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**Non-alcoholic liver fatty liver disease: What has changed in the treatment since the beginning?**

Baran B *et al*. NAFLD and treatment

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**Abstract**

Non-alcoholic liver fatty liver disease (NAFLD) is an umbrella term to describe the entire spectrum of this common liver disease. Patients with NAFLD, especially those with non-alcoholic steatohepatitis (NASH), most often have one or more components of the metabolic syndrome, but this is not universal. Although most patients with NAFLD share many clinical features, only a subset of patients develops significant liver inflammation and progressive fibrosis. On the other hand, not all patients with NASH exhibit insulin resistance. NASH can be seen in patients who are lean and have no identifiable risk factors. Many clinical studies tried numerous drugs and alternative medicine, but investigators have failed to present a safe and effective therapy for patients with NASH. As summarized, heterogeneity of pathogenic pathways in individual patients with NASH may warrant developing an individualized treatment according to the underlying pathogenic pathway. The differentiation of pathogenetic targets may require development of diagnostic, prognostic biomarkers and identification of genetic susceptibilities. For now, the evidence based medicine gives us only a few options including life-style modifications targeting weight loss, pioglitazone and vitamin E in non-diabetic patients with biopsy-proven NASH.

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**Key words:** Non-alcoholic steatohepatitis; Pathogenesis; Inflammation; Fibrosis; Life-style changes; Pharmacologic treatment

**Core tip:** Many clinical studies tried numerous drugs and alternative medicine, but investigators have failed to present a safe and effective therapy for patients with non-alcoholic steatohepatitis (NASH). As summarized, heterogeneity of pathogenic pathways in individual patients with NASH may warrant developing an individualized treatment according to the underlying pathogenic pathway. The differentiation of pathogenetic targets may require development of diagnostic, prognostic biomarkers and identification of genetic susceptibilities. For now, the evidence based medicine gives us only a few options including life-style modifications targeting weight loss, pioglitazone and vitamin E in non-diabetic patients with biopsy-proven NASH.

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**INTRODUCTION**

More than 30 years ago, Ludwig et al described an unnamed disease as non-alcoholic steatohepatitis (NASH) for the first time[[1](#_ENREF_1)]. This initial report however did not reveal the full spectrum of this multifaceted disease. After three decades, numerous studies have been conducted which contributed to the better understanding of the epidemiology, etiology, pathophysiology, natural history and treatment of the disease.

Non-alcoholic liver fatty liver disease (NAFLD) is an umbrella term to describe the entire spectrum of this common liver disease. NAFLD is among the causes of fatty liver and one of the leading etiologies of chronic liver disease. There are a number of factors associated with fatty liver and the diagnosis of NAFLD requires exclusion of secondary etiologies for hepatic fat accumulation such as heavy alcohol consumption (Table 1)[[2](#_ENREF_2)]. Histological features, which is predominantly macrovesicular steatosis, resembles alcohol-induced liver injury; however by definition it occurs in patients with little or no history of alcohol consumption. NAFLD is classically subdivided into non-alcoholic fatty liver or simple steatosis and NASH. In simple steatosis, fat accumulation in the liver is present without evidence of significant inflammation or liver fibrosis, whereas in NASH, liver steatosis is associated with hepatic inflammation, hepatocellular ballooning and fibrosis which may be indistinguishable with alcoholic steatohepatitis[[3](#_ENREF_3)].

NAFLD is seen in every geographic region worldwide and it is considered the most common liver disorder in Western countries. Worldwide estimated prevalence of NAFLD ranges from 6.3% and 33% in general population with a median prevalence of 20%[[4](#_ENREF_4)]. The estimated prevalence of NASH is much lower, that ranges from 3%-5%[[4](#_ENREF_4)]. The disease is mostly silent and is often discovered by routine laboratory investigations incidentally showing elevated transaminases.

The evidence indicates that although simple steatosis is a benign condition, NASH can progress to fibrosis and lead to end-stage liver disease[[5](#_ENREF_5)]. Among patients with cryptogenic cirrhosis, up to 70% have risk factors for NAFLD[[6](#_ENREF_6)]. The risk factors associated with the progression of the disease include elevated serum transaminases, inflammation in liver biopsy, older age, diabetes mellitus, high body mass index (≥28 kg/m2), presence of ballooning plus Mallory hyaline or fibrosis on biopsy and increased visceral adipose tissue[[7-10](#_ENREF_7)]. However, mechanisms which drive the progression from simple steatosis to NASH are not fully elucidated yet.

