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RESEARCH ARTICLE

NON-ALCOHOLIC FATTY LIVER DISEASE: EPIDEMIOLOGY AND TREATMENT

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disorders ranging from a fatty liverto non-alcoholic steatohepatitis (NASH) with or without fibrosis/cirrhosis. NAFLD is becoming increasingly common, with current estimates of prevalence of up to 30%. NAFLD is strongly associated with type 2 diabetes, the metabolic syndrome, obesity, and dyslipidemia, with prevalence estimated to be more than 60% in patients with these co-existing conditions.

Few treatments exist to treat NAFLD or NASHper se; rather, current management is primarily focused on treating metabolic co-morbidities. Weight loss is highly recommended. Insulin sensitizers, statins and renin-angiotensin-aldosterone system blockers may be used in patients with NAFLD, but only when indicated for type 2 diabetes, dyslipidemia and hypertension, respectively. Hepato-protective agents, such as Vitamin E and essential phospholipids may be useful adjunctive treatments in selected patients with NAFLD. Further study of these and other treatments are warranted to address the growing global burden of NAFLD and its serious clinical consequences.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver disorders (Baumeister2008) and is characterized by excessive fat accumulation in the liver (steatosis) (Ratziu2010). Up to 30% of patients with NAFLD develop non-alcoholic steatohepatits (NASH) (Fleischman 2014), in which steatosis is accompanied by liver-cell injury, inflammation, fibrosis and cirrhosis (Ratziu2010) (Figure 1). The potential for fibrosis caused by NASH may be similar to that induced by chronic hepatitis C (Charlotte 2010) and up to 20% of patients with NASH may develop cirrhosis (McCullough 2004; Harrison 2003). Other important and related consequences of NASH include increased risk of hepatocellular carcinoma and 35–85% higher mortality compared with the general population (Ekstedt 2006; Ong 2008; Chalasani 2012; Ratzui 2010).Furthermore, NASH is becomingly an increasingly common cause for liver transplantation (Agopian 2012).

Well-recognized risk factors for NAFLD include obesity, type 2 diabetes, metabolic syndrome and dyslipidemia (Chalansani 2012). Of note, NAFLD is associated with worsening insulin resistance and poor glycemic control in type 2 diabetes, progression of the metabolic syndrome and increased risk of cardiovascular disease (Ratziu 2010; Ekstedt 2006). Other common conditions also appear to be important risk factors for NAFLD including polycystic ovary syndrome, hypothyroidism and sleep apnea (Chalasani 2012).

Epidemiology of NAFLD

Current evidence suggests that up to 30% of the general population may have NAFLD (Vernon 2011; Fleishman 2014; Drapkina 2015).The prevalence of NAFLD is however difficult to determine in the general population because of varying diagnostic modalities and the lack of appropriate non-invasive screening tests. NAFLD prevalence has been estimated using liver biopsies in apparently healthy liver transplant donors (estimated prevalence of 20 to >50%), during autopsies(~15%), followingnon-invasive assessment using ultrasound imaging (~20–25%), and by hepatic triglyceride concentration (~32%) (reviewed by Vernon 2011). As an example of the limitations of some diagnostic approaches employed to estimate prevalence, elevated liver enzymeshave been used as surrogate measures of NAFLD (estimates of prevalence of ~5–21%); however, NAFLD can occur in the absence of serum alanine-aminotransferase (ALT) or aspartate aminotransferase above the upper limit of normal (ULN) (Vernon 2011).

With the growing epidemic of obesity, the prevalence of NAFLD is increasing (Vernon 2011). Data from the US National Health and Nutrition Examination Surveys conducted between 1988 and 2008 revealed a doubling in NAFLD prevalence from 5.5% in the 1988–1994 report to 11.0% in the 2005–2008 report (Younossi 2011). A more rapid increase in NAFLD prevalence was noted in alarge Japanese study (n=35,519); a 2.4-fold risefrom 13% in 1989 to 30% in 1998 (Kojima 2003).

