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CONTEMPORARY VIEW ON DIAGNOSIS AND TREATMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE

Summary

The paper summarizes the data about the features of diagnosis and management of non-alcoholic fatty liver disease (NAFLD). It is characterized by a chronic and progressive liver pathology that may progress to cirrhosis, end-stage liver disease, hepatocellular carcinoma, and be the cause of liver transplantation. The diagnosis of NAFLD can be made through imaging studies or liver biopsy with histologic confirmation. Although there are several non-invasive methods and biomarkers of advanced fibrosis. Measures aimed at promoting weight loss, healthy lifestyle and correction of metabolic risk factors remain the cornerstone of management of NAFLD. The paper represents results of study of efficiency of antioxidants, pioglitazon, pentoxifillin, ursodeoxycholic acid, bariatric surgery and liver transplantation in treatment of patients with NAFLD.

Keywords

Non-alcoholic fatty liver disease, steatosis, non-alcoholic steatohepatitis, non-invasive biomarkers of liver fibrosis.

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are the most common chronic liver diseases in the world [4, 17]. They are closely associated with obesity, type 2 diabetes mellitus, and metabolic syndrome (MetS). The epidemics of diabetes and obesity have also fueled an increasing prevalence of fatty liver disease [7, 28].

NAFLD is the most common cause of abnormal liver function test results in both adults and children [1, 2]. NAFLD in fact covers a histological spectrum ranging from simple steatosis to NASH, advanced fibrosis, and cirrhosis [1]. Simple steatosis without fibrosis or inflammation has a benign clinical course in most but not in all cases without excess mortality [4]. NASH, on the other hand, may have a more progressive course that can lead to cirrhosis in 10-15% of patients [7]. Survival is lower in patients with NASH based on the findings from long-term longitudinal studies [4, 23]. It is therefore imperative to distinguish simple steatosis from NASH in order to provide risk stratification and intervention slowing down disease progression for patients with the latter condition. Both NAFLD and NASH are associated with an often asymptomatic elevation of serum alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase. Ultrasound monitoring can suggest the presence of a fatty infiltration of the liver; differentiation between NAFLD and NASH, however, often requires a liver biopsy. Such differentiation is important because NASH is associated with a much higher risk of liver fibrosis and cirrhosis than NAFLD.

NAFLD is present in 20-40% of the general population in industrialized countries and is the most prevalent chronic liver disease [20]. It is more prevalent in obese and diabetic subjects. Among all subjects with NAFLD, features of NASH can be seen in 10-20%. The prevalence of NASH in western countries is approximately 2-6%. In the US, NASH is estimated to affect 5-6% of the general population [19, 20]. It has been suggested that NASH accounts for more than 50% of cryptogenic cirrhosis. NAFLD may progress to NASH with fibrosis, cirrhosis, and hepatocellular carcinoma. The term NASH was introduced in a description of 20 Mayo Clinic patients with a hitherto unnamed disease associated with hepatomegaly, abnormal ALT, a fatty liver histology, lobular hepatitis, and fibrosis mimicking alcoholic hepatitis in the absence of alcohol intake; most patients had obesity and diabetes mellitus. In the US, NAFLD is 3-5 times more prevalent in men than in women; such differences in gender might partly be explained by the fact that men have a higher body mass index (BMI) and that some male patients with NAFLD drink more alcohol than they report [3, 23]. The NAFLD prevalence in the US is particularly high in people of Hispanic (28%) or Asian (20-30%) origin [23, 27]. Due to the dramatic increase in obesity in the US and many other industrialized countries, there is also a dramatic increase in the prevalence of NAFLD and NASH [6]. In the US almost 50% of obese boys have NAFLD [23]. In many countries more than 80% of NAFLD patients have an increased BMI and 30-40% are obese; approximately 50% show signs of insulin resistance, 20-30% – type 2 diabetes, 80% – hyperlipidemia, and 30-60% – hy-

pertension. Correspondingly there is a strong association between NAFLD and NASH and the MetS throughout the world. In comparison with NAFLD patients, NASH patients are older, more obese and more often have high serum liver enzymes, diabetes mellitus and MetS [6, 12].

