



# Intrahepatic Cholestasis in Non-Alcoholic Fatty Liver Disease: Pathogenesis and Role of Ademetionine in Treatment

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**Aim:** to evaluate features of intrahepatic cholestasis (IHC) pathogenesis in non-alcoholic fatty liver disease (NAFLD), as well as role of ademetionine in treatment of this condition.

**Key statements.** NAFLD is the most frequent chronic diffuse liver disease. Increase in proportion of people with excess weight, obesity, and metabolic dysregulation leads to higher rates of NAFLD. Concomitant IHC is present in 30 % of NAFLD patients, while it is associated with more active disease course and possible worsening of prognosis. Impairment of adipocyte and hepatocyte metabolism, gut dysbiosis, and inherent factors are recognized as significant factors for NAFLD development. In NAFLD patients most of IHC cases are related to functional cholestasis. IHC in NAFLD is associated with increased risks of fibrosis and all-cause death. Ademetionine may restore transmethylation and improve rheologic properties of hepatocyte membranes in liver disease. In IHC patients treatment with ademetionine led to decreased serum bilirubin concentrations, as well as lowering of the liver transaminases' and alkaline phosphatase activities. At the same time improvement of symptoms severity, including itching, was noted. Taking into account the efficacy of ademetionine in IHC in NAFLD patients, its' use was included in the national clinical guidelines.

**Conclusion.** Use of ademetionine in NAFLD with concomitant IHC is feasible from pathogenesis perspective and may be effective in clinical practice.

**Keywords:** non-alcoholic fatty liver disease, intrahepatic cholestasis, S-adenosylmethionine

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## Внутрипеченочный холестаз при неалкогольной жировой болезни печени: патогенез и роль адеметионина в терапии

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**Цель исследования:** рассмотреть особенности патогенеза внутрипеченочного холестаза (ВПХ) при неалкогольной жировой болезни печени (НАЖБП), а также место адеметионина в терапии данного состояния.

**Основные положения.** НАЖБП — самое частое хроническое диффузное заболевание печени с неуклонной тенденцией к росту в связи с увеличением числа людей с избыточной массой тела, ожирением и метаболической дисрегуляцией. В 30 % случаев у больных НАЖБП выявляют сопутствующий внутрипеченочный холестаз (ВПХ), который ассоциирован с более активным течением болезни и возможным ухудшением прогноза этих пациентов. Существенную роль в развитии НАЖБП в настоящее время отводят нарушению метаболизма в жировой ткани и гепатоцитах, дисбиозу кишечника и наследственным факторам. У пациентов с НАЖБП большинство случаев ВПХ связано с функциональным холестазом. ВПХ при НАЖБП ассоциирован с повышением риска фиброза печени и смерти от всех причин. Адеметионин при заболеваниях печени способен восстанавливать активность процессов трансметилирования, а также улучшать реологические свойства мембран гепатоцитов. Терапия адеметионином у пациентов с ВПХ была ассоциирована с уменьшением концентрации билирубина в сыворотке, а также активности печеночных трансаминаз и щелочной фосфатазы, на этом фоне отмечали снижение выраженности клинических признаков, включая кожный зуд. Учитывая клиническую эффективность адеметионина при ВПХ на фоне НАЖБП, применение препарата включено в национальные клинические рекомендации.

**Заключение.** Применение адеметионина у пациентов с НАЖБП и сопутствующим ВПХ патогенетически обосновано и может быть эффективным в клинической практике.

**Ключевые слова:** функциональная диспепсия, дуоденальная эозинофилия, гистамин, S-метилметион-инсульфония хлорид

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## Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic disease closely associated with metabolic syndrome (obesity, type 2 diabetes mellitus, dyslipidemia and hypertension) in the absence of other reasons for liver injury. NAFLD is attributed to lipids accumulation in liver parenchymal cells and can be manifested as steatosis, steatohepatitis with or without fibrosis, cirrhosis [1]. In cases of NAFLD, even in the absence of liver cirrhosis, especially in case of obesity and type 2 diabetes mellitus, hepatocellular carcinoma may develop.

