

# Modern approaches to clinical and laboratory research in non-alcoholic fatty liver disease

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**Abstract:** Non-alcoholic fatty liver disease (NAFLD) is a pathological change in liver tissue due to excessive deposition of fatty droplets in hepatocytes (liver cells). This condition is also called steatosis, or fatty degeneration. With this disease, it is important to start treatment on time, otherwise an inflammatory process may begin. In this case, they talk about the development of steatohepatitis, which can later progress to fibrosis, and then to cirrhosis of the liver.

In this regard, the development of prognostic criteria for liver fibrosis in patients with NAFLD is of particular relevance for the subsequent identification of risk groups for the formation and progression of this condition and optimization of diagnostic and treatment algorithms.

**Keywords:** Non-alcoholic fatty liver disease (NAFLD), cholelithiasis (GI), hepatitis, steatohepatitis, hyperlipidaemia, fibrosis,

In recent years, neurohormonal regulatory factors have been given great importance in the pathogenesis of NAFLD [93]. In this regard, it is important to clarify and evaluate the role of hormonal regulatory links in the development of NAFLD.

The literature discusses the development of cholelithiasis (GI) in NAFLD [22]. Thus, in non-alcoholic steatosis and steatohepatitis, kidney stones were diagnosed in 18.2 and 31.1% of patients, respectively [163]. Steatosis is currently a secondary condition in relation to insulin resistance, obesity, dyslipidemia, which complicates its therapy. There is no data on the effectiveness of combined therapy of ursodeoxycholic acid with statins, ursodeoxycholic acid and metformin, the drugs most commonly used in this category of patients. Basic research carried out at the stage of steatohepatitis, fibrosis or complicated course. There are few publications on the functional state of the liver and biliary tract at the stage of steatosis. NAFLD at the stage of steatosis "dissolves" among the concomitant pathology. Meanwhile, the limited possibilities of early diagnosis, the complexity of pathogenesis and issues related to the features of the clinical course NAFLD, depending on the accompanying factors, create significant difficulties in choosing the optimal complex of therapeutic measures. Therefore, only an in-depth study of the functional state hepatobiliary system and clarification of the mechanisms of NAFLD formation they will open the way to a real improvement in the results of treatment of these patients and the prevention of gallstone formation. All of the above allows us to consider it relevant and timely to further develop the problem of investigating the mechanisms of NAFLD development and improving treatment methods.

Fatty hepatitis is a disease or syndrome that occurs due to fatty degeneration of liver cells. With fatty hepatitis, intra- and (or) extracellular deposition of fat droplets occurs. The histological sign of fatty hepatitis is the content of triglycerides in the liver of more than 10% of dry weight [132]. Non-alcoholic fatty liver disease (NAFLD) is a chronic multifactorial liver disease with a tendency to progression, which can be represented as liver steatosis, steatohepatitis or liver cirrhosis. In recent years, leading domestic and foreign hepatologists reasonably pay great attention to NAFLD [60, 90, 129, 131, 187, 245, 328, 319]. With the usual course of NAFLD, non-alcoholic steatohepatitis occurs in 12-40% of patients with hepatitis after 8-13 years. Of these, 15% of patients develop cirrhosis of the liver and liver failure. Out of 7% of patients with cirrhosis of the liver DIREG study 2. NAFLD was registered in 37.3%, which is 10.3% higher than in 2007 [60, 215].

The problem of the increase in the incidence of NAFLD is associated with a significant increase in the number of obese people [78, 180]. Moreover, the severity of the disease increases with an increase in the degree of obesity [268]. In obese people, NAFLD occurs in 30-100% of cases. Ultrasound examination

reveals signs of fatty liver dystrophy in most overweight patients [26, 217]. In children and adolescents, the frequency of fatty hepatosis in obesity reaches 50% according to the results of various research that will further contribute to the growth of patients

