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Effectiveness of the complex approach to the treatment of a non-alcoholic steatohepatitis combined with diabetes mellitus type 2

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Abstract

The use of S-adenosylmethionine in the treatment of 25 patients with non-alcoholic fatty liver disease (group 1) had high efficacy with the normalization of the functional, biochemical and cytokine profile of the blood. With the use of diabetic and pioglitazone in 25 patients in group 2, the cytotoxicity, mesenchymal-inflammatory syndrome, cytology, hemograms, and lipid metabolism have been stabilized, which confirms the positive lipidotropic effect of the complex effects of diabetone and pioglitazone on the functional state of hepatocytes and indicates a decrease in insulin resistance and improving the function of B cells. Integrated therapy with combined hypoglycemic and lipotropic therapy (diabetic, pioglitazone, geptral, group 3, 30 patients) showed the most pronounced anti-inflammatory effect. Pain syndrome remained tangible in 9 patients (30%, 1.8 times less than before treatment); dyspeptic syndrome-in 10 patients (33,3%, decreased by 1, 7 times), appetite decreased – in 10 patients (33,3%, a decrease of 1,9 times), astenovegetative syndrome-in 11 patients (36,7 %, decrease by 1.9 times). The applied combined hypoglycemic and lipotropic therapy on the background of basic therapy positively influenced the state of hepatocytes: the activity of ALT decreased to $(0.61 \pm 0.03) \mu\text{mol/l}$, AST $(0.52 \pm 0.04) \mu\text{mol/l}$, alkaline phosphatase - $(78,18 \pm 2,21)$ units/l, gammaglutamyltranspeptidases-up to $(52,34 \pm 1,26)$ unit/l, (the difference between pre and post treatment is likely, $p < 0,05$). During the ultrasound study, the redistribution of the number of patients in the side with the reduction of heavier stages of hepatosis, compared with the state of treatment. Particularly important is a significant decrease in the number of patients with the third stage of hepatosis with a decrease in the content of FNP-a, IL-6 and C-reactive protein and the growth of adiponectin.

Keywords: Nonalcoholic steatohepatitis, diabetes mellitus type 2, treatment

Introduction

The study included 80 patients with NASH against the background of diabetes type 2. Group 1-25 patients, average age of patients- $(54,45 \pm 1,2)$ years. Group 2-25 patients, age of patients was $(56,2 \pm 2,05)$ years. Group 3 (30 patients), age of patients was $(57,4 \pm 1,9)$ years. All patients had normal body mass. The control group comprised 15 healthy individuals.

In order to identify the diagnosis of NAFLD, the data of clinical, laboratory, biochemical and instrumental studies were taken into account in full compliance with the standards of examination of patients with pathology of the organs of the gastrointestinal tract. By the time of the examination, the patients did not receive treatment for NAFLD according to standard procedures. A compulsory diagnostic method was the implementation of an ultrasound study to determine the size of the liver and the stage of development of fatty liver disease.

The biochemical blood test included: determination of protein (total protein content, thymol test), lipid (total cholesterol content, triglycerides, high, low and very low density lipoprotein), pigmentary metabolism (total bilirubin), glucose levels in the onset of blood; general blood test.

The content of adiponectin was determined by the immune enzyme method (ELISA method, analyzer and test system, Mediagnost GmbH, Germany). Determination of the content of interleukin-6 (IL-6) was carried out in a supernatant from peripheral blood lymphocytes obtained after oxygen-free incubation and centrifugation, parameters were evaluated using the ECLIA (Sobas Roche) and tumor-alpha necrosis factor (FNP- α , immunochemical method with chemiluminescent detection, Immulite 100, Siemens AG, Germany). The content of C-reactive protein in blood was determined in blood serum using latex turbidimetric method - "Cobas 6000 (with 501 module; Roche Diagnostics (Switzerland).

NAFLD treatment was performed according to the "Unified clinical protocol of primary,

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Non-alcoholic steatohepatitis "(Order of the Ministry of Health of Ukraine dated November 06, 2014, No. 826) [4]. The diagnosis of NASH was established on the basis of symptoms, visualization results (ultrasound of the liver), laboratory and physical examination results.

Since diabetes type 2 is a risk factor for the treatment of these patients, the aim was to prevent the development of fibrosis and cirrhosis. Patients with NAFLD are given appropriate recommendations for changing lifestyle and eating behavior. In the first place, 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 exercise, smoking cessation and alcohol [4].

According to the Unified Clinical Protocol [12], they prescribed a baseline therapy with the inclusion of a metabolic drug with a proven efficiency 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 (heptral) was used for 8 weeks (group 1 to 25 patients), mean age of patients (54.45 ± 1.2) years, all patients had normal body mass.