NAFLD is the most common chronic liver diseases and the scale of the problem is increasing worldwide. For instance, in the population-based study performed in the USA the prevalence of NAFLD accounted for 30 % to 32 % [2]. In the Asia-Pacific region, the prevalence varies from 5 % to 30 % depending on the population [3].

In Russia, according to study DIREG2 conducted in 2014, 37.3 % of patients in general population suffered from NAFLD [4], and this value increased by more than 10 % from 2007 [5]. NAFLD is typical for patients aged over 40–50 [4].

Significant growth of NAFLD prevalence was reported in the last 20 years, herewith the disease remains the most common liver disorder; at the same time, the proportion of patients with other metabolic syndrome component also increases, namely: obesity, type 2 diabetes mellitus and insulin resistance [6].

NAFLD can have significant impact on clinical outcomes in patients: in case of NASH, the incidence of progressing to liver cirrhosis is up to 20 % [7]. In patients with NAFLD, secondary intrahepatic cholestasis (IHC) associated with more active disease and possible worsening of prognosis is found in 30 % of cases [8].

This article covers the specific features of pathogenesis and management of IHC in patients with NAFLD, and the place of adimetiонine in treating this condition at the present stage.

## Pathogenesis of intrahepatic cholestasis in NAFLD NAFLD pathogenesis

It was previously considered that early forms of NAFLD, i.e. isolated steatosis and NASH can

be separate conditions possibly resulting in common consequences. Nowadays, views on NAFLD have undergone a significant transformation. Modern theories offer to consider pathophysiological aspects of the disease from the point of view of “steatosis-NASH-cirrhosis” continuum, thus most patients must have previous steatosis for NASH development [9].

### *Fatty tissue dysfunction*

A number of endogenous and exogenous factors presented in Figure [10–12] play a leading role in steatosis development. Fatty tissue dysfunction appears long before the first signs of liver steatosis, most commonly as a result of increased fatty acids intake and overweight/obesity development [13]. In case of obesity free fatty acids (FFA) not digested by the fatty tissue are delivered to the liver, moreover in case of adipocyte dysfunction lipolysis can be increased significantly [14].

Increased circulating FFA concentrations due to competition with carbohydrates for metabolic niches results in enhancement of insulin resistance [15].

On the other hand, fatty tissue dysfunction is manifested by impaired adipokine homeostasis. In particular, increased fatty tissue weight produces more chemokines and cytokines that are able to potentiate insulin resistance, namely: monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin (IL) -6 and -8 [16].

### *Metabolism of hepatocytes*

Increased FFA circulating levels result in their enhanced uptake by hepatocytes [17]. Herewith, hepatic impairment with altered metabolic regulation including hepatic insulin resistance and a number of hereditary factors results in marked stimulation of *de novo* synthesis of triglycerides which can be potentiated 5-fold in patients with NAFLD [18].

The influence of increased fructose consumption is important to note in the context of the role of insulin resistance in NAFLD pathogenesis. Apart from enhancing insulin resistance of hepatocytes [18], fructose increases the expression of enzymes participating in *de novo* lipogenesis and acts as a substrate for this process [19].

The abovementioned factors contribute to significant accumulation and enhanced synthesis of fatty acids and triglycerides in the liver which