The degree of fatty infiltration in NAFLD is graded according to the percentage of hepatocytes with fat deposits: mild NAFLD involves less than 30% hepatocytes, moderate NAFLD – up to 60%, and severe NAFLD – above 60%. NAFLD may regress if the cause is eliminated. NASH is associated with insulin resistance, increased circulating levels of leptin, adiponectin, tumor necrosis factor (TNF) and some interleukins (IL). It is thought that there is an increased flow of free fatty acids from visceral fat to the liver contributing to abnormalities in intracellular lipid metabolism. Insulin resistance and increased free fatty acids may both affect mitochondrial oxidation of fatty acids causing free radical generation in hepatocytes. Thus, NASH is caused by two mechanisms or toxic "hits": the first mechanism is the hepatic accumulation of triglycerides (NAFLD) due to insulin resistance and the second is thought to be the generation of free radicals with subsequent release of mediators and cytokines. Insulin resistance has been closely linked to NAFLD in both clinical trials and laboratory-based studies [19]. The actual process by which NAFLD turns into NASH however remains ill-defined despite this double-hit theory. Likely, genetic factors (similar to those responsible for the MetS) as well as exogenic factors (like drugs, moderate amounts of alcohol, and other toxins) may contribute to the evolution of NAFLD into NASH. The role of hepatic iron in the progression of NASH remains controversial, but in some patients, iron may have a role in the pathogenesis of NASH by promoting oxidative stress.

The gut microbiota, now also called the gut microbiome, is involved in the pathophysiology of NAFLD as well as in obesity and MetS. All the metabolic products generated by the intestinal microbiome first enter the liver. Studies with germ-free mice have shown that inoculation of microbiota from conventionally raised fat mice results in obesity and fatty liver [16]. Genetically obese mice have a decreased ratio of bacteroides versus firmicutes compared with lean mice. Inoculation of gut microbiota from these obese mice to germfree mice led to an obese phenotype [2]. Similar effects occur when such mice are fed a Western diet or are inoculated with microbiota from an obese human. It has also been shown recently by many investigators that the microbiome differs between obese and lean animals and between obese and lean humans. As yet it is not completely known if intestinal products are the cause or only aggravate NAFLD and NASH. A recent study proposed that the altered microbiome in obesity might produce more ethanol and might thereby contribute to the development of NASH. Another recent paper shows that inflammasome or IL-18 deficiency enhances the progression of NASH and obesity by inducing microbiome dysbiosis [13]. This dysbiosis induced inflammation enters into the portal circulation through the influx of toll-like receptor (TLR) 4 and TLR9 agonists and thereby leads to an increase in TNF. It has also been shown for the first time that the composition of the microbiome and the obese/NASH phenotype can be transmitted to wild-type mice co-housed with genetically deficient mice. This report corroborates that the gut microbiome plays an important role in the development of NASH and obesity, probably via changes in the inflammasome [13].

The natural history of NAFLD in the general population is not well-defined since most data come from selected patients and tertiary centers. Correspondingly, published mortality and morbidity in hospitalized people with NAFLD are approximately 5 times higher than what is seen in the general population. In the general population the risk for liver-related death in NAFLD appears to be associated mainly with age, insulin resistance, and histological evidence of hepatic inflammation and fibrosis [1]. Probably 10% of NAFLD patients will progress to NASH over a period of 10 years. Cirrhosis later develops in 5-25% of patients with NASH and 30-50% of these patients die from liver-related causes over a 10-year period. Cirrhosis in patients with NASH can also decompensate into subacute liver failure, progress to hepatocellular cancer (HCC), and recur after liver transplantation [20]. Steatosis alone is reported to have a more benign clinical course, with cirrhosis developing in only 1-3% of patients [7, 19]. Patients with NASH and fibrosis also have a significant risk for hepatocellular carcinoma.