Racial differences in the prevalence of NAFLD have been reported (Vernon 2011). Studies in the USA have noted the highest prevalence rates in Hispanics (particularly of Mexican origin) (Bambha 2012; Fleischman 2014), followed by Caucasians, African Americans (Williams 2011; Kallwitz 2008; Wagenknecht 2009; Foster 2013) and Native-Americans, who have a low rate of 2.0% or less (Fischer 2009; Bialek 2008). The reasons for ethnic differences in NAFLD prevalence are currently unclear; however, genetic variations in the PNPLA3 gene, which encodes adiponutrin, may play a role, accounting for up to 72% of the ethnic variation (Romeo 2010).

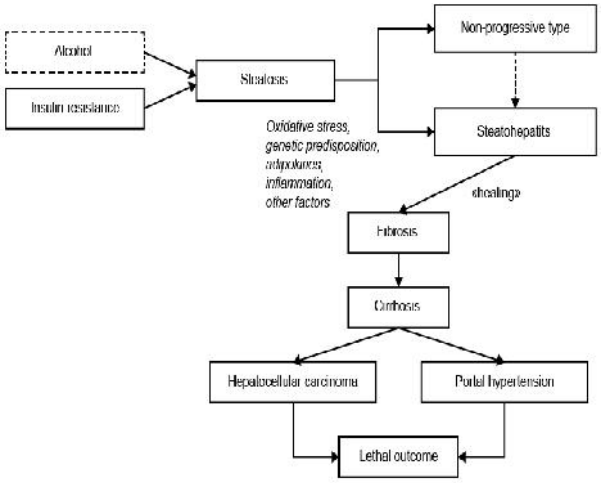

Figure 1 The pathologic progression of NAFLD (Tolman& Dalpiaz 2007)

NAFLD is the most common chronic liver disease in Western countries, but it also becoming prevalence in other regions, for example, in the Asia-Pacific region and also in countries, such as China and Brazil (Figure 2) (Gao 2013). We conducted the large-scale DIREG-1 study of the prevalence of NAFLD in the Russian Federation, based on liver ultrasound findings (Drapkina 2015). In 30,787 primary care patients, the general prevalence of NAFLD was 27% (Drapkina 2015, Ivashkin 2010). Of note, NAFLD was diagnosed in 64.3% of patients with type 2 diabetes and 61.5% of patients with obesity and in 66.9% with the metabolic syndrome. Most studies agree that type 2 diabetes and the metabolic syndrome and their clinical manifestations

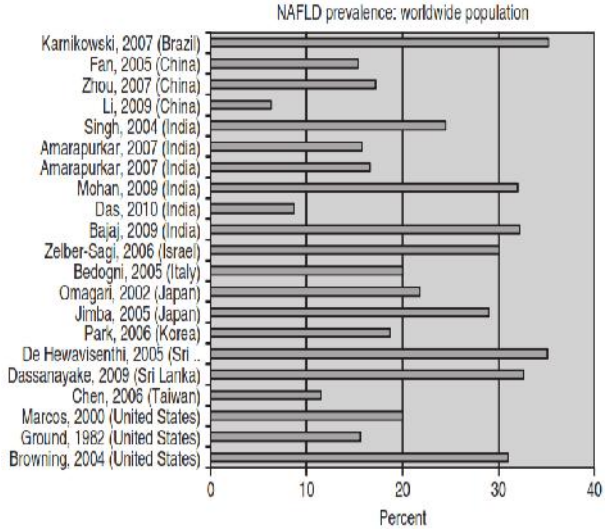

Figure 2 Prevalence rates of NAFLD in different regions of the world (Vernon 2011)

are associated with NAFLD (Kojima 2003; Bedogni 2005; Das 2010; Li 2009; Bajaj 2009; Dassanayake 2009; Mohan 2009; Drapkina2015).As many as two-third of patients with type 2 diabetes may have NAFLD (Leite 2009), and prevalence rates of up to 98% have been reported for non-diabetic obese patients (Ong 2005; Machado 2006; Colicchio 2005; Beymer 2003).

In the DIREG-1 study, the highest NAFLD prevalence across the age groups studied was found in patients aged 50 to 80 years (Dapkina 2015).Several studies have reported that the prevalence of NAFLD and the likelihood of disease progressionincreases with age (Caballeria 2010; Kojima 2003; Ong 2008; Adams 2004; Hashimoto 2005; Ascha 2010; Frith 2009).In contrast, one study showed no difference in age between patients with NAFLD demonstrating disease progression and those who did not (Hui 2005). In a Japanese study, the prevalence of NAFLD increased with age in women, but not in men (Kojima 2003). Most studies indicate that NAFLD prevalence is approximately twice as high in men than women (Caballeria 2010; Kojima 2003; Chen 2008; Sorrentino 2004).