Although the pathophysiological mechanisms behind the development of NASH are out of the scope of this review, a brief inspection over the recent understandings on the pathogenesis may improve the discussion of potential therapies. For decades, NAFLD has been thought to be a disease spectrum which progresses from simple steatosis to NASH and from NASH to advanced liver fibrosis. Therefore, variable clinical presentations of individuals with NAFLD have always been thought to be different stages of this pathophysiologic continuum. Under the influence of this idea, two-hit hypothesis was established to explicate the pathogenesis of the disease[[11](#_ENREF_11)]. According to this well-known explanation for the mechanism behind disease progression, initial insult occurs by development of macrovesicular steatosis due to excessive triglyceride accumulation in the liver. There is a range of conditions associated with lipid deposition in hepatocytes. Excessive triglyceride accumulation in the liver can occur from the excessive importation of free fatty acids from adipose tissue, from diminished hepatic export of free fatty acids or from impaired beta-oxidation of free fatty acids[[12](#_ENREF_12)]. Increases in visceral adipose tissue and intrahepatic fat correlate with increased gluconeogenesis, increased free fatty acid levels, and insulin resistance[[13](#_ENREF_13)]. Insulin resistance and subsequent hyperinsulinemia seem to be the major factor behind the alterations in the hepatic pathways of uptake, synthesis, degradation, and secretion of free fatty acids which ultimately leads to accumulation of lipids in the hepatocytes[[14](#_ENREF_14)]. These changes seem to make the liver susceptible to a second insult, resulting in an inflammatory response and progression of liver damage. The second hit occurs due to increased hepatic oxidative stress which is associated with increased free fatty acid metabolism, diminished antioxidant activity, increased proinflammatory cytokines, such as tumor necrosis factor alpha (TNFα) and endotoxin levels, and especially mitochondrial dysfunction and/or endoplasmic reticulum stress in the liver[[14](#_ENREF_14)]. Mitochondrial dysfunction, generation of reactive oxygen species and inflammatory response enhance endoplasmic reticulum stress with subsequent activation of hepatocyte apoptotic pathways and eventually hepatic fibrogenesis. Other oxidative stressors that may contribute to inflammation and fibrogenesis in patients with NAFLD include, but not limited to, hepatic iron, leptin, depressed antioxidant levels and intestinal microbiota[[15-18](#_ENREF_15)]. A very recent and important advancement in our understanding of hepatic fibrogenesis is the demonstration of the relationship between free cholesterol accumulation in hepatic stellate cells and progressive liver fibrosis in animal models[[19](#_ENREF_19)]. Free cholesterol accumulation in hepatic stellate cells increases and further sensitizes these cells to transforming growth factor-beta induced activation of liver fibrogenesis in NASH[[20](#_ENREF_20)].

