

## OPTIMIZATION OF TREATMENT OF PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS COMBINED WITH DIABETES MELLITUS TYPE 2

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*The goal is to optimize the treatment of patients with non-alcoholic fat liver disease combined with type 2 diabetes. The study was conducted on 25 patients with NAFLD – in the stage of NASH. Control group – 20 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. Results and conclusions. In the application of integrated treatment with combined hypoglycaemic therapy (diabetes 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 group of NASH, 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% (reduction 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, confirming the positive lipidotropic effect of the complex effect of diabetone and pioglitazone on the functional state of hepatocytes.*

**Key words:** *non-alcoholic fatty liver disease, diabetes mellitus type 2, complex combined treatment.*

**Problem statement and analysis of recent research.** The great scientific interest in hepatology today is isolated from the group of chronic diseases of the liver non-alcoholic fat liver disease (NAFLD), which has certain clinical manifestations, depending on the degree of damage to the liver – fatty hepatose, steatohepatitis and liver fibrosis [1]. These stages can progress with transformation into cirrhosis of the liver and hepatocellular

carcinoma. Diagnosis of NAFLD is performed in population surveys using ultrasonography and determination of aminotransferase activity. Sometimes the use of these methods is insufficient, which requires histological confirmation on the basis of life-time liver biopsy, if there are no contraindications for its implementation. According to various authors, the prevalence of NASH is 20-30%, with 2-3% of cases progressing [7,8]. Often the accumulation of fat in the liver is combined with the manifestations of diabetes, according to F. Bril F et al [6] in 60-80% of cases. The relationship between non-alcoholic steatohepatitis (NASH) and diabetes type 2 is difficult, with each negatively affecting another, which requires a multidisciplinary approach to the prevention and treatment of NAFLD in combination with diabetes, preventing liver fibrosis.

Functional state of the liver with NASH is characterized by varying degrees of severity of cytolytic, cholestatic, mesenchymal-inflammatory syndrome, manifestations of increased free radical oxidation of lipids, the presence of profound violations of cytokine status [4]. In accordance with the latest classification, diabetes type 2 refers to chronic hyperglycemia, which is due to insulin resistance and relative insulin deficiency. Thus, based on the above, the most appropriate method of therapy will be the use of medications that affect insulin resistance, and the purpose of treatment of NAFLD becomes the correction of metabolic disorders in the presence of diabetes mellitus and fatty hepatose and NASH, which requires a lot of attention and purposeful selection of drugs.

The purpose of the study is to optimize the treatment of patients with NAFLD, combined with diabetes type 2, by pathogenetic approach, depending on the specifics of the course of this disease.

**Material and methods of research.** The study was conducted on 25 patients with NAFLD – in the stage of NASH. Patients' age was  $(56.2 \pm 2.05)$  years. The control group consisted of 20 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 NAFLD treatment 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 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) [4]. 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 NAFLD treatment, these patients were aimed at preventing the development of fibrosis and cirrhosis. Patients with NHAHP are given appropriate recommendations for changing lifestyle and eating behavior. In the first place, for the correction of NAFL, 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). To achieve efficiency, diet therapy was recommended to be strengthened by regular exercise, smoking cessation and alcohol [2].

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 diabetes, a combination approach was used, namely: diabetone (gliclazide, 60-120 mg) – for correction of blood glucose content – an oral hypoglycemic drug, a derivative of sulfonylureas, which lowers blood glucose levels by stimulating insulin secretion B-cells of Langerhans islets of the pancreas and pioglitazone (in the middle, 1 time per day, regardless of food intake [3]).

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 is achieved on average by 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 in combination with hypoglycemic therapy in combination with metformin, derivatives of sulfonylureas, both with each of them separately and against the background of their combined use. Time of observation – 1 month.

