Frequency Of Occurrence of Non-Alcoholic Fatty Liver Heptoses in Patients Without Obesity

Khamidova M. I.

Assistant of the Department of Hospital therapy and Endocrinology
Andijan State Medical Institute
Andijan, Uzbekistan

ABSTRACT

It is generally believed that non-alcoholic fatty liver disease (NAFLD) is a component of the metabolic syndrome and is often combined with obesity, type 2 diabetes mellitus, atherogenic dyslipidemia and its other components. However, today there is no doubt that not all obese people develop NAFLD and, on the contrary, the presence of NAFLD is possible in people with normal weight. Data on the prevalence of NAFLD without obesity in different countries are very variable – from 3 to 30%. Both exogenous (for example, excessive consumption of cholesterol and rapidly digestible fructose) and genetically determined (allelic variants of genes encoding adiponutrin, cholesterol ester transporter protein, sterol-regulating element-binding factor) are considered as risk factors for development. Diagnostic methods are not fundamentally different from those for "classical" NAFLD. Based on the analysis of the conducted studies, there are grounds to assert that lifestyle modification in the form of physical exertion and dietary restrictions contributes to the improvement of biochemical parameters and histological picture. The effectiveness of medicinal methods requires further study.

Keywords: Non-alcoholic fatty liver disease without obesity, risk factors, diagnosis, treatment.

Non-alcoholic fatty liver disease (NAFLD) is defined as fatty liver infiltration detected by histological examination or non-invasive methods in persons who do not abuse alcohol and with no causes of secondary fat accumulation (for example, hepatitis C virus infection genotype 3) [1-3]. Today, NAFLD has taken a leading position among chronic liver pathology, displacing viral and alcoholic lesions. In economically developed countries, its prevalence ranges from 20 to 30% of the adult population [4-5]. The risk of NAFLD is due not only to the likelihood of progressive liver fibrosis with the development of cirrhosis and hepatocellular carcinoma, but also with an increased frequency of damage to the cardiovascular system, kidneys, thyroid gland and colon [6- 9].

According to the definition of the World Health Organization, the normal body weight is the body mass index (BMI) from 18.5 to 24.9 kg / m2, increased – from 25.0 to 29.9 kg / m2. The American Dietetic Association considers the ideal BMI from 20 to 25 kg/m2. BMI is usually interpreted as a surrogate marker of body fat content, but such an interpretation, especially among people with normal weight, cannot be considered adequate. It should be noted that when studying the issue of norm-pathology in general and differentiation of types of NAFLD in particular, racial and ethnic differences should probably be taken into account [1, 2, 12]. Thus, the risk of type 2 diabetes and cardiovascular pathology significantly increases in the Asian population with a lower BMI compared to Europeans [12]. In connection with the above, many authors distinguish between the concepts

of lean NAFLD (lean NAFLD, non-overweight NAFLD) and NAFLD-BO (non-obese NAFLD); the latter term unites individuals with normal and elevated BMI. In this review, the two mentioned groups are considered together, except when it is necessary to separate them.

Most studies show a significant prevalence of NAFLD-BO, although inferior to that of NAFLD-O [4, 11, 14-17]. In a study by Kim et al. the incidence of NAFLD was 16.1% in people with normal weight and 34.4% with an increased BMI, not reaching the degree of obesity [15]. In another study from Taiwan, NAFLD-BO was observed in 15-21% of residents of the Asia-Pacific region with BMI.

Currently, non—alcoholic fatty liver disease (NAFLD) is considered by a number of authors as a hepatic component of the metabolic syndrome and is associated with various risk factors — genetic, hereditary, metabolic, lifestyle factors - eating behavior, physical activity, smoking [1-3]. The basis of the pathogenesis of NAFLD is insulin resistance (IR) and abdominal obesity (AO), as a result of which the synthesis of fats in the liver increases, the oxidation of free fatty acids decreases, and the excretion of triglycerides is disrupted. Excessive synthesis of proinflammatory cytokines occurs in adipose tissue, which ultimately leads to damage to liver cells, the development of inflammation, apoptosis and fibrosis [4-6]. Patients with NAFLD have a proatherogenic serum lipid profile, impaired glucose regulation, which is an important factor in the development and progression of type 2 diabetes mellitus, atherosclerosis and cardiovascular pathology [7-9]. One of the main features of risk factors is the synergy of their action, since in practice, patients usually detect 2-3 or more risk factors that potentiate each other's action [10, 11]. Early diagnosis of IR in patients with NAFLD, as well as assessment of risk factors for the progression of this disease are relevant due to the possibility of timely correction of this condition and primary prevention of cardiovascular pathology.

The purpose of the study. The purpose of this study was to assess the risk factors for non-alcoholic fatty liver disease.