Although the traditional “two-hit” hypothesis has been dominated the literature to explain NAFLD pathophysiology for more than a decade, it has been dethroned as the relationship and interaction between insulin resistance, adipokines, liver inflammation, hepatocyte apoptosis and other numerous pathogenetic components were further elucidated during the recent years. It is evident that numerous complex pathways which interacts each other are responsible in the pathogenesis of NASH and progression to advanced fibrosis. These pathways of pathogenesis may not exist together in every individual with NAFLD and additional pathways can supervene at any time during the course of the disease, which leads to a heterogeneous patient cohort with diverse clinical presentations[[21](#_ENREF_21)]. Patients with NAFLD, especially those with NASH, most often have one or more components of the metabolic syndrome, but this is not universal[[22](#_ENREF_22), [23](#_ENREF_23)]. Although most patients with NAFLD share many clinical features, only a subset of patients develops significant liver inflammation and progressive fibrosis. A fine example of this heterogeneity is that insulin resistance can be observed in NASH in the absence of obesity and glucose intolerance. On the other hand, not all patients with NASH exhibit insulin resistance. NASH can be seen in patients who are lean and have no identifiable risk factors[[24](#_ENREF_24)]. There is consistent evidence on the relationship between genetic factors and NAFLD pathogenesis[[25](#_ENREF_25), [26](#_ENREF_26)], which may partially explain the heterogeneity of the disease. The single nucleotide polymorphism (rs738409 C>G) in the human patatin-like phospholipase domain containing 3 gene (*PNPLA3*) is the best example of this genetic factors associated with NAFLD pathogeness. It has been shown to be a strong predictor of hepatic steatosis, inflammation and fibrosis independent of body mass index and insulin resistance[[27](#_ENREF_27)]. With this insight, the traditional “two-hit” mechanism to explain disease progression in NAFLD has been challenged by the novel “multiple parallel hits” hypothesis[[28](#_ENREF_28)]. In this version of pathogenetic explanation, the initial insult to liver starts with insulin resistance and concurrent metabolic abnormalities (Figure 1). Hyperinsulinemia resultant of insulin resistance leads to above mentioned mechanisms of altered free fatty acid metabolism and fatty infiltration of the liver which makes liver susceptible to numerous injurious effects. A parallel interaction and intensification between these complex injurious mechanisms lead to mitochondrial dysfunction, subsequent induction of hepatocyte apoptotic pathways and fibrogenesis. Although the histopathological picture of steatohepatitis is universal, the evidence behind the “multiple parallel hits” theory indicates that each patient can have shared and distinct pathophysiological stories behind the progression from NAFLD to NASH. In this context, a need for individualized pathogenesis-based approach to medical therapy for patients with NAFLD has been conceptualized in the recent years. With this review, we aimed to summarize the evolution and current status of different treatment regimens that have been studied in patients with NAFLD.

**MANAGEMENT**

***General principles***

Although the increasing prevalence of NASH has led to a great demand for a medical therapy, three decades of research on pharmacological treatment has provided limited options. The only management guideline could only be published recently by American Association of the Study of the Liver Diseases (AASLD)[[2](#_ENREF_2)]. Since the definition of the disease, it was promptly recognized that obesity, glucose intolerance and type 2 diabetes, which are the conditions associated with insulin resistance, are frequently observed in patients with NAFLD. Due to the strong association between NAFLD and insulin resistance, there is a wide consensus to describe the condition as the hepatic component of the metabolic syndrome. Therefore, initial studies investigating treatment options in NAFLD focused on management of components of the metabolic syndrome (Table 2)[[29](#_ENREF_29)]. Cardiovascular risk factors are highly prevalent among patients with NAFLD and general lifestyle interventions including dietary changes and physical exercise to achieve weight loss has been recommended as the backbone of the management of the disease. The rationale for recommending lifestyle modifications as a first line treatment was based on the pathophysiological evidence obtained in studies showing improvement of insulin resistance and fatty acid metabolism after significant weight loss (>5%-10% of body weight)[[30](#_ENREF_30), [31](#_ENREF_31)]. These modifications in lifestyle may also improve steatosis and hepatic inflammation, especially if patients can incorporate and maintain these changes into their life for a sufficient period of time[[32](#_ENREF_32)]. However, most patients may experience problems regarding their adherence to lifestyle interventions in long-term. Only 15% of the patients may achieve greater than 10% weight loss, and even that patients may regain lost weight that leads recurrence of NASH[[33-35](#_ENREF_33)]. In addition to targeting weight loss by caloric restriction and exercise, the contents of diet is increasingly recognized as having utmost importance in lifestyle modifications. In several studies it was suggested to avoid drinks and foods that contain high fructose and trans-fats in patients with NASH[[36](#_ENREF_36), [37](#_ENREF_37)]. Hepatic metabolism of fructose causes ATP depletion in hepatocytes, increase lipotoxicity and enhance TNF expression[[38](#_ENREF_38)]. Fructose and trans-fats are responsible from altered insulin sensitivity, increased hepatic fat accumulation which is considered as initial insult in the pathogenesis of the disease[[36](#_ENREF_36), [37](#_ENREF_37), [39](#_ENREF_39)].

