NOVATEUR PUBLICATIONS
JournalNX- A Multidisciplinary Peer Reviewed Journal
ISSN No: 2581 - 4230
VOLUME 6, ISSUE 12, Dec. -2020

NON-ALCOHOLIC FATTY LIVER DISEASE: MODERN VIEW OF THE PROBLEM

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ABSTRACT:
Non-alcoholic fatty liver disease (NAFLD) - common chronic liver disease, characterized by pathological accumulation of fat droplets, not associated with alcohol. NAFLD is often a component of other diseases such as metabolic syndrome, diabetes, obesity, and contributes to the prevalence of among the population. In the early stages of NAFLD, specific treatment is ineffective and the disease progresses due to nonspecific clinical signs.
Keywords: non-alcoholic fatty liver disease, cirrhosis, lipids, obesity.

INTRODUCTION:

The urgency of the problem. Non-alcoholic fatty liver disease (NAFLD) is one of the most common forms of damage to the hepatobiliary system in the world in 21th century. According to facts of the literatures spreading of NAFLD is 20-40% [1, 8, 13, 19, 28, 29]. NAFLD (fatty dystrophy of the liver, fatty liver fatty infiltration) – is first disease of liver or syndrome, that is formed as a result of accumulation of excess fat in the liver, not less 5-10% from weight of organ, or hepatocytes must has lipids more 5 %. Mostly the NAFLD was detected in the following age groups: 50-59 age (31.1%), 40-49 age (23.6%), 60-69 age (18.1%). The most common risk factors in the population of NAFLD was dyslipidemia (2nd type of Fredriksen) - in 75.9% patients, arterial hypertension -69.9% and hypercholesterolemia – 68.8% [1,13].

Non-alcoholic fatty liver disease is not related to alcohol consumption, a chronic disease characterized by the accumulation of fat in liver cell and that plays an important role in diseases of the gastrointestinal tract [2, 11].

Thus type of NAFLD may be, as independent disease, combined with obesity, 2nd type of diabetes mellitus and dyslipidemia, and according to a several authors, secondary functional violations of liver, for instance, with dyslipidemia, they can manifest as a NAFLD. In the early stages of the NAFLD are characterized by ineffectiveness of specific treatment and progressive progression of the disease due to the nonspecific clinical signs [2, 21, 22].

NAFLD - progressive, chronic multifactorial steatosis of liver – (accumulation of fat in the liver, fatty dystrophy of hepatocytes), steatohepatitis – formation of inflammatory infiltrate around the site of necrosis in hepatocytes, non-alcoholic fibrosis-cirrhosis: destruction of liver architectonics and the disease complicated by connective tissue growth, that has been the main focus of local and foreign hepatologists for the last 10 years [2,13,27]. When the disease is periodic in 12-40% patients after 8-13 years may convert to non-alcohol steatohepatitis, from that in 15% patients may be liver cirrhosis and liver failure.

After 10 years liver cirrhosis may convert to hepatocellular carcinoma in 7 % patients. NAFLD - the facts in last 10 years confirm growth of disease [24, 31, 33]. NAFLD is widespread in Western Europe and USA. The spreading in common population of NAFLD L is not learnt well, but some authors determined that occurs 3-58% in Italy and USA [9, 31].

The growth rate of NAFLD is problem and that will evaluate with propensity to obesity. As the level of obesity increases, the severity of the disease also increases [2, 6, 13, 15, 25]. NAFLD 3-100 % occurs with obesity. In that situation when patients are checked at ultrasound examination, fatty dystrophy of liver will found [6, 26]. The scientific researches show that, NAFLD occurs 70% with 2nd type diabetes mellitus [23, 27]. Thus, the progressive progression and prevalence of the disease is one of the current problems of clinical medicine due to the observation of the time when the working capacity of the population is preserved, close clinical signs are observed in the late stages of the disease.

There are many causes of development of the fatty steatosis of liver. Primary steatosis mostly, appears on the basis of obesity, hyperlipidemia, 2nd type diabetes mellitus [4, 10, 13]. The cause of developing secondary fatty hepatosis is consumption drugs of some groups (steroid hormones, substitution hormonal therapy, antiarrhythmic and antibacterial drugs, cytostatic, non-steroideal anti-inflammatory drugs), chronic inflammatory diseases of the gastrointestinal tract, sudden weight loss, parenteral nutrition, gestational age hypoxia, Wilson Konovolova disease, lipoproteinemia, familial liver steatosis, glycogen accumulation disease [10,12]. Based on the entry of free fatty acids (FFA) into the liver, triglycerides accumulate in the liver the beta oxidation rate of FFA in the liver mitochondria decreases, and the synthesis of fatty acids increases. As a result, the synthesis of very low-density lipoproteins is reduced, triglycerides are excreted from the liver [12].