NAFLD and NASH require valid reporting about alcohol consumption. Since only approximately 10% of Western populations are completely abstinent from alcohol, one needs to set a threshold above which one assumes that alcohol at least contributes to the pathogenic process of NAFLD and NASH. Most authors use a daily alcohol ingestion of 20 g as such a threshold; others use lower values such as 10 g/day or as high as 40 g/day for men. The workup of NAFLD and NASH also includes checking into drug use, HBV and HCV infections, hemochromatosis, autoimmune liver disease and, in younger patients, Wilson's disease. In special groups of patients NASH may be accompanied by drug- and alcohol-induced liver disease and by HCV and HBV infections. The combination of NAFLD/NASH and HCV infection plays a particularly important clinical role because in this situation the rate of liver fibrosis is increased and the success of antiviral therapy is diminished. NASH can be induced by various drugs and toxins including corticosteroids, amiodarone, methotrexate, tetracycline, tamoxifen, and valproate. Thus, one needs to carefully assess the full clinical history of patients. In

practice NAFLD is often diagnosed by combining elevated levels of ALT and gamma-glutamyl transpeptidase with the sonographic appearance of an increase in the echodensity of the liver. However, a considerable number of patients with NAFLD and even with NASH and fibrosis have normal serum liver enzymes. Usually ALT is higher than aspartate aminotransferase (AST) unless there is already severe fibrosis or cirrhosis. Fasting serum glucose should be checked in all patients with NAFLD and NASH; one will also often find elevated serum insulin, insulin resistance, and/or diabetes. Many authors also recommend to routinely look for MetS, which is diagnosed when three of the following features are seen:

- waist circumference ≥102 cm for men and ≥88 cm for women,
- fasting glucose level ≥6,1 mmol/L,
- triglyceridemia ≥1,7 mmol/L,
- decrease in high-density lipoprotein cholesterol (<1,3 mmol/L in women; <1,03 mmol/L in men),
- blood pressure level ≥135/80 mmHg.

Ultrasound of the liver has a high sensitivity and specificity (both approaching 90%) for detection of fatty infiltration but does not allow assessment for the presence or degree of inflammation and fibrosis. Therefore, diagnosis of fat in the liver is easily made by ultrasound but diagnosis of NAFLD or NASH cannot be made without a liver histology. In addition, liver biopsy is still the best way to reliably differentiate NASH from NAFLD. Today most pathologists use the Brunt description to score the histological degree of NASH. Since NAFLD is a very frequent but also relatively benign disease, one aims to identify risks factors for NASH in order to avoid doing liver biopsies in all NAFLD patients. Risk factors for NASH include older age, excessive obesity, diabetes mellitus, other hepatotoxins, and clinical, laboratory or sonographic signs suggesting severe liver disease. Liver biopsy remains the gold standard for characterizing liver histology in patients with NAFLD [23]. However, it is expensive and carries some morbidity and a small mortality risk. Thus, it should be performed in those patients who benefit most from diagnostic, therapeutic and prognostic perspectives. Liver biopsy should be considered in patients with NAFLD who are at high risk to have steatohepatitis and advanced fibrosis. The presence of MetS and the NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis. Liver biopsy should also be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a biopsy [23]. There has been increasing interest in non-invasive methods to identify fibrosis in patients with NAFLD [11], – these include the NAFLD Fibrosis Score, Enhanced Liver Fibrosis (ELF) panel, and transient elastography (“Fibroscan”). The NAFLD Fibrosis Score is based on six readily available variables (age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio) and it is calculated using the published formula. In a meta-analysis of 13 studies consisting of 3064 patients, NAFLD Fibrosis Score was useful for predicting advanced fibrosis or cirrhosis [11]. Although a recent meta-analysis showed that transient elastography (“Fibroscan”) has a high sensitivity and specificity for identifying fibrosis in NAFLD it has a high failure rate in individuals with a higher BMI [23]. These problems have been mostly solved with a new probe developed for obese patients. In addition, special software has been developed for estimating the degree of steatosis. The technique is still not commercially available in the US and not reimbursed in many countries.