Another important consideration regarding nutrition and lifestyle should focus on the metabolic benefits of coffee consumption which recently has drawn great interest among researchers and practitioners in gastroenterology. There are several studies that have associated coffee consumption to improvement of NASH[[40](#_ENREF_40), [41](#_ENREF_41)], however the biological mechanisms behind the protective effect is not elucidated yet. The possible mechanisms of hepato-protective effects of coffee were discussed in detail elsewhere[[42](#_ENREF_42)]. Nonetheless, most studies investigating the effects of coffee consumption on NAFLD had methodological issues which necessitate careful explication of the results. There is a need for further investigations to explain the exact mechanisms and to unveil which compounds are responsible for the beneficial effects of coffee before having conclusions to recommend it as a treatment option.

In summary, the current evidence suggests that lifestyle modifications including dietary changes and exercise targeting significant weight loss can improve components of NASH and should be recommended for all patients as a part of primary care.

***Pharmacologic therapies***

Although many benefits may be accomplished with persistent lifestyle changes in patients with NASH, there is still an unmet need for pharmacological therapy to improve potentially progressive course of this disease. It has utmost importance to provide personalized treatment regimens for individual patients that can effectively target pathophysiological pathways of NAFLD. There are many studies that have been conducted for the treatment of the patients with NASH during the last 30 years. However, most studies were short in duration which made selection of an optimal endpoint as development of cirrhosis unfeasible. Previous studies have usually focused on surrogate outcomes including serum transaminase levels, markers of inflammation and histological findings. The management of patients with NAFLD consists of treating associated and co-morbid metabolic disturbances such as obesity, hyperlipidemia, hypertension, insulin resistance and type 2 diabetes mellitus. Initial choice of pharmacological treatments should focus on these associated conditions. It should be noted that there is evidence showing the superiority of diet and exercise than relying solely on pharmacological therapy[[43](#_ENREF_43)]. Pharmacological treatment options are summarized in Table 3[[2](#_ENREF_2), [21](#_ENREF_21)].

**INSULIN SENSITIZERS**

The use of insulin-sensitizing agents in the treatment is based on the role of insulin resistance in the development of NAFLD. Metformin and thiazolidinediones including pioglitazone and rosiglitazone are insulin-sensitizing agents that have been broadly studied in patients with NASH.

***Metformin***

Metformin has well-known beneficial effects on insulin resistance which contributes lowering of blood glucose by decreasing hepatic gluconeogenesis, inducing glucose uptake by muscles, and increasing fatty acid oxidation in adipose tissue. Several studies investigated the effect of metformin on aminotransferases and liver histology in patients with NASH. There is contradicting evidence regarding the improvement of aminotransferases under metformin therapy. Although many studies reported an improvement during treatment, some others did not provide similar results[[44](#_ENREF_44), [45](#_ENREF_45)]. The research evaluating histological improvement also provided conflicting results. A randomized placebo controlled study investigated the efficacy of metformin and failed to show an improvement in liver histology[[44](#_ENREF_44)]. This result was confirmed in a meta-analysis that included three randomized controlled trials with available histological data. In this meta-analysis, there was no difference between the patients receiving metformin or placebo, regarding any of the histological parameters including steatosis, inflammation or fibrosis[[46](#_ENREF_46)]. Therefore, metformin is not recommended as a primary treatment in guidelines, especially solely from the standpoint of NASH[[2](#_ENREF_2)]. Nevertheless, it can be used in diabetic patients with NAFLD for other indications.

