VOLUME LXXVI, ISSUE 3, MARCH 2023

ISSN 0043-5147
E-ISSN 2719-342X

Wiadomości Lekarskie
Medical Advances

Official journal of Polish Medical Association has been published since 1928

INDEXED IN PUBMED/MEDLINE, SCOPUS, EMBASE, EBSCO, INDEX COPERNICUS,
POLISH MINISTRY OF EDUCATION AND SCIENCE, POLISH MEDICAL BIBLIOGRAPHY

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ALUNA Publishing House

ORIGINAL ARTICLE

EFFICACY OF COMPREHENSIVE TREATMENT OF NONALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH PREDIABETES

DOI: 10.36740/WLek202303119

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ABSTRACT

The aim: To evaluate the effectiveness of the proposed treatment recommendations, which included lifestyle changes, as well as the treatment with ursodeoxycholic acid, rosuvastatin, and omega-3 PUFA, on the severity of cytolytic and cholestatic syndromes in patients with NAFLD and prediabetes.

Materials and methods: Fifty-five patients with confirmed prediabetes and concomitant NAFLD underwent a comprehensive clinical examination and were treated with rosuvastatin 10 mg/d, omega-3 PUFA at a dose of 1000 mg/d and ursodeoxycholic acid at a dose of 10 mg/kg/d.

Results: The data obtained after 12 months of proposed treatment revealed a statistically significant improvement of indicators of cytolytic syndrome in patients with prediabetes and NAFLD. There was no significant difference between mean values of ALT and AST of treated patients and the corresponding indicators of apparently healthy persons, which confirms the effectiveness of the recommended treatment.

Conclusions: Proposed therapy which included recommendations for lifestyle changes and treatment with ursodeoxycholic acid, rosuvastatin and omega-3 PUFA significantly improved hepatic steatosis and cytolytic syndrome in patients with prediabetes and NAFLD.

KEY WORDS: non-alcoholic fatty liver disease, prediabetes, ALT, AST, rosuvastatin, omega-3 PUFA and ursodeoxycholic acid

Wiad Lek. 2023;76(3):581-585

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a multifactorial disease which is rapidly becoming the most common disease worldwide [1]. In the general population, the prevalence of NAFLD is about 25% [2], however, higher prevalence rates were found in high-risk groups, which include people with type 2 diabetes, obesity, and metabolic syndrome [3].

Epidemiological research data [3-5] confirm the tendency to increase the incidence of NAFLD in case of insulin resistance arising from obesity, type 2 diabetes and the presence of metabolic syndrome. NAFLD occurs in ~50% of obese individuals, in >95% of morbidly obese patients undergoing bariatric treatment, in 60-70% of patients with type 2 diabetes, in ~69% of patients with hyperlipidemia, in ~39% patients with arterial hypertension and in ~ 42% of patients with metabolic syndrome, but also in ~ 7% of patients with normal body weight. Nowadays NAFLD is considered to be recognized as the most common cause of elevated liver enzymes [6]. NAFLD affects an estimated 1 billion people worldwide and is the leading cause of liver cirrhosis, hepatocellular carcinoma, and death from liver disease [7].

The American Association of Diabetology (ADA) recommend to use the term "prediabetes" for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal. Patients with prediabetes are defined by the presence of impaired fasting glucose and/or impaired glucose tolerance and/or A1C 5.7–6.4% [8]. Patients with prediabetes, as well as the patients with NAFLD, are at high risk of diabetes and cardiovascular disease [9].

It is interesting that the expansion of NAFLD among people with prediabetes compared to patients with type 2 diabetes, remain insufficiently studied. The question of the choice of treatment tactics in the case of NAFLD and prediabetes is debatable.

THE AIM

To evaluate the effectiveness of the proposed treatment recomendations, which included lifestyle changes, as well as the treatment with ursodeoxycholic acid, rosuvastatin, and omega-3 PUFA, on the severity of cytolytic and cholestatic syndromes in patients with NAFLD and prediabetes.