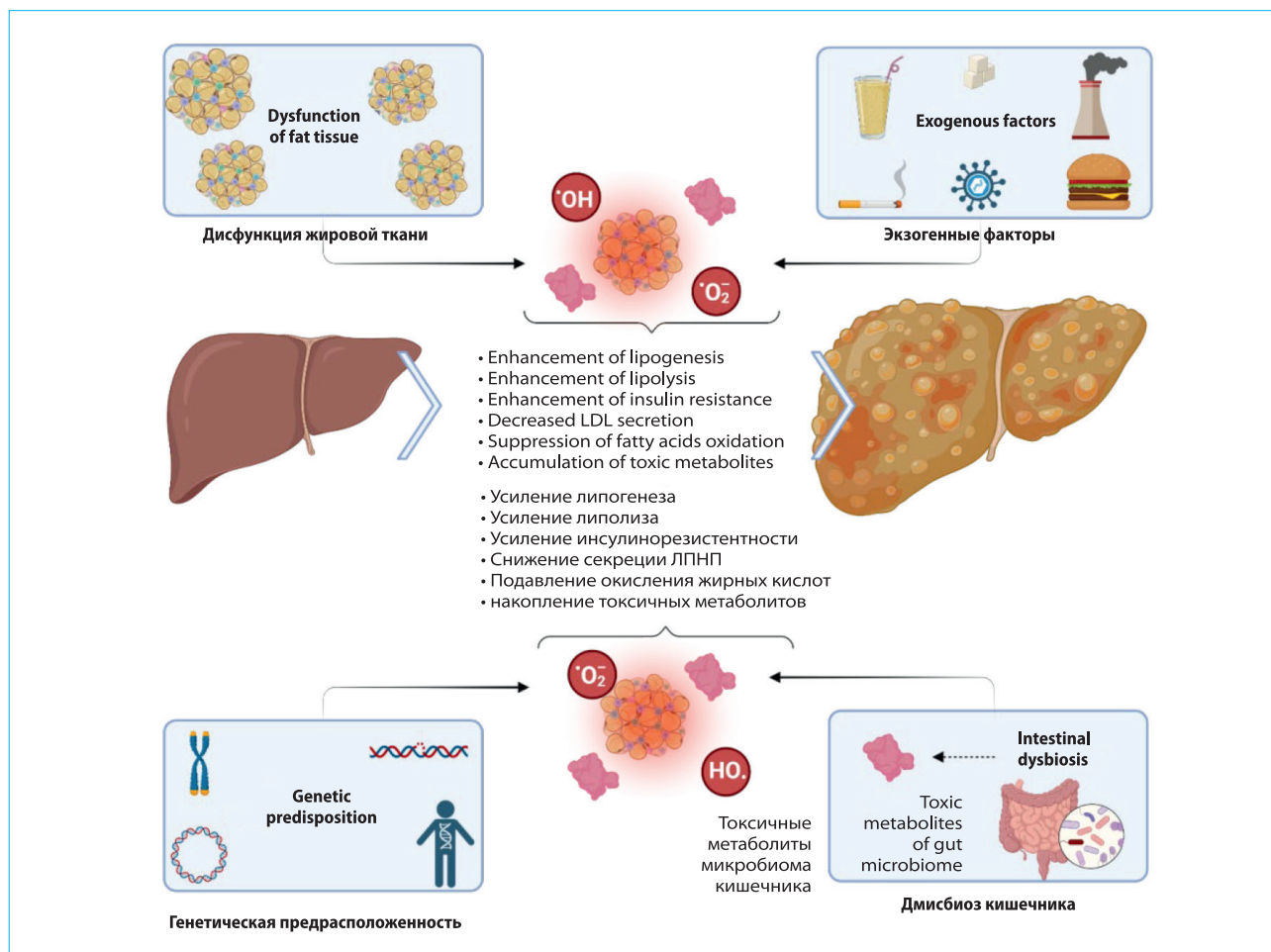


Fig. Main aspects of non-alcoholic isolated steatosis pathogenesis [10–12]

Рис. Основные аспекты патогенеза неалкогольного изолированного стеатоза [10–12]

participate in steatosis development. Under normal condition, there are two main liver elimination pathways for triglycerides: formation and secretion of low-density lipoproteins (LDL) and FFA oxidation. With high LDL concentrations in hepatocytes, membrane transporters cannot cope with the load, and thus, steatosis develops. Moreover, certain phenotypes of Kupffer cells in patients with developing steatosis cause inhibition of FFA oxidation [20].

### Gut microbiota

A number of changes in the gut microbiome is detected in patients with NAFLD. For patients with NAFLD, excessive bacterial growth in the small intestine [21] is typical, which can result in increased intestinal wall permeability [22]. A certain role in NAFLD development is assigned to waste products of gut microbiome: in mice with experimental NAFLD increased concentrations of circulating N,N,N-trimethyl-5-aminovaleric acid which inhibits FFA oxidation were detected [23].