NAFLD is considered to be the hepatic manifestation of MetS [10]. Obesity, a common feature of NAFLD and MetS, is associated with a chronic and subacute inflammatory state that is both systemic and focally localized in certain tissues such as liver. Consistent with the potential roles of inflammation, serum levels of proinflammatory cytokines are elevated in obese subjects [11]. NASH is a progressive form of NAFLD where in addition to simple steatosis, inflammation, hepatocyte ballooning, and sometimes, fibrosis are observed [12]. It is therefore of great interest to determine if NASH can be distinguished from simple steatosis by using proinflammatory biomarkers. Below we will discuss the current findings of the use of proinflammatory biomarkers for the diagnosis of NASH.

TNF-α plays an important role in insulin resistance, the pathognomonic feature of MetS, through inhibiting the tyrosine kinase activity of the insulin receptor [13]. Abiru et al. reported that patients with NASH had significantly higher serum TNF-α and its soluble receptor (sTNFR1) than those with simple steatosis, although they did not provide a cutoff value of the cytokine for clinical use [14]. A recent study further reported that patients with NASH had higher levels of TNF-α messenger ribonucleic acid (mRNA) than healthy controls. The authors proposed a TNF-α mRNA cutoff value of 100 ng/mL predicted NASH (area under receiver operating characteristic curves (AUROC): 0,685, sensitivity: 66,7%, specificity: 74,1%) [15]. The role of TNF-α in NASH is further supported by the beneficial effects of pentoxifylline, an antagonizer of TNF-α, on biochemical and histological activity associated with NASH.

IL-6 is implicated in insulin resistance, at least in part, through the induction of suppressor of cytokine signaling-3 in liver [19]. Several studies have reported a strong association between IL-6 and NASH. In a pilot study with a small cohort, patients with NASH received special diet plus exercise with or without antioxidant vitamin E (800 IU/day for 6 weeks). Plasma IL-6 levels were significantly higher in patients with NASH and the levels decreased with the therapy [20].

Not only the cytokine itself, but its soluble receptor is also significantly increased in patients with NASH than those with simple steatosis [14]. No cutoff value of the cytokine for differentiating NASH from simple steatosis was provided from either one of the studies. In the third small cohort study, morbidly obese patients were divided into 3 groups based on the histologic findings: non-NASH, probable NASH, and NASH. IL-6 level was correlated with the degree of steatosis until the patients met the criteria of NASH when their blood IL-6 levels decreased. Multivariate logistic regression analysis identified the level of IL-6 > 4,81 pg/mL (odds ratio (OR): 33,7, 95% confidence interval (CI): 1,7-680,7, $p \leq 0,022$) as an independent predictor of the degree of steatosis but not of NASH [21]. In the fourth study, NASH could be well distinguished from simple steatosis when using the cutoff value of IL-6 at 4,6 pg/mL (AUROC: 0,817, sensitivity: 58,1%, specificity: 100%). The authors concluded that IL-6 was highly specific in confirming the absence of NASH at normal values [22].

C-reactive protein (CRP) levels were elevated in NAFLD patients compared with controls matched by age and BMI and hence were reported to be an independent risk factor for NAFLD [23]. However, the study was limited by the lack of histologic diagnosis since NAFLD was diagnosed based on elevated ALT and sonographic evidence of fatty liver. It is still controversial whether CRP can differentiate NASH from simple steatosis. For example, high-sensitivity CRP (hs-CRP) levels were significantly higher in patients with NASH compared with those with steatosis in a Japanese study [24]. In addition, hs-CRP levels were significantly elevated in patients with NASH and advanced fibrosis compared with those with NASH and mild fibrosis. However, there was no relation between serum hs-CRP levels and either hepatic steatosis or necroinflammation grade. The AUROC for distinguishing between NASH and steatosis using hs-CRP was 0,833 [24]. In a Romanian study, CRP had an excellent performance in predicting the presence of NASH using a cutoff value of 3,5 mg/L (AUROC: 0,906, sensitivity: 82%, specificity: 88%). CRP, however, was not a predictor of severe fibrosis ($F \geq 3$) in that study [25].