Treatment

Guidelines for the management of NAFLD were published by the American Gastroenterological Association, American Association for the Study of Liver Diseases and American College of Gastroenterology in 2012 (Chalasani 2012); however, the evidence on which the recommendations are based is generally limited due to the paucity of data from well-controlled trials.Of note, there are no Food and Drug Administration (FDA)-approved agents available for the indication of NAFLD. The Chinese Society of EndocrinologyStudy Group of Liver and Metabolism published a consensus statement on the diagnosis and management of NAFLD in 2013 (Gao 2013), with generally similar recommendations to those in the US practice guidelines (Gao 2013; Chalasani 2012). Elsewhere, guidelines are lacking in Europe and the rest of the world, and there is little consensus on treatment.Of note, almost all studies on NAFLD therapies to date have been conducted in

Table 1 Summary of treatment options in patients with NASH (Baran&Akyuz 2014)

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 inhibitor (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.

small numbers of patients and have applied "soft" endpoints (eg, metabolic parameters or biopsy findings) rather than hard clinical endpoints, such as rates of mortality or hepatic complications. Furthermore, many studies have lacked an adequate control group.

The current strategy of NAFLD therapy includes lifestyle changes, weight loss and the use of insulin sensitizers in some patients. In selected cases, the use of antioxidant and cytoprotective drugs, polyunsaturated fatty acids, bile acids, angiotensin II receptor blockers (ARBs) or statins may be beneficial (Table 1).

Lifestyle modification and body weight reduction

Improved diet, physical activity and normalization of body weight are recognized as key to the treatment of NAFLD and NASH. Recent studies in NAFLD patients have demonstrated a reduction in the severity of steatosis and improvements in inflammation with lifestyle changes (Eckard2013), but rarely a benefit on fibrosis assessed by biopsy (Hickman 2004; Ueno 1997; Zelber-Sagl 2007); however, follow-up periods in these studies were relatively short. In the Diabetes Prevention Program (DPP) study, measures aimed at lifestyle modificationreduced the incidence of diabetes in patients with insulin resistancemore than metformin (Knowler 2002).

A meta-analysis of 517 studies of body weight reduction in NAFLD reported reductions in aminotransferases and hepatic steatosis assessed by ultrasound with lifestyle changes; however, only 15 of the studies were found methodologically adequate (Wang 2003). In more recent studies, significant weight loss (>5-10% of body weight) was associated with improvement of insulin resistance and fatty acid metabolism (Marra 2013; Thoma 2012). However, few patients (around 15%) are able to achieve a weight loss of 10% (Peng 2011; Franz 2007; Centis 2010) limiting the success of this approach. For some patients, body-weight reducing preparations or bariatric surgery (in case of morbid obesity and/or cardio-vascular comorbidity) are justified. One study of orlistatin NASH patients suggested a benefit on steatosis measured by ultrasound (Zelber-Sagi 2006), although results were inconsistent with another study that failed to show a benefit (Harrison 2009). Further data are required to determine if orlistat has a positive effect on steatosis, but it may be a useful treatment for promoting weight loss in obese patients with NAFLD.

Modification of diet to one high in monounsaturated and omega-3 polyunsaturated fatty acids, low in saturated fatsand high in fruit, vegetables and nuts is considered ideal for NAFLD patients (Musso2003; Esposito 2004; Spadaro 2008).NASH patients should avoid a omega-3-deficient diet and drinks and foods containing high fructose and transfat, which alter insulin sensitivity and lipid metabolism (Simopoulos 2013).

Insulin sensitizers

Metformin

Metformin is well known as a first-choicetreatment fortype 2 diabetes mellitus (Inzucchi 2015). Metformin activates AMP-kinase and its mechanism of action predominately involves reducing hepatic glucose production (Inzucchi 2012). Metformin is generally considered weight-neutral with chronic use.

