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WHAT IS THE PROFILE OF PATIENTS WITH TYPE 2 DIABETES AND NON-ALCOHOLIC FATTY LIVER DISEASE?

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ABSTRACT

Prevalence of non-alcoholic fatty liver disease (NAFLD) increases dramatically. Type 2 diabetes (DM2) increases the risk of developing NAFLD, and the presence of NAFLD increases the risk of developing type 2 diabetes. The aim of our work was to study the profile of patients with NAFLD and DM2. We analyzed the profile of 582 patients treated at the Department of Diabetology of the RSSPMCE in 2019. 27% patients had non-alcoholic steatosis (NAS), 8% non-alcoholic steatohepatitis (NASH) based on fibroscanning after detection of steatohepatosis on liver ultrasound. Patients with NAS and NASH did not differ in gender, age, and glycemic control, from patients without NAFLD. 40% patients without NAFLD, 40% with NAS and 54% of patients with NASH had arterial hypertension, isolated diastolic hypertension (IDAH) occurred in 10.4% of patients with NASH, in 7% of patients with NAS, and in 5% of patients without NAFLD.

Among patients without steatohepatosis diagnosed by ultrasound of the liver, there was a high proportion of people with an estimated NAFLD fibrosis score corresponding to stages 3-4 of fibrosis, which indicates the need for an active search for NAFLD in people with type 2 diabetes before the appearance of ultrasound signs of steatohepatosis in order to timely initiation of adequate treatment. We are continuing research to determine the optimal algorithm for the active search for NAFLD in people with type 2 diabetes.

KEYWORDS: non-alcoholic fatty liver disease, type 2 diabetes, steatohepatosis, steatohepatitis.

INTRODUCTION

Over the past 30 years together with the increase in obesity, the prevalence of non-alcoholic fatty liver disease (NAFLD) has increased dramatically.[1,2]

According to a meta-analysis published in 2016, 25.2% of the world's population has NAFLD, men are more likely to have NAFLD, and the prevalence increases with age.[3]

As for non-alcoholic steatohepatitis (NASH), its prevalence in the general population is estimated as 1.5-6.5%. Men and postmenopausal women are more likely to have NASH.[4-7]

In the US, 85 million people have NAFLD, 17 to 25 million have NASH, and these numbers are expected to rise to 100 million and 43 million, respectively, by 2030.[8]

NAFLD includes non-alcoholic steatosis (NAS), which is characterized by fatty hepatosis without inflammation, and non-alcoholic steatohepatitis (NASH), which involves inflammation and balloon transformation of liver cells with or without fibrosis. NAFLD progresses to NASH, then signs of fibrosis of varying severity appear, which may result in the development of cirrhosis with or without hepatocellular carcinoma. The stage of moderate fibrosis can be reversed. NASH has a more aggressive course with higher morbidity and mortality, especially in the presence of fibrosis.[9,10]

End-stage liver disease due to NAFLD is a cause of death and one of the leading causes of liver transplantation.[2]

There is a growing evidence that even steatosis and mild inflammation can lead to fibrosis and hepatocellular carcinoma.[11-13]

The average life span after the development of hepatic failure decompensation is 2 years.[14]

The presence of NAFLD leads to the appearance of insulin resistance in the liver, an increase in fasting glucose and an increase in the level of atherogenic lipoproteins.[15]

NASH is associated with elevated levels of inflammatory proatherogenic cytokines, hypercoagulation factors, and cell adhesion molecules.[16]

Type 2 diabetes (DM2) increases the risk of developing NAFLD. In turn, the presence of NAFLD increases the risk of developing type 2 diabetes. Several studies with long-term follow-up of patients have shown that diabetes and obesity accelerate the progression of fibrosis in NAFLD.[11-13,17,18]

Patients with NAFLD with concomitant type 2 diabetes and men with elevated levels of gamma-glutamyl transpeptidase (GGT) have an increased risk of cardiovascular events compared with those without NAFLD.[19,20]

By itself, NAFLD and NASH, according to the study by Younossi ZM et al., occurs among 57.8% and 65.26% of patients with type 2 diabetes, respectively. But here it should be noted that this applies to patients referred for liver biopsy, which is important, therefore it would be wrong to extrapolate these figures to the general population of patients with type 2 diabetes.[5]

Several studies have shown that NAFLD has a significant role in increasing the incidence of hepatocellular carcinoma (HCC) in patients with metabolic syndrome, type 2 diabetes and obesity.[21-24]

And the reason for this relationship lies not only in fibrosis, but also in the pathogenesis of metabolic disease. The soil for carcinogenesis in the liver is insulin resistance and stetohepatosis, which support inflammation triggered by adipose tissue, changes in adipokine levels, oxidative stress, lipotoxicity, and IGF-1 stimulation.[21-23,25]

Therefore, associations such as EASL (European Association for the Study of the Liver), EASD (European Association for the Study of Diabetes) and EASO (European Association for the Study of Obesity) recommend screening for NAFLD in individuals at high risk of cardiovascular disease, including patients with type 2 diabetes and metabolic syndrome.[26]

The aim of our work was to study the profile of patients with NAFLD and type 2 diabetes mellitus.