In contrast, a small cohort study (18 patients with NASH) reported that there was no correlation of CRP levels with either the degree of hepatic steatosis, inflammation, or the stage of liver fibrosis despite the fact that NASH patients had significantly higher CRP levels than 16 controls [2]. Similar to the previous study, an Australian group reported that patients with NASH and simple steatosis had similar hs-CRP levels. No relationship existed between hs-CRP levels and the grades of hepatic steatosis, necroinflammation, and fibrosis [27]. Both studies are underpowered due to inadequate sample sizes.

CRP may be a marker of hepatic steatosis but not of severity of NAFLD in obese patients [28].

Increased ferritin but normal transferrin saturation is frequently found in patients with hepatic steatosis. The simultaneous disorder of iron and glucose and/or lipid metabolism, in most of the cases associated with insulin resistance, is responsible for persistent hyperferritinemia and identifies patients at risk for NASH. Indeed, serum ferritin level was significantly higher in the NASH patients than those with simple steatosis, according to a Japanese study. In that study, the serum ferritin level was related with insulin resistance. The performance of serum ferritin for distinguishing NASH from simple steatosis was fair (AUROC: 0,732) and the optimal cutoff value was 196 ng/mL (sensitivity: 64,2%, specificity: 76,5%). In another study, the performance of serum ferritin for detecting NASH was improved (AUROC: 0,82) when using a higher cutoff value 240 ng/mL with the price of losing specificity (sensitivity: 91%, specificity: 70%). In a recent large cohort study using gender-specific cutoff values (> 300 ng/mL in women and > 450 ng/mL for men), serum ferritin levels greater than 1,5 times of upper limit of normal was associated with hepatic iron deposition, a diagnosis of NASH, and worsened histologic activity, and is an independent predictor of advanced hepatic fibrosis among patients with NAFLD. The authors concluded that serum ferritin is useful to identify NAFLD patients at risk for NASH and advanced fibrosis. A recent report from Japan stated that the extent of serum ferritin elevations did not predict the stage of NAFLD although hyperferritinemia was common in NAFLD patients. The study is limited by a possible selection bias since only 19% of the study subjects had a histologic diagnosis.

In summary, a variety of proinflammatory biomarkers such as TNF-α, IL-6, CRP, and ferritin have been studied for their associations with NASH. Their performance in distinguishing NASH from simple steatosis is either fair or good but not excellent. Controversies of the association of each proinflammatory marker with NASH exist and well accepted cutoff values of each marker remain unknown.

Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation. Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown [23]. Several studies have shown that rapid weight loss (very low calorie diet or starving) increases the risk of progression of liver disease and even liver failure. Patients should therefore be educated not to induce rapid weight loss, but to aim at a weight loss of less than 10% of their body weight over 6-12 months. It is unclear whether special diets are helpful; probably it is

more important that the patients simply eat healthy food like vegetables and fruits, rich in fiber and complex carbohydrates with a low glycemic index; they should avoid meat, saturated fat and products with less complex carbohydrates. Lifestyle modifications should include an increase in physical activity and sports as well as abstinence from alcohol. With the results of recent studies, coffee consumption does not need to be limited and may even have a positive impact on the development of liver fibrosis.

