

## WJG 20<sup>th</sup> Anniversary Special Issues (12): Nonalcoholic fatty liver disease

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

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## Abstract

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term to describe the entire spectrum of this common liver disease. In 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 have tried numerous drugs and alternative medicine, however, investigators have failed to identify a safe and effective therapy for patients with NASH. As summarized, the heterogeneity of pathogenic pathways in individual patients with NASH may warrant the development of an individualized treatment according to the underlying pathogenic pathway. The differentiation of pathogenetic targets may require the development of diagnostic and prognostic biomarkers, and the identification of genetic susceptibilities. At present, evidence-based medicine

provides 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 have tried numerous drugs and alternative medicine, but investigators have failed to identify a safe and effective therapy for patients with non-alcoholic steatohepatitis (NASH). As summarized, the heterogeneity of pathogenic pathways in individual patients with NASH may warrant the development of an individualized treatment according to the underlying pathogenic pathway. The differentiation of pathogenetic targets may require the development of diagnostic and prognostic biomarkers, and the identification of genetic susceptibilities. At present, evidence-based medicine provides 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*<sup>[1]</sup> described an unnamed disease as non-alcoholic steatohepatitis (NASH) for the first time. This initial report, however, did not reveal the full spectrum of this multifaceted disease. After

**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
Lipodystrophy	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.

three decades, numerous studies have been conducted which have contributed to a better understanding of the epidemiology, etiology, pathophysiology, natural history and treatment of the disease.

Non-alcoholic 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)<sup>[2]</sup>. Histological features, predominantly macrovesicular steatosis, resemble 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 from alcoholic steatohepatitis<sup>[3]</sup>.

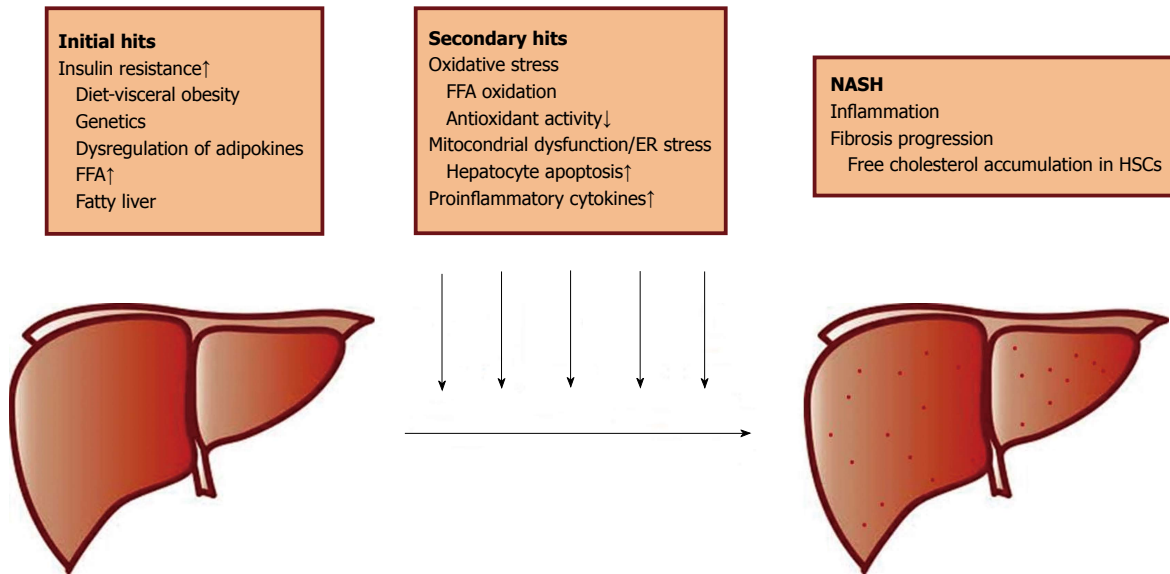
NAFLD is seen worldwide and it is considered the most common liver disorder in Western countries. The worldwide estimated prevalence of NAFLD ranges from 6.3% to 33% in the general population with a median prevalence of 20%<sup>[4]</sup>. The estimated prevalence of NASH is much lower, and ranges from 3% to 5%<sup>[4]</sup>. The disease is asymptomatic 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<sup>[5]</sup>. In patients with cryptogenic cirrhosis, up to 70% have risk factors for NAFLD<sup>[6]</sup>. The risk factors associated with progression of the disease include elevated serum transaminases, inflammation on liver biopsy, older age, diabetes mellitus, high body mass index ( $\geq 28 \text{ kg/m}^2$ ), presence of ballooning plus Mallory hyaline or fibrosis on biopsy and

increased visceral adipose tissue<sup>[7-10]</sup>. However, mechanisms which drive the progression from simple steatosis to NASH are not yet fully elucidated.