***Thiazolidinediones***

Thiazolidinediones, including [pioglitazone](http://www.uptodate.com/contents/pioglitazone-drug-information?source=see_link) and [rosiglitazone](http://www.uptodate.com/contents/rosiglitazone-drug-information?source=see_link), are insulin-sensitizing agents that have been shown to improve liver biochemical and histologic parameters in patients with NASH[[47](#_ENREF_47), [48](#_ENREF_48)]. Insulin-sensitizing effects of thiazolidinediones work on adipose tissue, muscle, and liver by increasing glucose utilization and decreasing gluconeogenesis. Although the exact mechanism by which the thiazolidinediones improve insulin sensitivity is not fully elucidated, it is considered to be associated with their effects on several peroxisome proliferator-activated receptors (PPARs) which regulate expression of crucial genes modulating insulin effects[[49](#_ENREF_49)]. The effects of thiazolidinediones on adipose tissue are particularly important to understand their potential benefits in patients with NAFLD. Thiazolidinediones are reported to enhance expression of genes that increase lipid storage and reduce expression of genes associated with inflammation including interleukin-6 and TNFα. In addition, thiazolidinediones have regulator effects through PPAR-gamma activation on the production of adipokines which have fundamental roles on the pathogenesis of NAFLD[[50](#_ENREF_50)]. There are several studies that investigated rosiglitazone for treatment of NASH. In summary, it has been shown that rosiglitazone improves aminotransferases and inflammation in histology, but has no beneficial effects on fibrosis stage[[48](#_ENREF_48), [51](#_ENREF_51)]. Pioglitazone has also been investigated in several studies which reported improvement of aminotransferases, histological inflammation and steatosis[[52](#_ENREF_52)]. In those studies a regression in fibrosis stage was not noticed, but there are also evidence indicating contrary. In a randomized placebo-controlled study in non-diabetic subjects with NASH demonstrated that pioglitazone therapy more than 12 month improved metabolic and histologic parameters including fibrosis stage[[47](#_ENREF_47)]. There is also a meta-analysis including 4 randomized controlled studies showing that pioglitazone but not rosiglitazone improves fibrosis[[53](#_ENREF_53)]. However, a large multicenter randomized controlled trial that randomized 247 patients with NASH into pioglitazone, vitamin E and placebo groups did not report a statistically significant improvement for fibrosis stage for either treatment arm[[54](#_ENREF_54)]. Despite these promising results there are serious concerns regarding safety of long-term treatment with thiazolidinediones including but not limited to weight gain, congestive heart failure, cardiovascular morbidity, increased bone fracture risk and an increase in bladder cancers[[49](#_ENREF_49), [55](#_ENREF_55), [56](#_ENREF_56)]. The benefits of therapy in patients with NASH are not durable after cessation of treatment as shown by Lutchman *et al*[[57](#_ENREF_57)], and the need for long-term treatment without an endpoint makes routine application of thiazolidinedione therapy questionable. Nevertheless, there is a general consensus and a guideline recommendation suggesting that thiazolidinediones, especially pioglitazone, can be used to treat patients with biopsy-proven NASH who have not responded adequately to lifestyle modifications[[2](#_ENREF_2), [21](#_ENREF_21)]. However, safety issues should be monitored carefully during the treatment.

**ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS**

Renin-angiotensin-aldosterone system (RAAS) has a central role in the pathogenesis of hypertension which is a component of metabolic syndrome. Experimental evidence suggests that RAAS has an influence over intracellular insulin signaling by several mechanisms which may result in worsening of insulin resistance. Angiotensin II, the primary effector mediator of the RAAS, induces serine phosphorylation of insulin receptor beta-subunit and the p85 regulatory subunit of PI3-kinase that negatively modulates early components of the insulin signalling cascade[[58](#_ENREF_58)]. Angiotensin II induced generation of reactive oxygen species which is mainly associated with activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme system, initiates and propagates the production of pro-inflammatory mediators including TNFα, interleukin-6, and platelet activator inhibitor 1[[59](#_ENREF_59)]. In animal models, it has been demonstrated that angiotensin II increases hepatic steatosis, impairs mitochondrial function, and contribute to progression of hepatic fibrosis[[60](#_ENREF_60)]. Despite this cumulative evidence of *in vitro* and *in vivo* studies, human data on the effects of RAAS inhibition on liver fibrosis are lacking. Several studies evaluated effects of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) on hepatic fibrosis in patients with hepatitis C under different settings. Those studies were mostly retrospective and provided conflicted results[[61-63](#_ENREF_61)]. In the NAFLD setting, no studies evaluated the effects of ACE-I, but there are a number of small scale studies that investigated effects of ARBs in this population. In summary, limited evidence suggested that ARBs including losartan, valsartan and telmisartan may improve transaminases, hepatic steatosis and inflammation in the NAFLD setting[[64](#_ENREF_64)], however there is a need for larger randomized-controlled trials to assess long-term effects of ARBs on hepatic fibrosis in NASH. Currently, the treatment with ACE-I and ARBs can only be recommended in NALFD patients with an established indication of anti-hypertensive therapy.