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

**Results and discussion.** Patients with diabetes mellitus type 2 complained of general weakness, urination, fatigue, headaches, bitterness in the mouth, abdominal discomfort, periodic pain in the right upper quadrant of the abdomen, flatulence. In these patients, fluctuations of hyperglycemia were common. With an increase in the duration of the disease, complaints in patients became more.

Subjective manifestations of treatment were: pain syndrome – in 14 patients (56%), dyspeptic syndrome – in 14 patients (56%), appetite loss – in 16 patients (64%), asthenovoeative syndrome – in 17 patients (68%) .

Objectively, subclassical sclera was detected: in 9 patients (36%), the expressed tongue overlap – in 10 patients (40%), liver enlargement – in 18 patients (72%), pain in the liver when palpated – in 11 patients (44% ), compaction of the liver parenchyma – in 15 patients. Palpatinously, one of the symptoms of liver damage was its increase – the protrusion at  $(2.52 \pm 0.06)$  cm from the edge of the rib arch (1.0 to 3.0 cm) in 15 patients (60.0%).

The ultrasound investigation revealed signs of fatty liver dystrophy – steatohepatosis (distal constriction of the signal, diffuse hyperhogenicity of the liver tissue, in comparison with the kidneys, and uncertainty of the contour of the vascular picture). In the refinement of the ultrasonographic picture of the liver, in the aggregate of signs (a slight increase in echogenicity, visualization of the wall of the mediums and large caliber veins) in 15.0% of cases, I was diagnosed as stage of fatty liver disease. Moderate elevation of echogenicity of the liver, visualization of only partial and segmental veins, corresponding to the II stage of hepatosis, was detected in 50.0% of cases. In 35,0% echogenicity of the liver was increased to a considerable extent, the walls of the intrahepatic veins were not visualized – the third stage of fatty hepatosis.

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  $(66,82 \pm 1,6)$  g/l. The patients have expressed signs of mesenchymal-inflammatory syndrome: on average, the thyme sample was  $(3.49 \pm 0.54)$  units. The level of total cholesterol was determined  $(5.54 \pm 0.18)$  mmol/l, that is, about the upper limit of the norm. The presence of the cytolytic syndrome was confirmed by a significant increase in the content of ALT - to  $(1.39 \pm 0.54)$  mmol/hl and AST up  $(1.61 \pm 0.07)$  mmol/hl. The level of alkaline phosphatase increased to  $(189.12 \pm 8.3)$  units/l, gammaglutamyltranspeptidase – to  $(94.27 \pm 4.34)$  units/l, as compared to the control group ( $p < 0.05$ ). That is, in patients with NASH combined with diabetes type 2, a deterioration of the functional state of the liver was observed, indicating an increase in the activity of indicator enzymes of transaminases and excretory enzymes. The content of triglycerides, on average, exceeded the upper reference limit –  $(3.77 \pm 0.41)$  mmol/l. At the same time, the content of very low density lipoproteins was  $(1.29 \pm 0.16)$  mmol/l. The low density cholesterol content in these patients reached  $(3.24 \pm 0.35)$  mmol/l, and high density –  $(2.76 \pm 0.44)$  mmol/l.

Regarding the peculiarities of the hemogram rates, we noticed that in the patients of this age group, the ESR index, on average, was  $(14.78 \pm 1.12)$  mm/h. The attention of a fairly large number of patients with elevated ESR, more than 30 mm h – in 4 patients (16%).

In the application of integrated treatment with combined hypoglycaemic therapy (diabetes and pioglitazone), the results of treatment showed a significant improvement in the subjective state of patients with NASH. Thus, complaints of feeling discomfort in the right hypochondrium, general weakness, bitterness in the mouth, flatulence, nausea and dizziness have diminished.