Although the pathophysiological mechanisms involved in the development of NASH are out of the scope of this review, a brief examination of the recent understanding of the pathogenesis may improve the discussion on 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 in individuals with NAFLD have always been thought to be different stages of this pathophysiologic continuum. Under this assumption, the two-hit hypothesis was established to explain the pathogenesis of the disease<sup>[11]</sup>. According to this well-known hypothesis for the mechanism of disease progression, an initial insult occurs during the 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 due to 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<sup>[12]</sup>. Increases in visceral adipose tissue and intrahepatic fat correlate with increased gluconeogenesis, increased free fatty acid levels, and insulin resistance<sup>[13]</sup>. Insulin resistance and subsequent hyperinsulinemia seem to be the major factors 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<sup>[14]</sup>. 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 (TNF $\alpha$ ) and endotoxin levels, and especially mitochondrial dysfunction and/or endoplasmic reticulum stress in the liver<sup>[14]</sup>. Mitochondrial dysfunction, the 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<sup>[15-18]</sup>. A very recent and important advancement in our understanding of hepatic fibrogenesis is the demonstrated relationship between free cholesterol accumulation in hepatic stellate cells and progressive liver fibrosis in animal models<sup>[19]</sup>. 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<sup>[20]</sup>.

Although the traditional "two-hit" hypothesis has dominated the literature to explain NAFLD pathophysi-



**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.

ology for more than a decade, it has been overtaken as the relationship and interaction between insulin resistance, adipokines, liver inflammation, hepatocyte apoptosis and other numerous pathogenetic components have been further elucidated in recent years. It is evident that numerous complex pathways which interact with each other are responsible for 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<sup>[21]</sup>. Patients with NAFLD, especially those with NASH, most often have one or more components of the metabolic syndrome, but this is not universal<sup>[22,23]</sup>. Although most patients with NAFLD share many clinical features, only a subset of patients develops significant liver inflammation and progressive fibrosis. An 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<sup>[24]</sup>. There is consistent evidence on the relationship between genetic factors and NAFLD pathogenesis<sup>[25,26]</sup>, 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 is the best example of these genetic factors associated with NAFLD pathogenesis. It has been shown to be a strong predictor of hepatic steatosis, inflammation and fibrosis independent of body mass index and insulin resistance<sup>[27]</sup>. With this insight, the traditional “two-hit” mechanism to explain disease progression in NAFLD has been challenged by the novel “multiple parallel hits” hypothesis<sup>[28]</sup>. In this version of

the pathogenetic explanation, the initial insult to the liver starts with insulin resistance and concurrent metabolic abnormalities (Figure 1). Hyperinsulinemia resulting from insulin resistance leads to the above-mentioned mechanisms of altered free fatty acid metabolism and fatty infiltration of the liver which makes the liver susceptible to numerous injurious effects. A parallel interaction and intensification between these complex injurious mechanisms lead to mitochondrial dysfunction, the 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 factors behind the progression from NAFLD to NASH. In this context, the need for an individualized pathogenesis-based approach to medical therapy for patients with NAFLD has been conceptualized in recent years. In this review, we aimed to summarize the evolution and current status of the different treatment regimens studied in patients with NAFLD.

## MANAGEMENT

### General principles

Although the increasing prevalence of NASH has led to a significant demand for a medical therapy, three decades of research on pharmacological treatment have provided limited options. The only management guideline to be published recently is by the American Association of the Study of the Liver Diseases (AASLD)<sup>[2]</sup>. 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 resis-

**Table 2** International diabetes federation definition of the metabolic syndrome

Increased waist circumference [ $\geq 94$  cm (men) or  $\geq 80$  cm (women)], with ethnic-specific waist circumference<sup>1</sup> 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

<sup>1</sup>For South Asia and Chinese patients, waist  $\geq 90$  cm (men) or  $\geq 80$  cm (women); for Japanese patients, waist  $\geq 90$  cm (men) or  $\geq 80$  cm (women). HDL: High density lipoprotein.