As yet, no drug has been approved by the US Food and Drug Administration or the European Medicines Agency to treat NASH. However, the new 2012 US guidelines recommend that vitamin E and/or pioglitazone may be given in some patients for treatment of NASH. These recommendations are based in particular on two National Institutes of Health-sponsored, randomized controlled clinical trials (RCTs) with vitamin E and pioglitazone, the PIVENS and the TONIC trial [8, 20]. The PIVENS study was a large multicenter RCT that randomized 247 non-diabetic patients with NASH to pioglitazone (30 mg/day), vitamin E (800 IU/day), or placebo for 24 months [20]. The primary endpoint was an improvement in >2 the NAFLD activity score points with at least 1 point improvement in hepatocellular ballooning and a 1 point improvement in either the lobular inflammation or steatosis score, and no increase in the fibrosis score. This goal was achieved in 19% of the placebo patients compared to 34% of the pioglitazone-treated patients (p=0,04 vs placebo) and in 43% of the vitamin E treated patients (p=0,001 vs placebo). As the study consisted of two primary comparisons (pioglitazone vs placebo and vitamin E vs placebo), a p-value of 0,025 was considered to be significant *a priori.* Therefore vitamin E but not pioglitazone met the primary endpoint although there were some histological benefits associated with pioglitazone [20]. It is noteworthy that pioglitazone was associated with a 4,7 kg weight gain compared to placebo (p<0,001). A recent meta-analysis including 5 RCTs showed that pioglitazone significantly improved steatosis and inflammation, but not fibrosis. Other studies also suggest that pioglitazone improves histological inflammation and fibrosis, and ameliorates cardio-metabolic endpoints in patients not responding to lifestyle intervention [5, 14]. The other large multicenter RCT, the TONIC study, used the sustained reduction of ALT as the primary endpoint and a change in histology as secondary endpoint [8]. The TONIC study compared the efficacy of vitamin E or metformin to placebo for treatment of NAFLD in children and adolescents (8-17 years of age). Although the primary outcome of a reduction of ALT was not different among the three groups, there was a significant improvement in histology (p<0,006) with vitamin E treatment compared to placebo over 96 weeks. In this study, metformin administered at 500 mg twice daily had no effect on aminotransferases and histology [8]. The recent US guidelines [23] state that vitamin E at a daily dose of 800 IU/day improves histology in non-diabetic adults with biopsy-proven NASH and should be considered as first-line treatment. It is also mentioned that vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis until further data supporting its effectiveness become available. In addition, the guidelines discuss the controversy as to whether vitamin E increases cancer risks. According to these guidelines [23], pioglitazone can be used in patients with biopsy-proven NASH. However, it needs be noted that the majority of patients who participated in pioglitazone trials were non-diabetic and that long-term safety and efficacy of pioglitazone in patients with NASH is not established. Metformin should not be used for treatment of NASH according to these guidelines [23].

In general, all drugs that induce weight loss might be beneficial in NAFLD and NASH, in particular when diet and lifestyle modification do not work. Both sibutramine and orlistat have shown to improve some characteristics of NAFLD and NASH such as the sonographic degree of liver steatosis as well as the histological degree of steatosis and fibrosis [10].

Antioxidants and cytoprotective agents have also been proposed to treat NAFLD and NASH including vitamin C, glutathione, betaine, N-acetylcysteine, S-adenosyl-L-methionine and ursodeoxycholic acid. In a Cochrane analysis, none of these agents showed significant benefit in validated randomized studies [17]. Recently, vitamin D deficiency has been proposed to be involved in the pathogenesis of NASH, and studies proposed that vitamin D supplementation may be useful for treatment of NASH [4, 21]. There is also a recent RCT suggesting that pentoxifillin might be useful for therapy of NAFLD [28]. Larger RCTs are needed for vitamin D and pentoxifillin.

Bariatric surgery has recently been shown to improve NASH [9, 18]. The recent US guidelines state that bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH. It appears premature to recommend bariatric surgery as an established option to specifically treat NASH [9].

Liver transplantation (LTx) is the final option for patients with end-stage liver disease due to cirrhosis and complications of portal hypertension with NASH. Due to the increase in the prevalence of NASH, there is also an increase in LTx due to end-stage liver disease caused by NASH. However, NASH can recur after LTx, particularly if patients have previously undergone jejunoileal bypass surgery. LTx does not cure the metabolic defect that causes NASH.