NAFLD [119,120]. The well-known study "Dionysos" (Dionysos study, 1994) demonstrated the presence of histologically confirmed steatosis in 46% of obese patients who do not abuse alcohol, and 95% of obese patients who consume more than 60 g of pure ethanol per day. Prevalence of NAFLD among patients with diabetes mellitus (DM) of the 2nd type reaches 70% [178, 315, 329]. According to the International Federation of Diabetes Mellitus, the incidence of type 2 diabetes will increase with 366 million to 552 million by 2030 [277]. The presence of type 2 diabetes mellitus in patients with NAFLD is an unfavorable prognostic criterion for the development of fibrosis, liver cirrhosis and hepatocellular carcinoma [214, 218, 220, 224, 265, 269, 309]. Thus, the high prevalence, the tendency to an increase in morbidity, the progression of the disease, the coverage of the most able-bodied part of the population, the severity of clinical manifestations only at late stages allows us to classify NAFLD as socially significant, certainly makes NAFLD one of the urgent problems of clinical medicine, hepatocellular carcinoma develops within 10 years [207, 261, 310, 322, 327, 332]. Studies in a number of papers indicate an increase in the prevalence of NAFLD over the last decade [207, 271, 321]. NAFLD is widespread in countries of Western Europe, USA [262]. The prevalence of NAFLD in the general population is unknown and, according to various authors who conducted a survey in Italy, the USA, ranges from 3 to 58% [125, 314, 333]. In Southeast Asian countries, the prevalence ranges from 21 to 27,3% [225, 243, 330].

There is no generally accepted treatment regimen for NAFLD. During treatment, it is necessary to assess the causal factor of development, background diseases such as hyperlipidemia, obesity, type 2 diabetes mellitus [93]. It is recommended to cancel drugs toxic to the liver, which is accompanied by normalization of liver functions [37].

Given the clear relationship between fatty hepatosis and obesity, normalization of body weight is recommended. A decrease in body weight helps to reduce the content of triglycerides and the degree of fibrosis in liver tissue [101]. A gradual decrease in body weight is desirable, since it is fast a decrease in sports or a strict diet can lead to pathological changes in the liver [213]. Currently, there are no drugs with one or another scientifically proven mechanism of influence on the exchange of liver cells and the excretion of fats from hepatocytes. However, drug treatment reduces lipid peroxidation, improves the detoxification function of hepatocytes, slows down mesenchymal inflammatory processes and the development of fibrosis [93, 187, 259]. Antioxidants used in the treatment do not lead to significant histological changes in the liver, although they affect mechanisms of lipid peroxidation [93].

According to a number of authors, the cause of liver damage is considered to be a pathological change in the membranes of liver cells and enzyme systems located on the membranes [62, 97]. The cell membrane is a regulator of the cell's relationship with the external environment [14]. The hepatic cell is bipolar, responsible for the processes of bile formation and bile excretion [97]. Phosphatidylcholine (PC) (80-90%), lecithin and phosphatidylethanolamine predominate in the membranes of liver cells [258]. Cholesterol is the main steroid of mebran. Membrane steroids are mainly represented by cholesterol. By excess cholesterol decreases the mobility of the membrane, increases the viscosity of the bilayer, slows down enzymatic processes [13, 97, 114].

"Essential" phospholipids are embedded in the membrane of hepatocytes on carrier proteins, which leads to a decrease in the level of cholesterol in the membrane [97]. In a healthy liver, endogenous phospholipids are formed in sufficient quantities for the good functioning of the membranes. In liver diseases, the process of phospholipid formation is disrupted, there is a need for essential phospholipids obtained from soybeans. This is a fraction of phosphatidylcholine (PC, lecithin), which contains a large number of 2 different polyunsaturated molecules fatty acids: oleic and linoleic [226, 240]. Mechanisms of cell membrane repair with essential phospholipids are distinguished: fillings cracks of membranes, restoration of their permeability and "fluidity", normalization of the enzyme systems, and then the cell itself. The normalization of the antigenic structure of the membranes is also noted, inflammation stops and immunocompetent cells are activated. Lipid metabolism and transport are restored [148]. Other hepatoprotectors are also widely used in the treatment of fatty hepatosis [131]. The purpose of ursodeoxycholic acid (UDCA) pathogenetically justified in NAFLD. The mechanisms of action of UDCA