tance, 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 the management of components of the metabolic syndrome (Table 2)<sup>[29]</sup>. Cardiovascular risk factors are highly prevalent among patients with NAFLD and general lifestyle interventions including dietary changes and physical exercise to achieve weight loss have 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)<sup>[30,31]</sup>. 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<sup>[32]</sup>. However, most patients may experience problems regarding long-term adherence to lifestyle interventions. Only 15% of patients may achieve greater than 10% weight loss, and even then patients may regain lost weight leading to recurrence of NASH<sup>[33-35]</sup>. In addition to targeting weight loss by caloric restriction and exercise, the content of the diet is increasingly recognized as having significant importance in lifestyle modifications. In several studies it was suggested that drinks and foods containing high fructose and trans-fats should be avoided in patients with NASH<sup>[36,37]</sup>. Hepatic metabolism of fructose causes ATP depletion in hepatocytes, increased lipotoxicity and enhanced TNF expression<sup>[38]</sup>. Fructose and trans-fats are responsible for altered insulin sensitivity and increased hepatic fat accumulation which is considered the initial insult in the pathogenesis of the disease<sup>[36,37,39]</sup>.

Another important consideration regarding nutrition and lifestyle has been focused on the metabolic benefits of coffee consumption, which has recently attracted great interest among researchers and practitioners in gastroenterology. Several studies have reported an associa-

tion between coffee consumption and improvement of NASH<sup>[40,41]</sup>, however, the biological mechanisms involved in this protective effect have not yet been elucidated. The possible mechanisms of the hepato-protective effects of coffee were discussed in detail elsewhere<sup>[42]</sup>. Nonetheless, most studies investigating the effects of coffee consumption on NAFLD had methodological issues which necessitate careful interpretation 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 recommending 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 in 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 the potentially progressive course of this disease. It is of utmost importance to provide personalized treatment regimens for individual patients that can effectively target the pathophysiological pathways of NAFLD. Many studies have been conducted on the treatment of patients with NASH during the last 30 years. However, the duration of most studies was short which made selection of an optimal endpoint in the development of cirrhosis unfeasible. Previous studies 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. The 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 compared with relying solely on pharmacological therapy<sup>[43]</sup>. Pharmacological treatment options are summarized in Table 3<sup>[2,21]</sup>.

### INSULIN SENSITIZERS

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

#### Metformin

Metformin has well-known beneficial effects on insulin resistance which contributes to the 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



**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 loss 5% weight loss reduces hepatic steatosis Greater weight loss may be needed to improve hepatic inflammation
Metformin	Not recommended	Not recommended for specific therapy of NASH Should 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 NASH There are questions regarding long-term safety
RAAS inhibition (ACE-I/ARBs)	Not recommended	Not recommended for specific therapy of NASH Can be used when indicated for treatment of hypertension
Incretin mimetics	Not recommended	Not recommended for specific therapy of NASH Can be used when indicated for type 2 diabetes mellitus
Vitamin E	Recommended in selected patients	Vitamin E 800 IU/d Evidence in non-diabetic biopsy-proven NASH There is evidence regarding increased all-cause mortality associated with vitamin E usage
Statins	Not recommended	Not recommended for specific therapy of NASH Can 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 hypertriglyceridemia
Pentoxifylline	Not recommended	Inconclusive evidence May warrant further investigation

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

histology in patients with NASH. There is contradictory evidence regarding the improvement of aminotransferases under metformin therapy. Although many studies reported an improvement during treatment, others did not report similar results<sup>[44,45]</sup>. 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<sup>[44]</sup>. 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<sup>[46]</sup>. Therefore, metformin is not recommended as a primary treatment in guidelines, especially solely from the standpoint of NASH<sup>[2]</sup>. Nevertheless, it can be used in diabetic patients with NAFLD for other indications.

### Thiazolidinediones

Thiazolidinediones, including pioglitazone and rosiglitazone, are insulin-sensitizing agents that have been shown to improve liver biochemical and histologic parameters in patients with NASH<sup>[47,48]</sup>. The insulin-sensitizing effects of thiazolidinediones act on adipose tissue, muscle, and liver by increasing glucose utilization and decreasing gluconeogenesis. Although the exact mechanism by which 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<sup>[49]</sup>. The effects of thiazolidinediones on adipose tissue are particularly important in understanding their potential