Material and methods of research. 1985 patients aged 20-65 years (1103 men and 882 women) were examined. We conducted a questionnaire using standardized medical questionnaires, including questions about health status, heredity, risk factors, including smoking, alcohol intake, physical activity, eating disorders. When assessing smoking, the criteria of the American BRFSS system (the Behavioral Risk Factor Surveillance System) were used, according to which all surveyed were divided into three categories: smokers; those who have given up smoking; never smoked. According to the criteria of physical activity (FA) according to the IPAQ questionnaire (International Physical Activity Questionnaire), all patients were divided into four categories: physically inactive, having a low FA level, having an average FA level, having a high FA level. At the same time, intense physical activity is understood as one that lasts more than 10 minutes and leads to an increase in the pulse by more than 20% (swimming, running, shaping). To clarify the amount of alcohol consumed, standardized questionnaires were used (AUDIT — Alcohol Use Disorders Identification Test, WHO 1982), the number of alcoholic units per week was calculated, the risk level of alcohol consumption was assessed in points (1-7 points — safe, 8-15 points — dangerous and 16-19 points — "harmful" level, damaging physical health and mental health). The DEBQ questionnaire (The Dutch Eating Behavior Questionnaire — The Dutch questionnaire of eating Behavior) was proposed for the assessment of eating behavior (PP). When analyzing the questionnaires, different types of PP violations were identified: restrictive, emotionogenic, and external types.

Anthropometric methods included height, body weight, waist circumference (OT), and calculation of body mass index (BMI). The criterion of abdominal obesity was a waist size of more than 94 cm in men and more than 80 cm in women (IDF, 2005). According to the BMI value, the nutritional status was assessed according to WHO criteria (1997).

The study of laboratory parameters was carried out on an empty stomach after an eight-hour period of hunger in the period from 08 to 10

hours. The study of venous blood serum was carried out on an autoanalyzer "Konelab-J20" (Finland) with sets of reagents "ThermoSlinical Labsystems". Blood lipid and carbohydrate spectrum parameters were determined: total cholesterol (OH), high-density lipoprotein cholesterol (HDL XC), low-density lipoprotein cholesterol (LDL XC), triglycerides (TG), glucose and glycosylated hemoglobin levels. The study of immunoreactive insulin (IRI) on an empty stomach was carried out by an enzyme immunoassay on an autoanalyzer "Immulite one, DPC" (USA). The laboratory panel for assessing the functional state of the liver included generally accepted indicators, such as the level of total bilirubin and its fractions, indicator enzymes of cytolytic syndrome — alanine and aspartic aminotransferase (ALT and AST, respectively), biochemical markers of cholestasis — alkaline phosphatase (ALP) and gamma-glutamyltranspeptidase (GGTP).

According to WHO recommendations, in clinical practice, it is proposed to use the upper quartile of the distribution of the HOMA-IR index in the general population to assess the presence of IR. Thus, the threshold value of insulin resistance expressed in HOMA-IR is defined as the 75th percentile of its cumulative population distribution. In our study, the threshold value of HOMA-IR was 2.6 points. IR was assumed with a HOMA-IR value greater than 2.6 points, a HOMA-IR value less than or equal to 2.6 points was assumed in insulin-sensitive (ICH) subjects.

Results and discussion. During liver ultrasound, signs of fatty hepatosis were detected in 526 out of 1985 people, which was 26.5% of the total group of patients initially included in the study. The diagnosis of NAFLD was established as an exclusion diagnosis in the absence of other etiological factors of liver damage in patients. The criteria for exclusion from the study were the following liver diseases and conditions: viral hepatitis and cirrhosis, alcoholic and toxic (including medicinal) liver damage, autoimmune liver diseases, accumulation diseases, congenital metabolic diseases. According to the exclusion criteria, 32 patients were not included in the further study: 21 patients with laboratory markers of viral hepatitis (antibodies to hepatitis C virus were detected in 19 patients, 2 people — HBsAd), 7 patients were excluded because they had been using various herbal preparations and biologically active dietary supplements for a long time, 4 patients had cross-autoimmune liver lesions (in particular, in combination with autoimmune thyroiditis), 2 people were diagnosed with hereditary iron metabolism disorders (primary hemachromatosis, subsequently confirmed by genetic research). As a result, ultrasound signs of fatty hepatosis, regarded as a manifestation of NAFLD, were detected in 494 patients, which amounted to 24.9% of patients in the general group.

We have divided the synergistic factors of NAFLD formation into factors pathogenetically related to the development of NAFLD (insulin resistance and abdominal obesity), and lifestyle factors (eating behavior, physical activity, smoking), which also affect the occurrence and progression of hepatosis.

Insulin resistance. When comparing the prevalence of NAFLD and IR in the study group, it was revealed that out of 615 patients with NOMA-IR > 2.6, 325 patients were diagnosed with ultrasound signs of NAFLD, which was 52.8%, the remaining 290 patients with IR had intact liver. On the other hand, out of 474 patients with NAFLD, the same 325 patients (65.8%) were insulin resistant.

Abdominal obesity. Abdominal obesity (AO) in our study was assessed by OT, and we also assessed obesity by BMI in patients with NAFLD (494 patients: 324 men and 170 women) and in patients without NAFLD (1491 patients: 766 men and 725 women).