In developing of steatosis “First impact” is – gathering of FFA in hepatocytes, decreasing of oxidation and inhibition of triglyceride elimination. Different level of inflammation and fibrinogenase are observed in response to oxidative stress molecules (aldehydes). Oxidative stress products induce the expression of matrix – linked genes. Oxidative stress associated with the immune response, fibrinogenase develops in the trigger. Stress of hepatocytes with lipids and FFA leads to the development of functional insufficiency in the mitochondria and the formation of steatosis occurs. Progressive progression of steatosis makes condition for developing steatohepatitis. Additional oxidative stress, peroxidase oxidized lipids disturb the cellular defense mechanism and inflammation and necrosis occur. NAFLD stimulates formation of free radicals from endogenous ketones, food nitrosamines, aldehydes, cytochrome P450 (CYP) 2E1. 18 CYP 2E1 ketone and fatty acids can be cytochrome mediators [10].

The inflammatory process may develop endotoxinemia in intestinal dysbacteriosis. Lipopolysaccharide, a gram-negative bacterium that enters the portal vein, activates Toll-like receptors in response to type 4 immunity and develops inflammation and fibrosis (254,273). In NAFLD, endotoxemia pro-inflammative cytokines (TNF), Interleukin-6,8 and this increase the expression of cytokine receptors [23,27].

Last studies have shown that adipose tissue, namely, visceral fats, alters endocrine content, produces adipokin-hormones, which affect lipid metabolism, as well as the function of other organs and systems [3]. Changes in the amount of adipokines increase tissue

infiltration monocytes and macrophages, pro-inflammation induct cytokines. Prolonged steatosis and local inflammation can lead to fibrosis and then may convert cancer. NAFLD over time increases the risk of cirrhosis, hepatocellular cancer, which results in liver resection and transplantation [5].

In obesity, the release of high concentrations of leptins in the blood stimulates the secretion of other neuropeptides: melanocytostimulating hormone, propiomelanocortsin, neuropeptide, corticotropin, corticotroping releasing factor. All of the above peptides cause dysfunction of the sympathetic nervous system, activate lipolysis in fat storage, accelerate the entry of FFA into the liver. FFA stimulates glycogenesis in the liver, inhibits insulin secretion, develops insulin resistance. Many patients on the visceral obesity develop on the basis of hyperleptinemia, hyperglycemia, metabolic syndrome (MS): persistent hypertension, severe IHD, obstructive apnea syndrome [7]. In the literatures emphasize that - high mortality rate and prevalence of cardiovascular disease from MS (10,32).

The development of fatty liver dystrophy occurs through exogenous and endogenous mechanisms. As a result of intestinal absorption of exogenous fatty acids, glycerin, glucose, galactose, fructose, the endogenous mechanism - increased peripheral lipolysis, decreased consumption of fatty acids from liver cells, increased fat synthesis, protein deficiency in liver cells, decreased liver enzyme activity, very low lipoprotein density increase in excretion by hepatocytes [2]. Dyslipoproteinemia (DLP) is characterized by a change in homeostatic constant, a violation of the functioning of systems. DLP can damage the liver as a target organ and cause atherosclerosis in the arteries parallel to it.

A group of researchers have noted that dyslipidemia is a disorder of the process of bile formation and secretion as a result of damage to the hepatocyte membrane. Other authors have suggested that DLP in hepatic steatosis is a “safe condition” and that the etiologic factor must be ruled out [20]. These ideas are complicated because in hepatic steatosis mitochondria, liver cell lysosomes are damaged, FFA is not consumed, cholestasis and hyperlipidemia may develop.

In NAFLD liver cell function is impaired, large amounts of cholesterol and small amounts of phospholipids and bile acids accumulate in the bile ducts, bile has lithogenic properties, and gallstone disease develops [13,20], resulting in impaired secondary metabolism [2]. NAFLD is 5 times more common in patients than in gallstone disease in the population. Gallstones were observed in 18.2% and 31.1% of patients with nonalcoholic steatosis and steatohepatitis. At the same time, cirrhosis of the liver and cholelithiasis were observed in 41.7% of patients [17].

Several authors link the formation of MS cholelithiasis in women with abdominal obesity, basal hyperinsulinemia, signs of insulin resistance, insulin response to the intake of exogenous fats. It was found that a number of factors, in the development of cholelithiasis, are associated with MS; accumulation of cholesterol in the bile, hypomotor disorders of the gallbladder, hyperinsulinemia [15]. Thus, the metabolic syndrome NAFLD and gallstone disease are clearly related to each other.

Hyperinsulinemia is the main link in the development of IR-HI-obesity-IR. Today, an increase in fat tissue reserves based on a high-calorie diet increases the stress on insulin. Lack of physical activity leads to insulin resistance in adipose tissue, hyperinsulinemia is formed as a result of decreased tissue sensitivity to insulin.