References

1. *Adams L.A. The natural history of nonalcoholic fatty liver disease: a population-based cohort study [Text] / L.A. Adams, J.F. Lymp, S.J. Sauver // Gastroenterology. – 2005. – Vol. 129. – P. 113-121.*
2. *An obesity associated gut microbiome with increased capacity for energy harvest [Text] / P.J. Turnbaugh, R.E. Ley, M.A. Mahowald [et al.] // Nature. – 2006. – Vol. 444. – P. 1027-1031.*
3. *Antioxidant supplements for nonalcoholic fatty liver disease and/or steatohepatitis [Text] / F. Lirussi, L. Azzalini, S. Orando [et al.] // Cochrane Database Syst. Rev. – 2007. – Vol. 24. – CD004996.*
4. *Bahcecioglu I.H. Demographic and clinicopathological characteristics of nonalcoholic fatty liver disease in the east-southeastern Anatolia regions in Turkey [Text] / I.H. Bahcecioglu, M. Koruk, O. Yilmaz // Med. Princ. Pract. – 2006. – Vol. 15. – P. 62-68.*
5. *Barchetta I. Liver vitamin D_3 receptor, CYP2R1, and CYP27A1 expression: relationship with liver histology and vitamin D3 levels in patients with nonalcoholic steatohepatitis or hepatitis C virus [Text] / I. Barchetta, S. Carotti, G. Labbadia // Hepatology. – 2012. – Vol. 56. – P. 2180-2187.*
6. *Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications [Text] / K. Cusi // Gastroenterology. – 2012. – Vol. 142. – P. 711-725.*
7. *Day C.P. Natural history of NAFLD: remarkably benign in the absence of cirrhosis [Text] / C.P. Day // Gastroenterology. – 2005. – Vol. 129. – P. 375-378.*
8. *Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial [Text] / J.E. Lavine, J.B. Schwimmer, M.L. Van Natta [et al.] // JAMA. – 2011. – Vol. 305. – P. 1659-1668.*
9. *Furuya C.K. Jr. Effects of bariatric surgery on nonalcoholic fatty liver disease: preliminary findings after 2 years [Text] / C.K. Furuya Jr., C.P. Oliveira, E.S. de Mello // J. Gastroenterol. Hepatol. – 2007. – Vol. 22. – P. 510-514.*
10. *Hyaluronic acid, an accurate serum marker for severe hepatic fibrosis in patients with non-alcoholic fatty liver disease [Text] / A. Suzuki, P. Angulo, J. Lymp [et al.] // Liver Int. – 2005. – Vol. 25. – P. 779-786.*
11. *Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity [Text] / J. Henao-Mejia, E. Elinav, C. Jin [et al.] // Nature. – 2012. – Vol. 482. – P. 179-185.*
12. *Influence of gender, race, and ethnicity on suspected fatty liver in obese adolescents [Text] / J.B. Schwimmer, N.Mc Greal, R. Deutsch [et al.] // Pediatrics. – 2005. – Vol. 115. – P. 561-565.*
13. *Managing nonalcoholic fatty liver disease. Recommendations for family physicians [Text] / I. Grattagliano, P. Portincasa, V.O. Palmieri, G. Palasciano // Can. Fam. Physician. – 2007. – Vol. 53. – P. 857-863.*
14. *Mc Cullough A.J. Pathophysiology of nonalcoholic steatohepatitis [Text] / A.J. Mc Cullough // J. Clin. Gastroenterol. – 2006. – Vol. 40. – P. 17-29.*
15. *Meta-analysis: Natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity [Text] / R. Gambino, M. Cassader, G. Pagano [et al.] // Annals of Medicine. – 2011. – Vol. 43. – P. 617-649.*
16. *Obesity alters gut microbial ecology [Text] / R.E. Ley, F. Bäckhed, P. Turnbaugh [et al.] // Proc. Natl. Acad. Sci. USA. – 2005. – Vol. 102. – P. 11070-11075.*
17. *One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study [Text] / M.A. Huang, J.K. Greenson, C. Chao [et al.] // Am. J. Gastroenterol. – 2005. – Vol. 100. – P. 1072-1081.*
18. *Orlistat reverse fatty infiltration and improves hepatic fibrosis in obese patients with nonalcoholic steatohepatitis (NASH) [Text] / O. Hussein, M. Grosovski, S. Schlesinger [et al.] // Dig. Dis. Sci. – 2007. – Vol. 52. – P. 2512-2519.*
19. *Pentoxifylline improves nonalcoholic steatohepatitis: a randomized placebo-controlled trial [Text] / C.O. Zein, L.M. Yerian, P. Gogate [et al.] // Hepatology. – 2011. – Vol. 54. – P. 1610-1619.*
20. *Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis [Text] / A.J. Sanyal, N. Chalasani, K.V. Kowdley [et al.] // N. Engl. J. Med. – 2010. – Vol. 362. – P. 1675-1685.*
21. *Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease [Text] / S.R. Weston, W. Leyden, R. Murphy [et al.] // Hepatology. – 2005. – Vol. 41. – P. 372-379.*
22. *Resolution of nonalcoholic steatohepatits after gastric bypass surgery [Text] / X. Liu, A.J. Lazenby, R.H. Clements [et al.] // Obes. Surg. – 2007. – Vol. 17. – P. 486-492.*
23. *The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology [Text] / N. Chalasani, Z. Younossi, J.E. Lavine [et al.] // Gastroenterology. – 2012. – Vol. 58. – P. 2005-2023.*
24. *The epidemiology and risk factors of NASH [Text] / A.J.McCullough, G.C.Farrell, J.George [et al.] // Fatty liver disease: NASH and related disorders. – Blackwell, 2005. – P. 23-37.*
25. *The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies [Text] / L.A. Adams, S. Sanderson, K.D. Lindor, P. Angulo // J. Hepatol. – 2005. – Vol. 42. – P. 132-138.*
26. *The metabolic syndrome as a predictor of nonalcoholic fatty liver disease [Text] / M. Hamaguchi, T. Kojima, N. Takeda [et al.] // Ann. Intern. Med. – 2005. – Vol. 143. – P. 722-728.*
27. *Tuyama A.C. Non-alcoholic fatty liver disease [Text] / A.C. Tuyama, C.Y. Chang // J. Diabetes. – 2012. – Vol. 4. – P. 266-280.*
28. *Vitamin D deficiency in obese rats exacerbates nonalcoholic fatty liver disease and increases hepatic resistin and Toll-like receptor activation [Text] / C.L. Roth, C.T. Elfers, D.P. Figlewicz [et al.] // Hepatology. – 2012. – Vol. 55. – P. 1103-1111.*