Another microbial metabolite synthesizing bacteroides and proteobacteria — 3-(4-hydroxyphenyl) lactate can worsen liver fibrosis [24].

### Hereditary factors

According to the results of a recent study conducted using the twin method (2015), both steatosis development and liver fibrosis are directly associated with hereditary factors [25]. High NAFLD risk is associated with certain gene variants coding synthesis of proteins regulating lipid metabolism [26, 27], and regulators of signal transduction via insulin receptors [26].

### Pathogenesis of intrahepatic cholestasis in NAFLD

As it was noted above, IHC is reported in one-third of patients with NAFLD [8]. It is important to note that IHC can develop in patients with any liver diseases regardless of etiology [28]. In contrast to extrahepatic cholestasis which develops due to external block for bile outflow in case of cholelithiasis, biliary strictures, neoplasms in adjacent organs

or sclerosing cholangitis, the so-called functional cholestasis is mainly observed in patients with IHC, which is associated with impaired synthesis and/or secretion by hepatocytes or with impaired intrahepatic duct obstruction [29].

Due to the below clinical features and the impact on the prognosis for the patients, a number of authors define NAFLD with IHC as a clinical variant of the disease [30]. Herewith, increased bile acids liver concentrations were detected in patients with NAFLD without signs of cholestasis [31], which is indicative of the change of bile acids metabolism due to the impact of NAFLD pathogenesis components.

A study in patients with obesity and NAFLD showed that NAFLD activity index directly correlates with bile acids serum levels and inversely correlates with adiponectin levels. Upon that, in the study population the potentiation of activity of sodium-taurocholate cotransporter of hepatocyte basolateral membrane bile acids and cholesterol-7- $\alpha$ -hydroxylase participating in their synthesis was noted. Authors concluded that the identified changes indicate at impaired activation of small heterodimer partner via stimulation of farnesoid X receptor under the influence of high concentrations of bile acids which can be one of the reasons for IHC in patients with NAFLD [32].

Oxidative stress and increased cholesterol concentrations in hepatocytes of patients with NAFLD additionally contribute to impaired metabolism and enterohepatic circulation of bile acids in patients with NAFLD [8].

Thus, patients with non-alcoholic steatosis or NASH are predisposed to IHC development due to metabolic disorder associated with bile acids synthesis, transport and secretion by hepatocytes.

### **Peculiarities of intrahepatic cholestasis in NAFLD**

IHC can have significant impact on disease progression and prognosis of the patients with NAFLD [30]. In the presence of NAFLD and IHC vs. patients without cholestasis, statistically significant greater liver fibrosis events accompanied by portal tract involvement, increased focal necrosis incidence, intrahepatic ducts edema and proliferation were noted [33].

In patients with NAFLD, two-fold increase in liver-related causes mortality with serum bilirubin increase by every 10  $\mu\text{Mol/L}$  (relative risk [RR] = 2.14 [95 %, confidence interval (CI) 1.09 to 4.22]) was identified [34].

As a result, IHC in a patient with NAFLD indicates at more severe disease course and increased risk of unfavorable clinical outcome for the patient. Therefore, the main tasks of IHC therapy should include improvement of the disease severity and its clinical and laboratory manifestations, including restoration of bile acids synthesis and

transport from hepatocytes to the bile ducts, as well as improvement in enterohepatic circulation of bile acids. Additionally, an important goal of the therapy is elimination of toxicity of hydrophobic bile acids [28].

### **Ademetionine mechanism of action**

#### **Physiological role of S-adenosylmethionine**

S-adenosylmethionine (SAdMe) participates in biochemical reactions of three main types: transmethylation, transsulfuration and aminopropylation [35]. SAdMe is the main methyl-group donor in methylation reactions of histones, phospholipids, nucleic acids, amines and proteins. The main transmethylation reactions in the liver are due to glycine-N-methyltransferase resulting in formation of S-adenosylmethionine form SAdMe. Herewith, S-adenosylmethionine limits transmethylation reactions rate, thus hydrolases function and S-adenosylmethionine remethylation reactions involving methyl adenosyl transferase I and III are highly important to ensure physiological functioning of the cell [36].