The mean values of OT in patients with NAFLD were higher than the threshold level in men and women, significantly differing from the comparison group: in men 95.8 ± 5.22 cm vs. 92.2 ± 5.96 cm, $p < 0.05$, in women 85.2 ± 4.32 cm vs. 75.3 ± 7.19 cm, $p < 0.001$, respectively, in patients with NAFLD and without NAFLD.

The mean BMI values were also significantly higher ($p < 0.05$) in patients with NAFLD. At the same time, within the groups, women's BMI values were higher than men's without significant differences. Abdominal obesity (FROM ≥ 94 cm in men and FROM ≥ 80 cm in

women) in general in the group was detected in 47.3% (939/1985) of patients. At the same time, AO was diagnosed significantly more often ($p < 0.0001$) in patients with NAFLD — in 78.5% (388/494) cases than in patients without NAFLD — in 36.9% (551/1491) cases. In the group of patients with NAFLD, obesity according to OT was detected in 69.1% (224/324) of men and 96.5% (164/170) of women.

The distribution of patients by BMI is presented in Table. 3. Overweight patients were more often detected in both groups: significantly more often ($p < 0.0001$) among patients with NAFLD — in 76.1% (376/494) cases than among patients without NAFLD — in 59.3% (884/1491) cases.

Among patients with NAFLD, I degree obesity was detected significantly more often ($p < 0.0001$) — in 16.2% (80/494) of patients: 27 men and 53 women. 7.7% (38/494) of patients with NAFLD had normal body weight. Among patients without NAFLD, obesity and confluence of circumstances were detected only in women in 2.4% (36/1491) and in 0.7% (10/1491) of men. Antlers with the expansion of the II and III stages were not included in the study. Thus, abdominal obesity according to OT was detected in 78.5% of patients with NAFLD, according to BMI — only in 16.2% of patients with NAFLD, significantly differing from patients without NAFLD. In the study group, when analyzing the responses, 56.8% of the surveyed (1127/1985) had various types of eating disorders (NPP): 489 men and 638 women. In the group with NAFLD, there were significantly more such patients ($p < 0,0001$) — 74,7% (369/494): 172 men and 197 women; in the group without NAFLD — 50.8% (758/1491). In both groups, the emotionogenic type of eating behavior prevailed, more pronounced in patients with NAFLD (41.5% vs. 20.7%). It was noted that in both groups, restrictive and emotionogenic types of NPP were most common in women, and the external type of NPP prevailed in men.

Physical activity. When analyzing the results of the physical activity assessment survey in our study, there were more physically inactive persons and those with low FA in the group with NAFLD than among patients without NAFLD: 7.1% and 22.5% versus 4.9% and 19.0%, respectively. In addition, among patients with NAFLD, a high level of FA was noted less frequently than in the comparison group (26.3% vs. 45.1%, respectively).

We regarded physically inactive and low—level patients as patients with low FA: in the group without NAFLD, such patients were 23.9% (357/1491) — 197 men and 160 women, in the group of patients with NAFLD - 29.6% (146/494) — 63 men and 83 women.

Smoking. Among all the patients included in the analysis, 22.6% (449/1985) were smokers (322 men and 127 women). There were almost 2 times more men smoking than women: 29.5% (322/1090 people) versus 14.2% (127/895 people). Among patients with NAFLD, 26.9% (133/494) were smokers: 85 men and 48 women. In the group of patients without NAFLD, 21.2% (316/1491) were smokers: 237 men and 79 women.

To assess the significance and reliability of the influence of synergetic factors on the risk of developing NAFLD, the method of calculating the odds ratio (OR) and their 95% confidence intervals (CI) was used.

As can be seen from Table 6, patients with IR have the highest chances of developing NAFLD, i.e. patients with IR are 8.07 times more likely to develop NAFLD than patients in the control group. Obese patients also have a high chance of developing NAFLD. In patients with AO calculated by OT, the chance of developing NAFLD increases by 6.24 times, and with obesity by BMI by 5.93 times. Among lifestyle factors, patients with eating disorders have significantly higher chances of developing fatty hepatosis — by 2.85 times compared to the control group. Other synergistic factors were significantly less. In our study, it was shown that by design we did not include powerlifters with the expansion of the II and III stages (according to IIMT).

Conclusions. In our study, the prevalence of NAFLD in the study group was 24.9%. At the same time, insulin resistance was detected in 65.8% of patients with NAFLD. Abdominal obesity in waist circumference was detected in

78.5% of patients with NAFLD, and in BMI only in 16.2% of patients with NAFLD, significantly differing from patients without NAFLD. Among lifestyle factors in assessing eating behavior among patients, the emotionogenic type of disorder prevailed, more pronounced in patients with NAFLD (41.5% vs. 20.7%). In addition, in our study, in the group with NAFLD, physically inactive individuals and those with a low FA level were significantly more than among patients without NAFLD. There were more smoking patients among patients with NAFLD than in the control group, but without a significant difference between the groups.

When analyzing risk factors, patients with IR have the highest chances of developing NAFLD, in whom the formation of fatty hepatosis is observed almost 8 times more often than in the control group. Patients with AO also have a high chance of developing NAFLD, such patients have a more than 6-fold increased risk of developing fatty liver infiltration.

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