benefits in patients with NAFLD. Thiazolidinediones are reported to enhance the expression of genes that increase lipid storage and reduce expression of genes associated with inflammation including interleukin-6 and TNF $\alpha$ . In addition, thiazolidinediones have regulatory effects through PPAR-gamma activation on the production of adipokines which have fundamental roles on the pathogenesis of NAFLD<sup>[50]</sup>. Several studies have investigated rosiglitazone for treatment of NASH. In summary, it has been shown that rosiglitazone improves aminotransferases and inflammation on histology, but has no beneficial effects on fibrosis stage<sup>[48,51]</sup>. Pioglitazone has also been investigated in several studies which reported improvements in aminotransferases, histological inflammation and steatosis<sup>[52]</sup>. In these studies, a regression in fibrosis stage was not observed, but there is also evidence indicating the opposite result. A randomized placebo-controlled study in non-diabetic subjects with NASH demonstrated that pioglitazone therapy for more than 12 mo improved metabolic and histologic parameters including fibrosis stage<sup>[47]</sup>. There is also a meta-analysis including 4 randomized controlled studies showing that pioglitazone, but not rosiglitazone, improves fibrosis<sup>[53]</sup>. However, a large multicenter controlled trial that randomized 247 patients with NASH into pioglitazone, vitamin E and placebo groups did not report a statistically significant improvement in fibrosis stage for either treatment arm<sup>[54]</sup>. Despite these promising results there are serious concerns regarding the 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<sup>[49,55,56]</sup>. The benefits of therapy in patients with NASH are not durable after cessation of treatment as shown by Lutchman *et al*<sup>[57]</sup>, and

the need for long-term treatment without an endpoint makes the 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<sup>[2,21]</sup>. However, safety issues should be monitored carefully during treatment.

## ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

The renin-angiotensin-aldosterone system (RAAS) has a central role in the pathogenesis of hypertension which is a component of the 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 signaling cascade<sup>[58]</sup>. Angiotensin II induced generation of reactive oxygen species which is mainly associated with activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme system, initiates and propagates the production of pro-inflammatory mediators including TNF $\alpha$ , interleukin-6, and platelet activator inhibitor 1<sup>[59]</sup>. In animal models, it has been demonstrated that angiotensin II increases hepatic steatosis, impairs mitochondrial function, and contributes to progression of hepatic fibrosis<sup>[60]</sup>. Despite this cumulative *in vitro* and *in vivo* evidence, human data on the effects of RAAS inhibition on liver fibrosis are lacking. Several studies evaluated the effects of angiotensin-converting enzyme inhibitors (ACE- I) and angiotensin receptor blockers (ARBs) on hepatic fibrosis in patients with hepatitis C under different settings. These studies were mostly retrospective and provided conflicting results<sup>[61-63]</sup>. In the NAFLD setting, no studies evaluated the effects of ACE- I, but there are a number of small scale studies which investigated the effects of ARBs in this population. In summary, limited evidence suggests that ARBs including losartan, valsartan and telmisartan may improve transaminases, hepatic steatosis and inflammation in the NAFLD setting<sup>[64]</sup>, however, there is a need for larger randomized-controlled trials to assess the long-term effects of ARBs on hepatic fibrosis in NASH. Currently, treatment with ACE- I and ARBs can only be recommended in NAFLD 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, 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<sup>[65]</sup>. Two groups of incretin mimetics were developed for the treatment of type 2 diabetes mellitus: GLP-1 analogs and dipeptidyl peptidase-4 inhibitors<sup>[65,66]</sup>. These drugs mimic the physiological effects of incretin hormones and improve glycemic control in patients with type 2 diabetes mellitus. Growing pre-clinical evidence shows that incretin-based therapies have the potential to improve hepatic steatosis in animal models of obesity and diabetes<sup>[67]</sup>. 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 ( $\alpha$ -tocopherol) is a well-known antioxidant and this feature is the best studied of its many other biological functions. Vitamin E functions as a free radical scavenger which protects polyunsaturated fatty acids from peroxidation<sup>[68]</sup>. There are also other functions of vitamin E independent of antioxidant activity, which may have a role in NAFLD pathogenesis, including inhibition of cell proliferation, platelet aggregation and monocyte adhesion<sup>[69]</sup>. In 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 the placebo and pioglitazone groups. However, only 42% of patients receiving high dose vitamin E (800 IU/d) for 96 wk achieved an improvement in histological parameters compared with 19% in placebo-treated patients<sup>[54]</sup>. A more recent 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<sup>[70]</sup>. In line with this evidence, the recent guideline by the 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<sup>[2]</sup>. However, it is crucial to note that there have been some serious concerns regarding the safety of long-term vitamin E treatment. Meta-analyses have reported an increase in all-cause mortality with vitamin E treatment, while other studies have not reported this association<sup>[71-73]</sup>. Moreover, vitamin E at a dose of 400 IU/d has been found to be associated with an increased risk of prostate cancer<sup>[74]</sup>. Physicians who choose

to initiate vitamin E therapy should consider the potential risks of long-term treatment with this drug. In particular, in patients with diabetes and significant cardiovascular risk factors, vitamin E treatment should be avoided until sufficient data on long-term safety and efficacy are established.