#### **S-adenosylmethionine in liver diseases**

Significant decrease of SAdMe depo in the liver of patients with liver diseases was demonstrated over 70 years ago [37]. Suppression of methyl adenosyl transferase genes expression is observed in patients with cirrhosis irrespectively of its etiology. Plus, exogenous and endogenous factors which stimulate oxidative stress in hepatocytes inhibit methyl adenosyl transferases [38,39]. In transgenic methyl adenosyl transferase knockout mice, among other liver disorders, steatohepatitis development was observed by the age of 8 months [40].

It is also important to highlight the role of SAdMe in the glutathione metabolism as the main oxidation-reduction system in the hepatocytes. SAdMe metabolite homocysteine is one of the main sources of cysteine needed for reduced glutathione synthesis [39]. Simultaneously, in patients with NAFLD administered with SAdMe increased glutathione levels in the liver were reported [41], while the oxidative stress and glutathione reserves are considered to be one of the most important components of cholestasis pathogenesis [42].

SAdMe can influence hepatocytes apoptosis. Non-clinical studies demonstrated that SAdMe presence in the culture medium can prevent hepatocytes apoptosis *in vitro* due to exogenous stimuli [43, 44].

The role of SAdMe metabolism disorder in IHC is worth noting. One of hepatocytes abnormalities during IHC development is attributed to decreased cellular membrane flow at which delayed bile acids secretion from the cells is observed [45–47]. SAdMe participates in supporting physiological

cellular membrane flow due to inclusion of phospholipids methylation in this process, while decrease in SMAe depo results in decreased activity of membrane transporter of bile acids [48, 49].

In this regard, SAME and its metabolism disorder play an important role in liver diseases, including development of steatohepatitis and intrahepatic cholestasis due to decreased molecule participation in methylation reactions, including membrane phospholipids methylation, inhibition of glutathione synthesis and the absence of impact on hepatocytes apoptosis in case of SAME resource depletion. The above data allow to conclude that restoration of SAME reserves and metabolism is one of the therapeutic targets for patients with NAFLD accompanied by IHC.

### Ademetionine clinical performance

One of the first SAME efficacy studies in patients with IHC was performed by Frezza et al. (1990). The study included 220 patients with confirmed chronic non-infectious liver disease accompanied by the signs of IHC: not less than two-fold increase in serum alkaline phosphatase (AP) activity and total and conjugated bilirubin levels. Patients with viral hepatitis or alcohol-induced hepatitis, as well as with drug-induced liver injury were not included in the study. Following the randomization, the patients received SAME at the dose of 1600 mg/day or placebo for 2 weeks [50].

2 weeks after the SAME therapy, significant decrease in total bilirubin levels was observed: the value decreased by more than two-fold, from  $76.7 \pm 4.6$  to  $37.6 \pm 3.7$   $\mu\text{Mol/L}$ , while in placebo group the value changed from  $77.2 \pm 4.7$  to  $57.9 \pm 5.6$   $\mu\text{Mol/L}$  ( $p < 0.01$  for intergroup comparison). Moreover, by the end of Week 2 decrease in serum AP and alanine aminotransferase (ALT) levels was noted vs. values in the placebo group ( $p < 0.05$  in both cases). Baseline itching scores according to 10 cm Visual Analog Scale (VAS) accounted for  $5.3 \pm 0.3$  and  $5.3 \pm 0.2$  cm in patients from SAME and placebo groups, respectively. By the end of therapy, the values decreased to  $2.7 \pm 0.2$  and  $4.1 \pm 0.2$  cm, respectively ( $p < 0.05$ ). Similar changes were noted for weakness severity ( $p < 0.05$  for intergroup comparison). Thus, in case of IHC with chronic non-infectious non-toxic liver disease, SAME administration was associated with decrease in total bilirubin levels, AP and ALT activity, as well as with improvement of weakness and itching [50]. Later on, the same group of authors noted in the publication by Manzillo et al. (1992) that intravenous administration of SAME at the dose of 800 mg/day for 2 weeks in patients with IHC and chronic liver disease was associated with significantly higher response rate compared

to placebo therapy [51]. Podymova et al. (1998) obtained similar results for intravenous therapy with SMAe at the dose of 800 mg/day IV for the first 16 days, then at the dose of 1600 mg/day orally for another 16 days in patients with chronic diffuse liver diseases [52].