Pain syndrome remained tangible in 10 patients (40%, 1.4 times less than before treatment); dyspeptic syndrome – in 12 patients (48%, decreased by 1.7 times), appetite decreased – in 12 patients (48%, decrease by 1.7 times), astenovegetative syndrome – in 13 patients (52%, decrease in 1, 3 times)

Objectively detected: subcurrent scleras reduced by 1.5 times; tongue bursts – 2 times; the liver remained enlarged in 14 patients (44%, a decrease of 1.3 times); the pain of the liver during palpation was preserved in 11 patients (32%, a decrease of 1.4 times); sealing of parenchyma of the liver was observed in 10 patients (40%, reduction in 1,5 times). The liver acted from the underlying arc in 14 patients ( $1.35 \pm 0.0$ ) cm.

The liver, acting from the edge of the arch, on the average, was ( $2.32 \pm 0.12$ ) cm, which is smaller compared with the state of treatment ( $p < 0.05$ ). In the ultrasound study, the number of patients with stage I hepatosis was determined in 45.0% of patients (an increase of 3 times), stage II – 35.0% (decrease by 1.4 times), stage III – by 20.0% (reduction in 1,75 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.

In all patients, cytolysis, mesenchymal-inflammatory syndrome significantly decreased, hemogram values improved, stabilization of the protein and lipid metabolism, confirming the positive combined effect of diabetone and pioglitazone. This can be explained by the leading role of pioglitazone. Insulin sensitizers (thiazolidinediones, glitazones) are a group of drugs that increase insulin sensitivity, reducing insulin resistance. The use of thiazolidinediones is directed directly to insulin resistance and to the improvement of the function of B cells. Their mechanism of action includes the activation of specific gamma receptor gamma receptors (PPAR-g): PPAR-g gamma receptors that are activated by the peroxisome proliferator are found in the fatty, muscular tissues and in the liver, endothelial cells [14]. Thiazolidinediones bind to PPAR-g, activate them, participate in the regulation of gene expression that are responsible for the production of a number of proteins that increase insulin sensitivity.

The applied combined anti-hyperglycemic therapy on the background of basic therapy positively influenced the state of hepatocytes: ALT activity significantly decreased to ( $0.71 \pm 0.04$ )  $\mu\text{mol} / \text{l}$ , AST ( $1.02 \pm 0.06$ )  $\mu\text{mol} / \text{L}$ , alkaline phosphatase – ( $98.13 \pm 3.1821$ ) units / l, gammaglutamyl-transpeptidases – up to ( $67.23 \pm 1.12$ ), (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 score is a marker of NAFLD and can characterize the transformation of liver steatosis in NASH, and the combined increase in ALT and gamma-glutamyltranspeptidase reflects the high activity of inflammation in the liver tissue and can be used in the non-invasive differential diagnosis of steatohepatose and NAFLD [12].

The decrease in the manifestations of mesenchymal-inflammatory syndrome was demonstrated by a decrease in the thyme sample to  $(3.02 \pm 0.28)$  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  $(69.84 \pm 1.87)$  g/l. The level of total cholesterol reached  $(4.42 \pm 0.23)$  mmol/l. The content of total bilirubin after treatment was  $(16.78 \pm 0.36)$  mmol/l, before treatment  $(18.74 \pm 0.28)$  mmol/l ( $p > 0.05$ ). Our results are in agreement with the data of E. Filipova et al [10], S.L. Wang et al [15], which showed an improvement in the hyperglycemic profile, had a positive effect on the lipid profile of patients on NAFLD in combination with diabetes type 2. The result of treatment with pioglitazone was a decrease in the activity of NASH, confirmed by biopsy of the liver [9, 11]. The use of pioglitazone, according to G. Musso et al. [13], suspends the progression of liver fibrosis, which has great prognostic and clinical significance.