MATERIALS AND METHODS

We analyzed the profile of 582 patients treated at the Department of Diabetology of the RSSPMCE in 2019. The diagnosis of NAS and NASH was made on the basis of liver ultrasound in the presence of diffuse hyperechogenicity of the liver parenchyma and heterogeneity of its structure; fuzziness and / or accentuation of the vascular pattern; distal attenuation of the echo signal.[27]

Glycemia was determined on an automatic biochemical analyzer BS-380 "Mindray" by glucose oxidase method in venous blood on an empty stomach using HUMAN "Glucose" reagents (Germany). Glycated hemoglobin was determined by the HbA1c analyzer (automatic machine) Huma Nex A1c with HUMAN reagents (Germany). Liver enzymes were tested for on an automatic biochemical analyzer BS-380 "Mindray" by the kinetic method using "ASAT", "ALAT" HUMAN reagents (Germany). Thrombocyte counting was performed using an automatic hematology analyzer VS-5800. Blood albumin was determined on an automatic biochemical analyzer BS-380 "Mindray" using the "Albumin" HUMAN reagent (Germany).

FIB-4 scale was calculated to all patients using the formula:[28]

FIB-4 = age * AST / platelets (109 / L) * √ALT

The result of 0-2 was regarded as mild fibrosis, from 3 to 4 – as moderate fibrosis, 5-6 – as severe fibrosis / cirrhosis.

Also, NAFLD fibrosis score was calculated to all patients using the following formula:

NAFLD Score = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg / m2) + 1.13 × NTG / SD (yes = 1, no = 0) + 0.99 × AST / ALT - 0.013 × Platelets (× 109 / L) - 0.66 × Albumin (g / dl).[9]

The presence of fibrosis was assessed as follows:

A score of less than -1.455 was regarded as the absence of significant fibrosis (F0-F2);

A score above 0.675 was considered significant fibrosis (F3-F4);

Intermediate scores (from -1.455 to 0.675) were regarded as F2-F3.

Statistical processing of the results was carried out using Microsoft Excel 2013. Average values are presented as arithmetic mean ± standard deviation. The reliability of the indicators was assessed at $p < 0.05$.

RESULTS AND DISCUSSION

Of the 582 examined patients, 157 (27%) were diagnosed with non-alcoholic steatosis (NAS), 48 (8%) - non-alcoholic steatohepatitis (NASH) based on fibroscanning after detection of steatohepatosis on ultrasound of the liver.

Patients with NAS and NASH did not differ in gender and age, as well as in terms of glycemic control, from patients without NAFLD. The duration of diabetes mellitus was higher among patients without diagnosed NAFLD (Table 1).

Table 1. Comparative characteristics of patients with type 2 diabetes mellitus with and without NAFLD

Parameter	No NAFLD	NAS	NASH
n	377	157	48
Age, years	58.8±10.6	58.9±8.9	52.5±8.3[§]*
Gender (male/female, %)	48/52	42/58	48/52
Duration of diabetes, years	11.0±6.1	9.5±6.0[x]	6.0±4.3[§]*
BMI, kg/m^2	29.3±4.9	31.5±4.2[x]	32.7±4.5[§]
Fasting glycemia, mmol/L	9.1±3.2	8.9±2.8	10.3±1.9
HbA1c, %	10.1±2.3	9.6±2.4	10.3±1.9

Note: data are given in M ± SD

** at p <0.05 between groups with NAS and NASH*
[x] at p <0.05 between groups with and without NAFLD
[§] at p <0.05 between groups with NASH and without NAFLD

According to a number of studies with a follow-up period from 2.2 to 13.8 years, about a third of patients diagnosed with NAFL and NASH will progress to fibrosis, and in 20%, some regression of the disease is possible.[11,13,18,25,29]

Another study showed that within 7.6 years, the development of cirrhosis and decompensation of NAFLD was observed only in 3.1%.[30]

The transition from one stage of the disease to another occurs within about 7.7 years.[31]

However, in individuals with NASH, the rate of development of fibrosis is 2 times higher, and can be as little as 6 years.[12,13]

As fibrosis progresses, signs of steatosis, inflammation and balloon transformation of hepatocytes decrease in parallel with a decrease in transaminase levels.[17]

In our study, we did not find an association between the duration of diabetes mellitus and the degree of liver damage. There was also no correlation between glycemic control and the severity of fibrosis.

Results from cross-sectional population studies have shown that NAFLD is independently associated with predictors of cardiovascular disease such as endothelial dysfunction, vascular stiffness, and myocardial dysfunction.[19,32-34]

40% patients without NAFLD, 40% with NAS and 54% of patients with NASH had arterial hypertension, while isolated diastolic hypertension (IDAH) occurred in 10.4% of patients with NASH, in 7% of patients with NAS, and in 5% of patients without NAFLD.