In hyperinsulinemia, primarily carbohydrate metabolism is impaired. in IR, the pancreatic compensatory HI increases to a

clear limit, then in the case of decompensation, glucose tolerance or insulin-independent type II DM (NRDTI) develops. Secondly, as a result of strong lipolysis from fat reserves, it provides energy to the tissues in the form of fatty acids, lipoproteins are formed in the liver. As the amount of glucose and insulin in the liver increases, more triglycerides are formed from glucose, and the amount of LDLP increases and the amount of HDLP decreases. An increase in the amount of insulin in the liver increases the amount of LDLP. Elimination of LDLP depends on the amount of insulin. Resistance to IR lipoprotein lipase is formed and elimination of LDLP is reduced. An increase in the formation and elimination of LDLP leads to an increase in the amount of triglycerides (LDLP) in the blood plasma. The decrease in the amount of HDLP is associated with the breakdown of LDLP, which is the cause of hyperinsulinemia. Thus, an increase in IR and insulin levels is characterized by dyslipidemia that is a decrease in the amount of HDLP in the blood plasma and an increase in the amount of LDLP. Developmental dyslipoproteinemia is atherogenic in nature. Third, IR and compensatory HI increase natrium reabsorption in the distal renal tubules and increase circulating blood volume, retain water, resulting in the formation of arterial hypertension. Also HI compensator increases the activity of the sympathetic nervous systemFourth, the fibrinolytic activity of the blood changes, as a result of HI, the amount of fat in the reserve increases, the synthesis in the fat reserve increases, plasminogen activity slows down, fibrinolysis decreases, and cell aggregation increases. The factors listed are a hallmark of metabolic syndrome and are currently characterized by changes in metabolism. In the scientific literature, insulin resistance is one of the risk factors for NAFLD [2,14,16,17].

NAFLD is asymptomatic in most patients (48-100%). The remaining patients have abdominal discomfort and blunt pain under the right rib. Patients with cardiovascular pathology, digestive, endocrine and tumor diseases, as well as other diseases of the liver are often diagnosed suddenly at the time of complaint [2,26,29].

There will be no changes in blood biochemical analysis. Sometimes urobilinogenuria, hypertriglyceremia can be detected. ALT activity can significantly exceed the norm by 1.5-2 times. Obesity, 2nd type DM, hyperlipidemia, thymol test, increased levels of alpha 2 and gamma globulin are seen [2,14].

An anamnesis of alcohol is denied at NAFLD. Transferin, often sialic acid and mitochondrial isoenzyme AST is sensitive and specific, but is rarely used [1,14,17]. Because a perfectly collected anamnesis is an important diagnostic method in general practitioners.

FibroMax is a new non-invasive method that provides accurate information about liver fibrosis,–an innovative, unparalleled method for diagnosing path morphological changes in the liver (fibrosis, steatosis, cirrhosis), proposed by the French company Bio Predictive for use all over the world. This method has been validated and validated in over 40 clinical studies. Analysis results are submitted in accordance with the generally accepted international METAVIR system.

Liver biopsy - the study of a local tissue sample in order to diagnose organ diseases - has faded into the background due to its high invasiveness and a large number of contraindications.

FibroMax is a highly effective, reliable and non-invasive (non-traumatic) method. During the study, ten biochemical parameters are determined: Apo lipoprotein A1, macroglobulin, GGT (gamma glutamyltransferase), total bilirubin, ALT

(alanine aminotransferase), AST (aspartate aminotransferase), total cholesterol, haptoglycerides, glucose and triglycerides. The age, weight, height and gender of the person must be taken into account. Mathematical processing of data is carried out using five algorithms, which makes it possible to assess the degree of pathological changes and inflammation in the liver, regardless of localization.

FibroMax calculation algorithms: FibroTest - detection of liver fibrosis (proliferation of connective tissue) with the definition of the clinical stage (F0, F1, F2, F3, F4). ActiTest - determination of the degree of viral necrotic-inflammatory activity (A0, A1, A2, A3). SteatoTest (SteatoTest) - diagnosis of steatosis (fatty degeneration of the liver) of the liver. NashTest - detection of non-alcoholic steatohepatitis. AshTest - diagnosis of alcoholic steatohepatitis.

The test results are shown in the form of five diagrams, each consisting of two bars: the first is a scale with values from 0 to 1, the second (colored) reflects the degree of the disease.

This test helps to diagnose fibrosis, cirrhosis, steatosis, alcoholic and non-alcoholic steatohepatitis based on the assessment of the amount of apolipoprotein A1, ALT, ASAT, total bilirubin, cholesterol, Gamma-HT, glucose, haptoglobin, alpha-2-macroglobulin and triglycerides in blood [13,16].

CONCLUSION:

Like fatty hepatosis, non-alcoholic steatohepatitis is an independent disease that should be kept in mind when conducting differential diagnostics in patients with a stable increase in serum ALT and AST, especially in the presence of obesity, diabetes, and hyperlipidemia. The diagnosis is confirmed by liver biopsy. FibroMax is a non-traumatic diagnostic method, a unique alternative to liver biopsy. In connection with the noted steady increase in the prevalence of obesity, MS and DM among the population, the problem of diagnosis and treatment of NAFLD will become even more urgent. Poor coverage in the medical literature leads to little awareness of doctors about the possible outcomes of this condition and presents a huge problem. The complexity of diagnosis verification, the search for reliable and highly informative markers of the disease and new non-invasive diagnostic methods make it necessary to conduct further research. This is the goal of the multicenter studies that are currently being planned.

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