**INCRETIN-BASED THERAPIES**

The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are secreted from intestinal endocrine cells in response to a meal, have been demonstrated to induce glucose-dependent insulin secretion, slow gastric emptying, inhibit inappropriate post-meal glucagon release and reduce food intake[[65](#_ENREF_65)]. There are two groups of incretin mimetics which were developed to be used for the treatment of type 2 diabetes mellitus: GLP-1 analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors[[65](#_ENREF_65), [66](#_ENREF_66)]. These drugs mimic the physiological effects of incretin hormones and improve glisemic control of the patients with type 2 diabetes mellitus. Growing pre-clinical evidence shows that incretin-based therapies have the potential to improve hepatic steatosis in the animal models of obesity and diabetes[[67](#_ENREF_67)]. However, in the absence of human trials it is not appropriate to recommend treatment with incretin mimetics in patients with NAFLD, if this is the sole indication.

**VITAMIN E**

Oxidative stress and depletion of endogenous antioxidants is essential in the pathogenesis of disease progression in NASH. Many drugs with antioxidant features were tried in studies for the treatment of NASH with variable conclusions. Vitamin E (α-tocopherol) is a well-known antioxidant which is the best studied feature of it beside many other biological functions. Vitamin E functions as a free radical scavenger which protects polyunsaturated fatty acids from peroxidation[[68](#_ENREF_68)]. There are also other functions of vitamin E independent of antioxidant activity, that may have some role in NAFLD pathogenesis, including inhibition of cell proliferation, platelet aggregation and monocyte adhesion[[69](#_ENREF_69)]. With this context, vitamin E was investigated in several studies for the treatment of NASH with different results. The largest randomized controlled study on vitamin E, the PIVENS trial, demonstrated a greater histological improvement in inflammation in non-diabetic patients with biopsy-proven NASH compared with placebo and pioglitazone groups. However, only 42% of patients receiving a high dose vitamin E (800 IU/d) for 96 wk achieved an improvement in histological parameters compared with 19% in placebo-treated patients[[54](#_ENREF_54)]. A newer study, the TONIC trial, included pediatric patients with biopsy-proven NASH which were randomized to vitamin E, metformin and placebo arms. In this study, patients treated with either medication did not achieve sustained ALT reductions, but histological improvement was significant in the children taking vitamin E[[70](#_ENREF_70)]. In the line of these evidence, the recent guideline by AASLD recommends vitamin E at a daily dose of 800 IU/d in non-diabetic adult patients with biopsy-proven NASH as a first-line pharmacologic therapy[[2](#_ENREF_2)]. However, it is crucial to note that there have been some serious concerns regarding the safety of long-term vitamin E treatment. There are meta-analyses that have reported an increase in all-cause mortality with vitamin E treatment while others reported against this association[[71-73](#_ENREF_71)]. Moreover, vitamin E at a dose of 400 IU/d has been found to be associated with an increased risk of prostate cancer[[74](#_ENREF_74)]. Physicians who choose to initiate vitamin E therapy should consider the potential risks of long-term treatment with this drug. Especially in patients with diabetes and significant cardiovascular risk factors, vitamin E treatment should be avoided until sufficient data for long-term safety and efficacy will be established.

**STATINS**

There is convincing evidence showing that cardiovascular events are the most common cause for death in patients with NAFLD, which necessitates management and optimization of cardiovascular risks in every patient[[75](#_ENREF_75)]. However, there is a considerable degree of preoccupation to avoid statins in patients with elevated transaminases and chronic liver diseases. Contrary to concerns about safety, there is substantial evidence demonstrating that statins are safe in patients with chronic liver disease including NAFLD and NASH. Therefore, patients with NAFLD and dyslipidemia should be treated by statins as indicated by relevant guidelines[[76](#_ENREF_76), [77](#_ENREF_77)]. Other than the management of dyslipidemia in patients with NAFLD, the evidence behind usage of statins to change the natural course of NAFLD is absent. Although there are several small-scale studies that found a benefit from statins on liver enzymes, data regarding histological improvement is lacking[[78](#_ENREF_78), [79](#_ENREF_79)]. Until more data showing histological benefit is available, there is no indication for statins to specifically treat NASH.