Early meta-analysis of placebo-controlled studies of SAME in patients with IHC and chronic liver diseases performed by Frezza et al. (1993) established that the use of the drug product for 15 to 30 days was more effective than placebo in terms of itching relief, normalization or two-fold decrease of baseline bilirubin, ALT, AP and  $\gamma$ -glutamyltransferase ( $\gamma$ -GT) levels [53].

Virukalpattigopalratnam et al. (2013) studied the efficacy of using ademetionine originator product for treating NAFLD with concomitant IHC ( $n = 250$ ) in routine clinical practice in India. When using ademetionine, improvement in biochemical abnormalities and IHC signs were noted in patients based on the blood tests. With clinical and laboratory improvement, significant decrease in the number of business days spent on the sick leave and the number of visits to doctors were noted [54].

N.V. Kharchenko (2013) conducted a post-market observational study of efficacy of using ademetionine originator product in treating IHC with chronic liver diseases ( $n = 447$ ). Pregnant patients with IHC and patients administered with hepatoprotectors before ademetionine prescription did not participate in the study. Severity of clinical symptoms and laboratory parameters were assessed 2 weeks and 2 months after the treatment initiation. By the end of the study, icterus of skin or mucosa resolved in 67 % of patients ( $n/N = 205/306$ ), itching resolved in 71.4 % of patients ( $n/N = 187/262$ ), fatigue resolved in 42.4 % of patients ( $n/N = 154/363$ ) [55].

After 2 months of therapy, total bilirubin level normalized in half of the patients, normalized ALT, aspartate aminotransferase (AST) and AP serum activity were noted in about 40 % of patients [55]. Stel'makh et al. (2021) obtained similar results when using ademetionine originator drug product in a group of patients with different liver diseases and concomitant IHC [56].

### Discussion

IHC is a serious complication of NAFLD associated with more severe course of the disease, accelerated fibrosis development increased mortality risk. A number of non-clinical and clinical studies demonstrated that in case of IHC SAME metabolism disorder in the hepatocytes resulting in abnormal methylation processes is observed, including

membrane phospholipids methylation, hepatocytes tendency towards apoptosis is increased and negative impact on the glutathione oxidation-reduction system is reported. This makes restoration of SAME metabolism and improvement in oxidative severity via glutathione metabolism improvement one of clinical targets of conducting therapy in patients with IHC accompanying NAFLD.

A number of controlled clinical studies and routine clinical practice studies were performed, in which efficacy of using oral and parenteral ademetonine medicinal products was studied. When receiving short-term therapy lasting up to 2 months, decreased severity or complete relief of such IHC symptoms as icterus, fatigue and itching were reported.

At the same time, hepatic transaminases, AP,  $\gamma$ -GT serum activity and total bilirubin concentrations decreased.

Positive impact of ademetonine both on symptoms severity and laboratory abnormalities intensity in patients with IHC accompanying

NAFLD allowed to include ademetonine in the recommendations of the Russian Scientific Liver Society, Russian Gastroenterological Association, Russian Association of Endocrinologists, Russian Association of Gerontologists and Geriatricians and National Society for Preventive Cardiology (2022) as the drug recommended for cholestasis correction [1].

## Conclusion

The use of ademetonine in patients with NAFLD and concomitant IHC is pathogenetically substantiated due to SAME reserves depletion in case of IHC. In clinical practice, ademetonine use results in decreased severity of cholestasis symptoms and improvement of laboratory parameters of liver cholestasis and cytolysis. In summary, ademetonine is an effective medicinal product for treating IHC in patients with NAFLD and can be recommended for inclusion in complex therapy for this condition.

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