## STATINS

There is convincing evidence to show that cardiovascular events are the most common cause of death in patients with NAFLD, which necessitates management and optimization of cardiovascular risks in each patient<sup>[75]</sup>. However, there is a considerable degree of preoccupation with avoiding 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 with statins as indicated by relevant guidelines<sup>[76,77]</sup>. Other than the management of dyslipidemia in patients with NAFLD, evidence on the use of statins to change the natural course of NAFLD is absent. Although there are several small-scale studies that found statins benefitted liver enzymes, data regarding histological improvement is lacking<sup>[78,79]</sup>. Until more data showing histological benefit are available, there is no indication that statins should be used to specifically treat NASH.

## URSODEOXYCHOLIC ACID

Ursodeoxycholic 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 also has anti-apoptotic, cytoprotective and anti-inflammatory effects<sup>[80]</sup>. In a pilot study, a possible benefit of ursodeoxycholic acid was suggested in the treatment of NASH<sup>[81]</sup>. However, this was not confirmed in larger randomized controlled trials using histological assessment<sup>[82,83]</sup>. According to the latest guideline issued by the AASLD, ursodeoxycholic acid therapy is not recommended for the treatment of NAFLD or NASH<sup>[2]</sup>.

## 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 the treatment of NASH in several studies, and variable conclusions were reached. In a pilot study, 44 patients who participated in a weight loss program were randomized to receive orlistat or placebo. Orlistat significantly improved ALT levels and liver steatosis, however, steatosis was assessed by ultrasound only, which is an unreliable method in the absence of histological confirmation<sup>[84]</sup>. In a well-designed study, patients receiving caloric restriction and vitamin E (800

IU/d) with or without orlistat showed similar improvements in transaminases, liver steatosis and inflammation<sup>[85]</sup>. Histologic parameters were improved regardless of orlistat therapy only in patients who achieved significant weight loss ( $\geq 9\%$ ). Based on these data, the efficacy of orlistat in the 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 which 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<sup>[86]</sup>. The favorable effects of n-3 PUFAs on lipids, blood pressure, atherosclerosis, and especially on inflammation provide a hypothetical basis for research on patients with NAFLD. The experimental evidence suggests a potential benefit for omega-3 fatty acids in the treatment of NAFLD, however, the results of human studies were inconclusive due to small sample size and methodological flaws<sup>[87]</sup>. 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 in alanine aminotransferase levels<sup>[88]</sup>. Considering the available evidence, there is limited data for suggesting n-3 PUFAs for the specific treatment of patients with NAFLD.

## PENTOXIFYLLINE

Pentoxifylline inhibits the production of TNF $\alpha$  which has been associated with a possible role in the progression of NAFLD<sup>[89]</sup>. 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<sup>[90]</sup>. The largest placebo-controlled trial randomized 55 patients with biopsy-proven NASH to receive pentoxifylline 1200 mg/d or placebo<sup>[91]</sup>. 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 has evolved significantly, however, the reasons that shape the heterogeneity among patients and the factors that influence the development and progression of inflammation are not yet well understood. Although growing evidence achieved by basic research has improved our

knowledge on hepatic inflammation and fibrogenesis, translational studies have not provided a solution from bench to bedside, to help clinicians who care for patients with NAFLD. Many clinical studies have tried numerous drugs and alternative medicine, but investigators have failed to identify a safe and effective therapy for patients with NASH. As summarized, the heterogeneity of pathogenic pathways in individual patients with NASH may warrant the development of an individualized treatment according to the underlying pathogenic pathway. The differentiation of pathogenetic targets may require the development of diagnostic and prognostic biomarkers, and the identification of genetic susceptibilities. At present, evidence-based medicine provides 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 too premature to provide a pathogenesis-based management algorithm, however, it is suggested that the initial management strategy should be tailored according to individual patient characteristics including the 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 the metabolic syndrome should be targeted in those patients, particularly aiming to improve insulin resistance. Drug therapy, especially vitamin E, may be the initial choice in lean patients without insulin resistance.

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