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СУЧАСНІ ПОГЛЯДИ НА ДІАГНОСТИКУ ТА ЛІКУВАННЯ НЕАЛКОГОЛЬНОЇ ЖИРОВОЇ ХВОРОБИ ПЕЧІНКИ

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Резюме

У статті узагальнено дані про особливості діагностики та лікування неалкогольної жирової хвороби печінки (НАЖХП). Вона характеризується хронічним і прогресуючим ураженням печінки, яке може прогресувати зі стеатозу до стеатогепатиту, цирозу й гепатоцелюлярної карциноми, а також може стати причиною трансплантації печінки. Діагноз НАЖХП можна встановити за допомогою візуальних методів дослідження та біопсії печінки з гістологічним підтвердженням. Також існують неінвазивні біомаркери фіброзу. Основні методи лікування спрямовані на зменшення маси тіла пацієнтів, ведення здорового способу життя і корекцію метаболічних чинників ризику. У статті також наведені результати вивчення ефективності використання антиоксидантів, піоглітазону, пентоксифіліну, урсодезоксихолевої кислоти, баріатричної хірургії та трансплантації печінки в терапії хворих на НАЖХП.

Ключові слова: неалкогольна жирова хвороба печінки, неалкогольний стеатогепатит, неінвазивні біомаркери фіброзу печінки.