**URSODEOXYCHOLIC ACID**

Ursodeoxycolic acid decreases the cholesterol content of bile by reducing the secretion of cholesterol from the liver and the fractional reabsorption of cholesterol by the intestines. It is has also anti-apoptotic, cytoprotective and anti-inflammatory effects[[80](#_ENREF_80)]. In a pilot study, a possible benefit of ursodeoxycolic acid was suggested in the treatment of NASH[[81](#_ENREF_81)]. However, this was not confirmed in larger randomized controlled trials using histological assessment[[82](#_ENREF_82), [83](#_ENREF_83)]. According to the latest guideline issued by AASLD, ursodeoxycolic acid therapy is not recommended for the treatment of NAFLD or NASH[[2](#_ENREF_2)].

**ORLISTAT**

Orlistat is a reversible inhibitor of gastric and pancreatic lipases which prevents lipid absorption throughout the small intestines. It is indicated in the treatment of obesity and type 2 diabetes mellitus. In combination with lifestyle modifications, orlistat was evaluated in treatment of NASH in several studies that reached variable conclusions. In a pilot study, 44 patients who participated in a weight loss program were randomized to receive orlistat or placebo. Orlistat improved ALT levels and liver steatosis significantly, however steatosis was assessed by ultrasound only, which is an unreliable method in the absence of histological confirmation[[84](#_ENREF_84)]. In a well-desinged study, patients receiving caloric restriction and vitamin E (800 IU/d) with or without orlistat showed similar improvements in transaminases, liver steatosis and inflammation[[85](#_ENREF_85)]. Only in patients who achieved significant weight loss (≥9%) histologic parameters were improved regardless of orlistat therapy. Based on these data, the efficacy of orlistat in treatment of patients with NASH is indefinite, and can only be used as an adjunct for weight loss in the treatment of obesity.

**OMEGA-3 FATTY ACIDS**

Observational and clinical studies that have examined the effects of the long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs) on cardiovascular risk factors showed significant benefits on cardiovascular outcomes[[86](#_ENREF_86)]. The favorable effects of n-3 PUFAs on lipids, blood pressure, atherosclerosis, and especially on inflammation provide hypothetical basis for research on patients with NAFLD. The experimental evidence suggest a potential benefit for omega-3 fatty acids in treatment of NAFLD, however results of human studies were inconclusive due to small sample size and methodological flaws[[87](#_ENREF_87)]. A recent meta-analysis of 9 studies including 355 patients with NAFLD demonstrated that treatment with n-3 PUFAs improves the degree of hepatic steatosis, decreases aspartate aminotransferase levels and an insignificant trend for improvement alanine aminotransferase levels[[88](#_ENREF_88)]. Considering the available evidence there is limited data for suggesting n-3 PUFAs for specific treatment of patients with NAFLD.

**PENTOXIFYLLINE**

Pentoxifylline inhibits production of TNFα which has been associated with a possible role in progression of NAFLD[[89](#_ENREF_89)]. A recent study also showed that pentoxifylline therapy significantly reduces oxidized lipid products which have been known to play a key role in the pathogenesis of NASH[[90](#_ENREF_90)]. The largest placebo-controlled trial randomized 55 patients with biopsy-proven NASH to receive pentoxifylline 1200 mg/d or placebo[[91](#_ENREF_91)]. The investigators reported that patients treated with pentoxifylline showed significant improvement in hepatic steatosis, lobular inflammation and fibrosis. Despite these results, the evidence regarding the benefits of pentoxifylline therapy in NASH is still inconclusive; however this drug may warrant further investigation in a larger patient population.

**CONCLUSION**

Since the description of NASH three decades ago, our understanding regarding the pathophysiology of the disease evolved significantly, however reasons that shape the heterogeneity among patients and factors that influence the development and progression of inflammation are not yet well-understood. Although growing evidence achieved by basic research improved our knowledge on hepatic inflammation and fibrogenesis, translational studies have not been able to provide a solution from bench to bedside, to help clinicians who care for patients with NAFLD. Many clinical studies tried numerous drugs and alternative medicine, but investigators have failed to present a safe and effective therapy for patients with NASH. As summarized, heterogeneity of pathogenic pathways in individual patients with NASH may warrant developing an individualized treatment according to the underlying pathogenic pathway. The differentiation of pathogenetic targets may require development of diagnostic, prognostic biomarkers and identification of genetic susceptibilities. For now, the evidence based medicine gives us only a few options including life-style modifications targeting weight loss, pioglitazone and vitamin E in non-diabetic patients with biopsy-proven NASH. The current evidence is premature to provide a pathogenesis-based management algorithm, however it can be suggested to tailor initial management strategy according to individual patient characteristics including presence of obesity and/or insulin resistance. It seems life-style modifications should be the first step in NASH patients with obesity and/or insulin resistance. The components of metabolic syndrome should be targeted in those patients, particularly aiming to improve insulin resistance. Yet drug therapy, especially vitamin E, can be the initial choice in lean patients without insulin resistance.