Metformin for the treatment of NAFLD has been assessed in several studies, with control groups receiving nutrition recommendations or vitamin E or placebo(Lavine 2011; Haukeland 2009; Loomba 2009; Marchesini 2001;Uygun 2004; Bugianesi 2005;Duseja 2007). While some studies demonstrated an improvement in transaminase levels (Marchesini 2001; Schwimmer2005;Uygun 2004; Bugianesi 2005;Duseja 2007), other studies showed no change (Haukeland 2009; Loomba 2009). A meta-analysis including three randomized controlled trials of metformin in NAFLD patients with available histological data showed no difference between active treatment and placebo on steatosis, inflammation or fibrosis (Rakoski 2010). Consequently, although metformin may be used to treat concurrent diabetes in NAFLD patients, it is not recommended as a primary treatment of NASH (Chalasani 2012; Gao 2013).

Thiazolidinediones

Thiazolidinediones (TZDs) are activators of peroxisome proliferator-activated receptor (PPAR) ɣthat improve insulin sensitivity in skeletal muscle and reduce hepatic glucose production (Inzucchi 2012). They are also capable of inhibiting lipogenesis in hepatocytes (Sharma 2007).

Studies of rosiglitazone in patients with NASH demonstrated improvements in liver biochemistry and histological parameters but no effect on stage of fibrosis (Aithal 2008; Ratziu 2008; Neuschwander-Tetri2003); however, rosiglitazone was withdrawn from most markets worldwide in 2010 because it was associated with increased cardiovascular mortality (Nissen 2007). Studies with pioglitazone have produced inconsistent results regarding it effect on fibrosis in NASH patients. One study in non-diabetic NASH patients demonstrated an improvement in metabolic and histological parameters including stage of fibrosis (Aithal 2008). In contrast, no effect on fibrosis was observed in another randomised trial (Sanyal 2010).

US guidelines suggest that pioglitazone can be used to treat patients with biopsy-prove NASH, but cautions that the evidence is based on studies that included largely non-diabetic patient populations, and that the long-term safety and efficacy of pioglitazone in patients in NASH has not been established (Chalasani 2012). There are safety concerns with the long-term use of TZDs, including weight gain, congestive heart failure, cardiovascular morbidity, increased bone fracture risk and increased incidence of bladder cancers (Yki-Jarvinen 2009; Bilik 2010; Dormandy 2009). Moreover, not all patients respond to TZD therapy (Nissen 2007), and the increased weight gain associated with these agents may reduce patient compliance with therapy.

Incretin analogues

Glucagon-like peptide-1(GLP-1)is secreted in the intestine during the postprandial period. Injectable GLP-1 receptor agonists mimic the effects of endogenous GLP-1, stimulating

pancreatic insulin secretion in a glucose-dependent fashion, suppressing pancreatic glucagon output, slowing gastric emptying and decreasing appetite (Inzucchi 2012). An advantage of GLP-1 receptor agonists is modest weight loss. Dipeptidyl peptidase 4 (DPP-4) inhibitors, administered orally, enhance circulating concentrations of active GLP-1 (Inzucchi 2012). Their major effect appears to be in the regulation of insulin and glucagon secretion; however, they are weight neutral.

The efficacy of incretinmimetics for improving steatosis has been demonstrated in animal models of obesity and diabetes (Ding 2006; Samson 2013). A recent pilot study investigated the effects of the GLP-1 receptor agonist, liraglutide, in 19 Japanese patients with NASH and glucose intolerance (Eguchi 2014). Liraglutide significantly improved liver function and histological features; however, further large-scale studies are needed.

Dyslipidemia therapies

Statins

Statins are first-line therapy for the treatment of dyslipidaemia, a major risk factor for cardiovascular disease (Reiner 2011). Since patients with NAFLD are at high risk of cardiovascular disease, many are prescribed statins to control abnormal lipid levels. Statins may also have effects beyond lipid lowering. Their so-called pleiotropic properties may include anti-inflammatory and anti-oxidative effects, which may confer additional benefits for NAFLD patients (Nseir 2013).

Elevated hepatic transaminases (>3xULN) occur in 0.5–2.0% of statin-treated patients; however, whether these elevations are an indicator of true hepatotoxicity has not been determined (Reiner 2011). The use of statins is often avoided in patients with elevated transaminases and liver disease (Baran&Akyuz 2014), and guidelines recommend that statin therapy be discontinued in patients with persistent transaminase levels above 3 x ULN (Reiner 2011).