Table I. Biochemical blood analysis indicators of patients of the group Ia 6 and 12 months after treatment (M±m)

Indicators	Group of comparisons				Reliability indicator
	Group Ia (n=28)			Control group (n=30) Before treatment	After 6 months
	Before treatment	After 6 months	After 12 months		
ALT, U/L	37,65 ±12,12	34,72 ±10,24	31,24 ±9,07	27,99 ±6,39	p0-6=0,33 p0-12=0,03* p6-12=0,18 p12-III=0,12
AST, U/L	34,51 ±12,37	30,48 ±9,68	27,71 ±8,60	29,17 ±5,66	p0-6=0,18 p0-12=0,02* p6-12=0,27 p12-III=0,45
GGT, U/L	48,52 ±10,90	46,53 ±11,12	47,22 ±9,42	43,58 ±9,30	p0-6=0,50 p0-12=0,64 p6-12=0,80 p12-III=0,15

Note: ww n- number of patients; p0-6 - the significance of the difference of the indicators before and after 6 months of the treatment; p0-12 - the significance of the difference of the indicators before and after 12 months of the treatment; p6-12 - the significance of the difference of the indicators after 6 and 12 months of the treatment; p12-III - the significance of the difference of the indicators of the patients after 12 months of treatment and indicators of group of apparently healthy person; * – the difference between the indicators is statistically significant as compared before and after the treatment and as compared to group of apparently healthy person.

Table II. Biochemical blood analysis indicators of patients of the group Ib 6 and 12 months after treatment (M±m)

Indicators	Group of comparisons				Reliability indicator
	Group Ib (n=27)			Control group (n=30)	p
	Before treatment	After 6 months	After 12 months		
1	2	3	4	5	6
ALT, U/L	37,56 ±13,27	41,79 ±12,63	44,21 ±9,77	27,99 ±6,39	p0-6=0,24 p0-12=0,04* p6-12=0,44 p12-III<0,01*
AST, U/L	37,06 ±15,04	39,42 ±13,41	38,71 ±14,12	29,17 ±5,66	p0-6=0,55 p0-12=0,68 p6-12=0,85 p12-III=0,001*
GGT, U/L	46,64 ±12,25	44,32 ±11,96	45,74 ±12,80	43,58 ±9,30	p0-6=0,49 p0-12=0,79 p6-12=0,68 p12-III=0,47

Note: n - number of patients; p0-6 - the significance of the difference of the indicators before and after 6 months of the treatment; p0-12 - the significance of the difference of the indicators before and after 12 months of the treatment; p6-12 - the significance of the difference of the indicators after 6 and 12 months of the treatment; p12-III - the significance of the difference of the indicators of the patients after 12 months of treatment and indicators of group of apparently healthy person; * – the difference between the indicators is statistically significant as compared before and after the treatment and as compared to group of apparently healthy person.

MATERIALS AND METHODS

Seventy-eight patients with impaired glucose tolerance underwent comprehensive clinical examination. Fifty-five patients with confirmed prediabetes and concomitant NAFLD were included to the study. Exclusion criteria were: age older than 74 years; coronary heart disease; connective tissue diseases; oncological diseases; type I and II diabetes mellitus; cirrhosis; previously transferred viral hepatitis; toxic (alcohol – consumption of more than 40 g of ethanol/d), medicinal (use of hepatotoxic drugs), severe metabolic liver diseases; Wilson's disease; autoimmune hepatitis; recent significant weight loss, parenteral nutrition for 2 weeks or more; chronic diseases of the gastrointestinal tract, accompanied by impaired absorption (malabsorption syndrome); refusal of the patient to participate in the study.

There were two groups of the patients, which were comparable in terms of age, sex, and NAFLD stage. Division of patients into groups was carried out in an arbitrary order, by means of random numbers.

As the initial examination of patients with prediabetes and NAFLD revealed very high cardiovascular risk, all patients were prescribed with rosuvastatin at a dose of 10 mg/d. Patients of group Ia (n=28) were treated with rosuvastatin 10 mg/d, omega-3 PUFA at a dose of 1000 mg/d and ursodeoxycholic acid at a dose of 10 mg/kg/d to improve hepatic steatosis.

Patients of the Ib group (n=27) made up the comparison group and, apart from rosuvastatin, did not take any medicines.

Patients of both groups followed dietary recommendations and in order to increase their physical activity performed 30-minute walks per day. A control group of apparently healthy individuals (n = 30) was used for comparison. Evaluation of the effectiveness of treatment was carried out 6 and 12 months after the initiation of the therapy.