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| **Table 1 Common causes of secondary liver steatosis** |
| **Macrovesicular steatosis** | **Microvesicular steatosis** |
| Alcohol consumption | Reye’s syndrome |
| Parenteral nutrition | Acute fatty liver of pregnancy |
| Hepatitis C | HELLP syndrome |
| Starvation/Malnutrition | Genetic metabolic diseases (*e.g.*, LCAT deficiency, cholesterol ester storage disease) |
| Abetalipoproteinemia | Heat stroke |
| Lipodistrophy | Drugs (valproate, anti-retroviral drugs) |
| Celiac disease |  |
| Wilson’s disease |  |
| Drugs (*e.g.*, corticosteroids, tamoxifen, amiodarone) |  |

HELLP syndrome: Hemolysis, elevated liver enzymes and low platelets syndrome; LCAT: lecithin-cholesterol-acyltransferase.

|  |
| --- |
| **Table 2 International Diabetes Federation definition of the metabolic syndrome** |
| Increased waist circumferenc**e [≥94 cm (men) or ≥80 cm (women)],** with ethnic-specific waist circumference1 cut-points; plus any two of the following: |
| Triglycerides >150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides |
| HDL cholesterol <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, or treatment for low HDL |
| Systolic blood pressure >130, diastolic blood pressure >85 mmHg, or treatment for hypertension |
| Fasting plasma glucose >100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes; an oral glucose tolerance test is recommended for patients with an elevated fasting plasma glucose, but not required |
| 1For South Asia and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women). HDL: High density lipoprotein. |

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| **Table 3 Summary of treatment options in patients with non-alcoholic steatohepatitis** |
| **Intervention** | **Recommendation** | **Notes** |
| Weight loss | Highly recommended | Diet and exercise should target significant weight loss5% weight loss reduces hepatic steatosisGreater weight loss may be needed to improve hepatic inflammation |
| Metformin | Not recommended | Not recommended for specific therapy of NASHShould be used when indicated for treatment of type 2 diabetes mellitus |
| Thiazolidinediones | Recommended in selected patients | There is evidence for pioglitazone usage in non-diabetic patients with biopsy-proven NASHThere are questions regarding long-term safety  |
| RAAS inhibition (ACE-I/ARBs) | Not recommended | Not recommended for specific therapy of NASHCan be used when indicated for treatment of hypertension |
| Incretin mimetics | Not recommended | Not recommended for specific therapy of NASHCan be used when indicated for type 2 diabetes mellitus |
| Vitamin E | Recommended in selected patients | Vitamin E 800 IU/day Evidence in non-diabetic biopsy-proven NASHThere is evidence regarding increased all-cause mortality associated with vitamin E usage. |
| Statins | Not recommended | Not recommended for specific therapy of NASHCan be used safely when indicated for dyslipidemia |
| Ursodeoxycholic acid | Not recommended | A RCT showed no benefit of UDCA |
| Orlistat | Not recommended | Can be used as an adjunct for weight loss in selected cases. |
| Omega-3 fatty acids | Not recommended | Can be used to treat hypertrigliseridemia |
| Pentoxifylline | Not recommended | Inconclusive evidenceMay warrant further investigation |

NASH: Non-alcoholic steatohepatitis; ACE-I: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; UDCA: Ursodeoxycholic acid; RCT: Randomized-controlled trial.

Figure 1 Pathogenesis of non-alcoholic liver fatty liver disease. FFA: free fatty acid; ER: endoplasmic reticulum; NASH: non-alcoholic steatohepatitis; HSCs: hepatic stellate cells.