Significant changes were not detected in the hemogram scores. Thus, the hemoglobin content remained within the reference limits of the norm  $(134,56 \pm 3,18)$  g/l, before treatment  $(136,93 \pm 2,67)$  g/l, color index 0,9-1,0; the content of erythrocytes-to treatment  $(4,42 \pm 0,18) \times 10^{12}/l$ , after –  $(4,58 \pm 0,06) \times 10^{12} / l$ ; the amount of leukocytes to –  $(6.84 \pm 0.36) \times 10^9/l$  and  $(6.72 \pm 0.24) \times 10^9/l$  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

1. In the application of integrated treatment with combined hypoglycaemic therapy (diabetes and pioglitazone), the results of treatment showed a significant improvement in the subjective state of patients with NASH. 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 decreased by 1.4 times; dyspepsia syndrome – 1.7 times, loss of appetite – 1.7 times, astenovegetative syndrome – 1.3 times. Objectively, the subcategory of sclera has decreased by 1.5 times; tongue bursts – 2 times; liver decrease in 1,3 times, pain of the liver during palpation decreased by 1,4 times; the compaction of the liver parenchyma decreased by 1.5 times).

2. During the ultrasound study in the NASH group, the redistribution of the number of patients in the direction of reduction of heavier stages of

hepatosis was observed: the number of patients with stage I of hepatosis was 45.0% (increase 3 times), with the second stage – 35.0% (reduction in 1,4 times), with the third stage – at 20,0% (a decrease of 1,75 times, compared with the state of treatment).

3. In all patients, cytolysis, mesenchymal-inflammatory syndrome, cytology, hemograms, and lipid metabolism have been stabilized, which confirms the positive lipidotrophic effect of the complex effect of diabetes and pioglitazone on the functional state of hepatocytes, and confirms the reduction of insulin resistance and the improvement of the B-cells

Prospects for further research in this direction. 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 fat liver disease, combined with diabetes, with the use of integrated treatment regimens.

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## ОПТИМІЗАЦІЯ ЛІКУВАННЯ ХВОРИХ НА НЕАЛКОГОЛЬНИЙ СТЕАТОГЕПАТИТ, ПОЄДНАНИЙ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

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***Мета** – оптимізація лікування хворих на неалкогольну жиркову хворобу печінки, поєднану з цукровим діабетом 2 типу.*

***Матеріал і методи.** Дослідження проведено на 25 хворих на НАЖХП у стадії НАСГ. Контрольна група – 20 здорових осіб. Для ідентифікації діагнозу НАЖХП комплексно враховували дані клініко-лабораторних, біохімічних та інструментальних досліджень, згідно зі стандартами обстеження хворих із патологією органів шлунково-кишкового тракту.*

***Результати і висновки.** При застосуванні комплексного лікування з комбінованою цукрознижувальною терапією (діабетон і піоглітазон) результати лікування показали значне поліпшення суб'єктивного і об'єктивного стану хворих. Скарги значно зменшилися. Больовий синд-*



ром зменшився в 1,4 рази; диспепсичний синдром – у 1,7 рази; зниження апетиту – у 1,7 рази, астеновегетативний синдром – у 1,3 рази; субіктеричність склер – в 1,5 рази; наліт язика – у 2 рази; печінка – в 1,3 рази, болючість печінки при пальпації – в 1,4 рази; ущільнення паренхіми печінки – в 1,5 рази. За ультразвуковим дослідженням у групі НАСГ відбувся перерозподіл кількості хворих у бік зменшення більш важких стадій гепатозу: I стадія гепатозу визначена в 45,0% (збільшення у 3 рази), II стадія – у 35,0% (зменшення в 1,4 рази), III стадія – у 20,0% (зменшення в 1,75 рази). В усіх хворих достовірно знизилися показники цитолізу, мезенхімно-запального синдрому, покращилися показники гемограми, стабілізувалися показники білкового і ліпідного обміну, що підтверджує позитивну ліпідотропну дію комплексного впливу діабетону і піоглітазону на функціональний стан гепатоцитів.

**Ключові слова:** неалкогольна жирова хвороба печінки, цукровий діабет 2 типу, комплексне комбіноване лікування.