All patients underwent a comprehensive clinical examination, which included the collection of anthropometric data, an objective examination, and the collection of venous blood for laboratory analysis.

For the diagnosis of NAFLD, the method of ultrasound diagnosis of the liver was used, taking into account the fact that ultrasound can reveal an increase in the echogenicity of the liver and confirm the diagnosis of NAFLD under conditions of fatty infiltration of the liver of more than 33%. The criteria for the presence of steatosis were a diffuse homogeneous increase in echogenicity of the liver ("white liver") with greater echogenicity than the right kidney (hepatorenal index) and dorsal attenuation of the ultrasound signal.

Statistical processing of the obtained results was performed on a personal computer using the Microsoft Office Excel 2003 and Statsoft Statistica 8.0 software packages. The discrepancy was considered probable if the probability value was equal to or greater than 95% ($p<0.05$).

RESULTS

During the period of observation and treatment among patients of the Ia group, there was a tendency to decrease cytolysis indicators, namely: the average value of the ALT level after 12 months of treatment statistically significantly decreased by 17.03% from the initial value ($p=0.03$), and the average value of the AST level – by 19.71% ($p=0.02$) (Table I).

The average value of the GGT level in patients of group Ia did not statistically significantly change during the study, and it also significantly did not differ from the average value of the GGT level of apparently healthy individuals (Control group) ($p=0.15$).

It turned out to be interesting that after 12 months of treatment, the average values of ALT and AST levels of patients of group Ia approached the corresponding indicators of individuals of control group and did not statistically differ from them ($p=0.12$ and $p=0.45$, respectively). This indicates the effectiveness of the selected therapeutic scheme.

The change in individual indicators of the biochemical blood analysis of patients in the Ib group was not statistically significant, except for the average value of the ALT level (Table II). Moreover, the change in the average value after 12 months was statistically significant: an increase of this indicator by 17.71% was observed compared to the indicator before treatment ($p=0.04$). When comparing the average values of ALT and AST levels after 12 months with the corresponding indicators of practically healthy individuals, a statistically significant difference was found: the average values of ALT and AST levels in patients of control group were statistically significantly lower ($p<0.01$ and $p=0.001$, respectively).

DISCUSSION

Currently, approved treatment for NAFLD is rather controversial and mainly is aimed at correcting risk factors. Screening and early intervention for obesity, prediabetes and type 2 diabetes, dyslipidemia and hypertension are cost-effective and safe [10]. Insulin resistance, increased serum insulin levels and oxidative stress are risk factors for NAFLD, diabetes and hypertension [11]. In animal models, ursodeoxycholic decreased fasting glucose, insulin, and hepatic insulin resistance, showing that this medication is effective in treating NAFLD in patients with diabetes [12]. Kim et al. in their study showed reduction of ALT, AST, and GGT levels in patients with liver dysfunction [13]. Moreover, there are studies, which demonstrate effectiveness of co-administration of ursodeoxycholic acid with rosuvastatin/ezetimibe in a non-alcoholic fatty liver disease model [14]. Tzanaki I. et al. in their review demonstrated the importance of effective lipid lowering therapy in patients with NAFLD [15].

However, there is no information in terms of treatment NAFLD in patients with prediabetes. The current study aims to evaluate the effectiveness of co-administration of ursodeoxycholic acid with rosuvastatin and omega-3 PUFA in special category of patients. These are patients with NAFLD and prediabetes – individuals who do not meet criteria for diabetes, nevertheless are at one-step to cardiovascular diseases.

CONCLUSIONS

Lifestyle changes alone in patients with prediabetes and NAFLD were not effective in terms of cytolytic and cholestatic syndromes. Treating NAFLD in prediabetic patients with ursodeoxycholic acid, rosuvastatin, omega-3 PUFA, dietary and physical activity recommendations showed reduction of AST and ALT, which ensures the effectiveness of the proposed program of complex treatment.

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The work was carried out in accordance with the plan of the research program of the Department of Therapy and Family Medicine of the Faculty of Postgraduate Education and Pre-University Training of Uzhhorod National University "Optimization of prevention and treatment of obesity and diabetes mellitus by Helicobacter pylori associated diseases", where the author is co-author.

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Conflict of interest:
The Authors declare no conflict of interest.