In order to influence the course of diabetes, a combination approach was used, namely: diabetic (gliclazide, 60-120 mg)-for correction of blood glucose content-oral hypoglycemic preparation, sulfonyleurea derivative, which reduces blood glucose levels due to stimulation of insulin secretion B-cells of pancreatic Langerhans and pioglitazone (once daily, irrespective of food intake) [6]. The initial dose was 15 or 30 mg, if necessary, it was gradually increased to 45 mg.

For the purpose of glytazone reduction of glycosylated hemoglobin values is achieved by an average of 0.5-1.5%, which corresponds to a decrease in the average glycemia by 1-3 mmol/l. Currently, these drugs are recommended for use in order to reduce the incidence of glycemia in patients with type 2 diabetes mellitus in combination with glycemic control combined with metformin, derivatives of sulfonyleureas, both with each of them individually and against the background of their combined use. Time of observation-1 month. In order to influence the course of diabetes, a combined approach was used, namely: diabetone (gliclazide, 60-120 mg, for correction of glucose content in the blood). S-adenosylmethionine (heptral) was used to influence the course of NASH. The study was conducted on 30 patients with NASH combined with type 2 diabetes (group 3).

The statistical processing of the obtained results was carried out using statistical statistic data package Statistica on Pentium-IV personal computer and application of parametric and non-parametric methods for estimating the obtained results. The reliability of the difference in values between independent quantitative values was determined with a normal distribution according to Student's criterion, and in other cases, using the Mann-Whitney U-criterion.

Research and Discussion

It was found that in group 1 of patients with the inclusion of S-adenosylmethionine (heptral), the results of treatment

showed a significant improvement in the subjective state of patients, reduced complaints of discomfort in the right hypochondrium, general weakness, nausea. In the ultrasound study in the group of NASH, the redistribution of the number of patients in the side with the decrease of heavier stages of hepatosis has taken place. During the ultrasound study in the NASH group, the redistribution of the number of patients towards 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-at 24.9% (reduction in 2 times), the third stage-in 22,2% (reduction in 1,5 times).

Indicators of the cytokine profile revealed an increase in the adiponectin content in group 1 by 1.18 times, in the group NASH-in 1.44 times; the level of FNP- α -at stage I of hepatosis decreased by 1.46 times; in the II stage-in 1,64 times; in III-by 1.26 times. The content of IL-6 decreased in patients with the corresponding stages I, II and III-in 1,30; 1.35 and 1.45 times, with fatty hepatose-1.06 times. At the same time, the index of content of C-reactive protein at stages I, II and II decreased by 1.26 times; 1.24 times and 1.22 times; in group 1-in 1,09 times.

In group 2, with the application of integrated treatment with combined hypoglycaemic therapy (diabetic and pioglitazone), the results of treatment showed a significant improvement in the subjective and objective state of patients. Complaints have decreased significantly. Pain syndrome decreased by 1.4 times; dyspepsia syndrome - 1.7 times; decrease in appetite-in 1,7 times, astenovegetative syndrome-in 1, 3 times; subcurrent sclera-1.5 times; tongue bursts-2 times; liver-in 1,3 times, pain of a liver at a palpation - in 1,4 times); densification of liver parenchyma - 1.5 times). During the ultrasound study in the NASH group, the redistribution of the number of patients in the direction of reducing the heavier stages of hepatosis has taken place: the I stage is defined as 45% (increase 3 times), stage II - 35.0% (decrease by 1.4 times), stage III - 20.0% (decrease by 1.75 times). In all patients the cytolysis, mesenchymal-inflammatory syndrome, hemograms improved, the indicators of protein and lipid metabolism were stabilized, which confirms the positive lipidotropic effect of the complex influence of diabetes and pioglitazone on the functional state of hepatocytes.

The cytokine background in patients under the influence of treatment was characterized by the following changes: the level of FNP- α decreased by 1.4; in the II stage - in 1,52 and in the third - in 1,2 times. The content of IL-6 decreased in patients with the corresponding stages I, II and III - in 1,2; in 1.18 and 1.41 times. The content of C-reactive protein content at stages I, II and II decreased by 1.21; in 1.19 and 1.2 times. An increase in the content of adiponectin was found to be 1.44 times. In all patients, the cytolysis, mesenchymal-inflammatory syndrome, cytology, hemograms, and lipid metabolism have been stabilized, which confirms the positive lipidotropic effect of the complex effects of diabetes and pioglitazone on the functional state of hepatocytes and indicates a decrease in insulin resistance and improved B cell function.

In group 3, with the application of combined treatment with combined hypoglycaemic (diabetic and pioglitazone) and lipotropic (geptral) therapy, the results of treatment showed a significant improvement in the subjective and objective state of patients. Complaints about the feeling of discomfort in the right hypochondrium, general weakness, bitterness in the mouth, flatulence, nausea and dizziness have decreased

significantly. Pain syndrome remained tangible (1.8 times fewer patients than prior to treatment); dyspeptic syndrome - decreased by 1.7 times, appetite decreased - (a decrease of 1.9 times), astenovegetative syndrome - (a decrease of 1.9 times). The applied combined hypoglycemic and lipotropic therapy on the background of basic therapy positively influenced the state of hepatocytes: the activity of ALT decreased to $(0.61 \pm 0.03) \mu\text{mol/l}$, AST $(0.52 \pm 0.04) \mu\text{mol/l}$, alkaline phosphatase - $(78,18 \pm 2,21) \text{ units/l}$, gammaglutamyltranspeptidases - up to $(52,34 \pm 1,26) \text{ unit/l}$, (the difference between pre and post treatment is likely, $p < 0,05$).