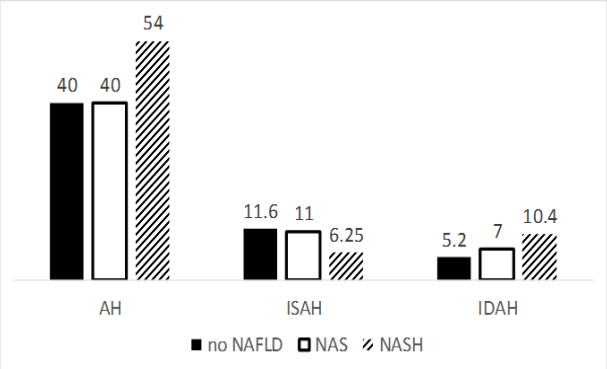

Fig. 1. ***The incidence of arterial hypertension among patients with and without NAFLD.***
Note: AH - arterial hypertension, ISAG - isolated systolic arterial hypertension, IDAH - isolated diastolic arterial hypertension, NAFLD - non-alcoholic fatty liver disease, NAS - non-alcoholic steatosis, NASH - non-alcoholic steatohepatitis.

NASH manifests itself histologically as steatosis of more than 5% of liver tissue, inflammation of the lobules (infiltration with mononuclear cells), balloon transformation of hepatocytes with varying degrees of fibrosis.

The gold standard for diagnosing NASH is liver biopsy. But since this is an invasive procedure, the question naturally arises: what are the indications for a biopsy? Clinical indications for liver biopsy include:
1. Metabolic syndrome with elevated ALT-to-AST ratio (high level of evidence);
2. Type 2 DM with an increase in ALT-to-AST ratio;
3. Biopsy during bariatric surgery;
4.Biopsy during cholecystectomy (low quality evidence).

Laboratory findings with high evidence level supporting biopsy are:
1. ALT> AST;
2. Low platelet count;
3. Low albumin levels.

If there are signs of fatty hepatosis on ultrasound and an increase in the level of liver enzymes and / or a change in

their ratio, in the presence of risk factors for progression of fibrosis or in the presence of metabolic syndrome, a biopsy is recommended. If there are no risk factors or metabolic syndrome, the authors recommend a trial lifestyle change (weight loss through diet and exercise and smoking cessation) for 6-12 months. In the absence of positive dynamics, a liver biopsy is recommended.

If there are signs of fatty hepatosis on ultrasound without changing the level of liver enzymes, but if there are signs of cirrhosis or severe fibrosis on ultrasound, a biopsy is recommended. If there are no signs of cirrhosis or fibrosis, further tactics for choosing a biopsy or trial treatment depends on the risk factors for the progression of fibrosis and the presence of components of the metabolic syndrome.[35]

Since the biopsy procedure is invasive, and the definition of indications for it is not clear enough, several scales have been developed to identify patients with NAFLD at an increased risk of adverse outcomes. This is FIB-4, which includes age, ALT, AST, platelet count; APRI (AST to platelet ratio index), which takes into account AST and platelet count; NAFLD fibrosis score, taking into account age, ALT, AST, platelet count, albumin level and the presence of impaired fasting glucose or diabetes; and BARD, the list of factors of which includes the AST / ALT ratio, BMI and the presence of type 2 diabetes.[36-38]

We studied the data of the FIB-4 and NAFLD fibrosis scores in patients with and without signs of fatty hepatosis on ultrasound (Table 2).

Table 2. FIB-4 and NAFLD fibrosis scores among the examined patients.

	No NAFLD	NAS	NASH
FIB-4			
0-2 points	92%	97.3%	84.4%
3-4 points	8%	1.3%	15.6%
5-6 points	-	1.3%	-
NAFLD fibrosis score			
<-1.455 (F0-F2)	22%	9.6%	10.4%
-1.455 to 0.675 (F2-F3)	56.8%	26.7%	16.7%
> 0.675 (F3-F4)	18.7%	63.7%	73%

It should be noted that 13% of patients without NAFLD had a decrease in platelet levels (for comparison, a low platelet level was observed in 9.4% of patients with NAS and 20% of patients with NASH), as well as blood albumin levels below 35 g / L in 6 % (for comparison, a low level of albumin was observed in 7% of patients with NASH and was not observed in patients with NASH), which was associated with other pathologies - chronic kidney disease and anemia, which probably influenced the results of the calculation on the FIB-4 scale.

CONCLUSIONS

NAFLD is a common condition in type 2 diabetes. In our study, 27% and 8% of patients with type 2 diabetes had diagnosed NAS and NASH, respectively. In patients with NAS and NASH, isolated diastolic arterial hypertension was more often observed.

Glycemic control has not been shown to be a factor that could increase the risk of steatosis. We also did not observe the relationship between the presence of NAFLD and the duration of type 2 diabetes. However, among patients without steatohepatosis diagnosed by ultrasound of the liver, there is a high proportion of people with an estimated NAFLD fibrosis score corresponding to stages 3-4 of fibrosis, which indicates the need for an active search for NAFLD in people with type 2 diabetes before the appearance of ultrasound signs of fatty hepatosis in order to timely initiation of adequate treatment. We are continuing research to determine the optimal algorithm for the active search for NAFLD in people with type 2 diabetes.

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