил высокие показатели уровня липопротеидов низкой и очень низкой плотности и низкий уровень липопротеидов высокой плотности, установлены большое содержание триглицеридов у мужчин и высокий показатель тимоловой пробы у женщин. Результаты комплексного (с включением s-аденозилметионина) лечения больных НАСГ показали значительное улучшение субъективного состояния больных: уменьшились жалобы на чувство дискомфорта в правой подреберной области, общая слабость, тошнота и головокружение. По результатам ультразвукового исследования установлено, что в группе НАСГ уменьшилось количество больных с более тяжелыми стадиями гепатоза: количество больных с I стадией гепатоза определена в 52,9% больных (увеличение в 3,5 раза), II стадия - в 24,9% (уменьшение в 2 раза), III стадия - в 22,2% (уменьшение в 1,5 раза). У всех больных достоверно уменьшились показатели цитолиза, мезенхимно-воспалительного синдрома, улучшились показатели гемограммы, стабилизировались показатели белкового и липидного обмена, что подтверждает положительное мембранотропное действие аденозинметионина на мембранные структуры гепатоцитов и свидетельствует о противовоспалительном, гепатопротекторном и регенераторном действии препарата в лечении больных стеатогепатитом в сочетании с сахарным диабетом 2 типа.

**Ключевые слова:** неалкогольный стеатогепатит, сахарный диабет, аденозилметионин, лечение.