During the ultrasound study, the redistribution of the number of patients in the direction of reducing the heavier stages of hepatosis, compared with the state of treatment. Of particular importance is a significant decrease in the number of patients with the third stage of hepatosis: the I stage of hepatosis is defined in 15 patients (50,0%) (an increase of 3 times), stage II - in 11 patients (36,7%), a decrease of 1,5 times), stage III - in 4 patients (13.3%), (decrease by 2.5 times).

As a result of the complex combined approach to the treatment of diabetes, pioglitazone and geptral in patients with NASH combined with type 2 diabetes, the level of FNP- α decreased significantly in 1.52 times and reached $(20.46 \pm 0.28) \text{ pg/ml}$ ($p < 0.05$). We observed an increase in the content of IL-6 before treatment $(21.22 \pm 0.46) \text{ pg/ml}$ and its decrease at the end of treatment to $(13.26 \pm 0.44) \text{ pg/ml}$ ($p < 0.05$).

Analyzing changes in the content of C-reactive protein in the deployment and flow of NASH, we found that its level in patients with NASH before treatment was $(21.09 \pm 0.18) \text{ pg/ml}$, and after the course of combined therapy - $(12.40 \pm 0, 52) \text{ pg/ml}$ ($p < 0.05$). Elevated levels of C-reactive protein indicate signs of systemic inflammation [5] and the direct involvement of C-reactive protein in co-operation with FNP- α and IL-6 in the progression of the development of pathological changes in the liver from fatty hepatosis to NASH, especially in patients with NAFLD, combined with CD.

It was found that the adiponectin content in patients with NASH in combination with type 2 diabetes was significantly lower than in patients with NAFLD, namely: $(2.63 \pm 0.25) \mu\text{g/ml}$, which is consistent with the data obtained by N.R. Mykhal'chyshyn *et al.* [7]. For these authors, the reduction of adiponectin below $4.6 \mu\text{g/ml}$ can be used as a diagnostic marker for NAFLD in patients with diabetes type 2. As a result of complex treatment, the adiponectin level reached $(4.01 \pm 0.08) \mu\text{g/ml}$ ($p < 0,05$).

In all patients, cytolysis, mesenchymal-inflammatory syndrome significantly decreased, hemogram rates improved, and lipid and metabolic parameters were stabilized.

Conclusion

1. The use of S-adenosylmethionine in the treatment of 25 patients with non-alcoholic fatty liver disease (group 1) had a high efficiency with the normalization of the functional, biochemical and cytokine profile of the blood.
2. With the use of diabetic and pioglitazone in 25 patients in group 2, the cytolysis, mesenchymal-inflammatory syndrome significantly decreased, hemogram values improved, the lipid and metabolic parameters were stabilized, confirming the positive lipidotrophic effect of the complex effect of diabetes and pioglitazone on the functional state of hepatocytes and indicating a decrease manifestations of insulin resistance and improvement of the function of B-cells.

3. Complex therapy with combined hypoglycemic and lipotropic therapy (diabetes, pioglitazone, geptral, group 3, 30 patients) revealed the most pronounced anti-inflammatory effect. Pain syndrome remained tangible in 9 patients (30%, 1.8 times less than before treatment); dyspeptic syndrome - in 10 patients (33,3%, decreased by 1,7 times), appetite decreased - in 10 patients (33,3%, a decrease of 1,9 times), astenovegetative syndrome - in 11 patients (36,7 %, decrease by 1.9 times). The applied combined hypoglycemic and lipotropic therapy on the background of basic therapy positively influenced the state of hepatocytes: the activity of ALT decreased to $(0.61 \pm 0.03) \mu\text{mol/l}$, AST $(0.52 \pm 0.04) \mu\text{mol/l}$, alkaline phosphatase - $(78,18 \pm 2,21) \text{ units/l}$, gammaglutamyltranspeptidases - up to $(52,34 \pm 1,26)$, (the difference between pre and post treatment is probable, $p < 0,05$). During the ultrasound study, the redistribution of the number of patients in the side with the reduction of heavier stages of hepatosis, compared with the state of treatment. Particularly important is a significant decrease in the number of patients with the third stage of hepatosis with a decrease in the content of FNP-a, IL-6 and C-reactive protein and the growth of adiponectin.
4. Based on the results obtained, we believe that the application in the complex of the proposed agents that affect specific pathogenetic links of NASH is appropriate in the treatment of this disease.

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