are numerous. The hepatoprotective effect is realized due to the hydrophilic group, which is embedded in the bilayer of phospholipids of the hepatocyte and cholangiocyte membranes, normalizes its fluidity, which normalizes the cell structure. The litholytic effect is carried out by increasing the formation of liquid crystals with cholesterol. Hypocholesterol effect occurs due to a decrease in MMC-CoA reductase, which reduces its secretion into the bile and reabsorption in the intestine. Anticholestatic – due to the displacement of a pool of toxic reduction of the concentration of hydrophobic bile acids due to increased exocytosis in liver cells during activation of Self-dependent 1-protein kinase and increased excretion of hydrophobic bile acids into the intestine. Antioxidant – by activating glutathione-reducing enzymes, reducing the concentration of free radicals. The anti-apoptotic and antifibrotic effect is manifested in the protection of mitochondria from damage, reduction of oxidative stress, suppression of apoptosis stimulated by toxins, regulation of cell proteins responsible for apoptosis, contributing to the reverse development of fibrosis. The immunomodulatory effect is carried out by reducing the expression of class I HLA molecules on liver cells and HLA Class II on cholangiocytes, a decrease in the formation of immunoglobulins and cytokines (interleukins-1,2,4 and 6, TNF- $\alpha$ ,  $\gamma$ -interferon) [110].

Perhaps UDCA should also be considered as an important preventive agent for NAFLD: it has been proven that UDCA prevents the development of liver steatosis in the experiment [177]. UDCA affects the expression of the farnesoid X-receptor  $\alpha$  (FXRa), which, in addition to regulating the activity of the enzyme cholesterol-7- $\alpha$ -hydroxylase (CYP7A1), increases the number of nuclear peroxisome proliferator-activated  $\alpha$  receptors (PPAR $\alpha$ ), very low density lipoprotein receptors and enhances the activity of serum lipoprotein lipase blood [58, 201]. UDCA stimulates the expression of FXRa to a lesser extent than primary bile acids. It is possible that UDCA increases the concentration of primary and secondary bile acids in the intestine, stimulating their effect on FXRa. Therefore, the effect of UDCA on lipoprotein levels may be important only when used in combination with other lipid-lowering drugs [48]. According to the literature, the use of UDCA has a positive effect on biochemical parameters, leads to a decrease in the activity of ALT, AST, alkaline phosphatase,  $\gamma$ -glutamyltranspeptidase and reduction of the severity of steatosis and inflammation according to the results of biopsy [16, 331]. Patients with hyperlipidemia are indicated for observation and, possibly, specific lipid-lowering therapy.

## Findings

The course of non-alcoholic fatty liver disease at the stage of steatosis is subclinical, and the clinical picture of non-alcoholic fatty liver disease is due to concomitant diseases of the gastrointestinal tract and components of the syndrome insulin resistance with corresponding metabolic changes: obesity in 100% of cases, diseases of the cardiovascular system - in 43.2%, impaired tolerance to carbohydrates – in 22%, dyslipidemia – in 20% were found in patients.

In patients with non-alcoholic fatty liver disease, according to the results of instrumental studies – dynamic hepatobiliscintigraphy, the absorption capacity of hepatocytes with impaired passage from the liver parenchyma into the ducts decreases with an increase in the concentration-depositing function of the gallbladder and a slowdown in its motor-evacuation function. In patients with non-alcoholic fatty liver disease at the stage of steatosis, significant associations of absorption and excretory liver function were established according to dynamic hepatobiliscintigraphy and values of metabolic (cholesterol, triglycerides, low-density lipoproteins, atherogenicity coefficient, total protein, body mass index, age of patients) and hormonal (cortisol, insulin, thyroid-stimulating hormone and thyroxine) indicators. The interrelation of the motor-evacuation function of the gallbladder was determined according to the data of dynamic hepatobiliscintigraphy and metabolic (cholesterol, low-density lipoproteins, atherogenicity coefficient, age) and hormonal (cortisol, insulin, thyroid-stimulating hormone, gastrin) indicators.

The effectiveness of combined therapy of ursodeoxycholic acid with statins and ursodeoxycholic acid with metformin has shown safety for the functional state of the liver and improvement of biochemical parameters of bile. Combination of ursodeoxycholic acid and atorvastatin leads to a significant decrease in atherogenic dyslipidemia, which is accompanied by a decrease in the lithogenic properties of bile. The use of a combination of ursodeoxycholic acid and metformin can significantly reduce the level of glycemia. The use of the constructed prognostic model of the probability of the formation of non-alcoholic steatosis by body mass index and atherogenicity coefficient makes it possible to diagnose the early stage of non-alcoholic fatty

liver disease. Using a calculated prognostic model of the probability of liver fibrosis development in non-alcoholic fatty liver disease by the level of insulin and triglycerides allows you to determine the risk of progression of steatosis.

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