Several small statin studies have been conducted in patients with NAFLD or NASH (Nseir 2013; Athyros 2010; Foster 2011). These indicate that statins are safe and effective dyslipidemia agents in this patient group. In addition, the majority of studies reported an improvement in levels of AST and ALT and a decrease in the degree of steatosis in statin-treated patients (Nseir 2013; Athyros 2010; Foster 2011); however, large randomized controlled trials are needed to confirm these findings. Based on current evidence, US guidelines recommend the use of statins in NAFLD patients to treat dyslipidemia, but not to treat NAFLD per se (Chalasani 2012).

Ezetimibe

Ezetimibe, an intestinal cholesterol absorption blocker, has shown positive effects on steatosis in pre-clinical studies (Ushio 2013; Wang 2014). However, the results of recent small clinical studies with ezetimibe in NAFLD patients have been inconclusive. No effects of ezetimibe on liver fat, liver histology or hepatic transaminase levels were reported in the MOZART trial (Loomba 2014). Another study observed improvement in hepatic fibrosis, but the study was terminated early because of a significant elevation in glycated hemoglobin level with ezetimibe (Takeshita 2014).

Ursodeoxycholic acid

Ursodeoxycholic acid, a secondary bile acid produced as a by-product by intestinal bacteria, has been shown to be effective in the non-surgical treatment of cholesterol gallstones and primary biliary cirrhosis (Xiang 2013). It has a number of liver-protective properties, including anti-apoptotic effects, lowering serum tumor necrosis factor (TNF)-α concentrations,decreasing endoplasmic reticulum stress andimproving hepatic insulin sensitivity (Xiang 2013).A pilot study in patients with NASH suggested a potential benefit of ursodeoxycholic acid (Laurin 1996); however, this was not confirmed in subsequent larger randomized controlled trials (Lindor 2004; Leuschner 2010). A recent systematic review of studies of ursodeoxycholic acid in NAFLD patients suggested that it may be effective, particularly when combined with other drugs; however, the heterogeneity of the study results precluded further meta-analysis (Xiang 2013). Further well-designed trials are needed to fully evaluate the efficacy and safety of ursodeoxycholic acid as part of treatment regimens for steatohepatitis.

Oxidative stress and antioxidants

Oxidative stress and free radicals have been implicated in the pathogenesis of NAFLD and NASH and there is an association between the levels of lipid oxidation products and disease state (Sumida 2013). Vitamins E and C and also betaine and N-acetylcysteine have been tested in the treatment of steatohepatitis (Sanyal 2010; Lavine 2011; Oz 2006; Miglio 2000; Abdelmalek 2006; Gulbahar 2000). Based on observations that vitamin E improved inflammation in non-diabetic patients with biopsy-proven NASH (Sanyal et al 2010),US societies recommend vitamin E (800 IU/day) in this patient group (Chalasani 2012).However, it is worth noting that the evidence for the efficacy of vitamins is limited and the use of high doses of vitamin E (more than 400 units daily) is associated with a statistically reliable increase in morbidity from all causes (Miller 2005). Chinese guidelines state that vitamin E can be considered as the first-line liver protectant (Strength 1; Evidence B) (Gao 2013).

Essential phospholipids

Membrane fluidity plays a significant role in the function of biological membranes, and fluidity is influenced by the composition of phospholipids. Essential phospholipids (EPL) contain a highly purified extract of polyenylphosphatidylcholine (PPC) molecules from soybean (Gundermann 2011).The main active ingredient is thought to be 1,2-dilinoleoylphosphatidylcholine (DLPC). In animal models, EPL influenced membrane-dependent cellular functions and showed anti-oxidant, anti-inflammatory, anti-fibrotic, apoptosis-modulating, membrane-protective, regenerative, cell-signaling and receptor-influencing, as well as lipid-regulating effects (Gundermann 2011, Arvind 2006; Sas 2013; Dajani 2013).

Omega-3 fatty acids

Several small studies have shown an association between intake of omega-3 fatty acids (1–2 g/day) and a reduction in the degree of steatosis, and ALT and AST levels (Parker 2012; Spadaro 2008; Tanaka 2008). Improvements in plasma TNFα, insulin resistance and fibrosis have also been observed (Spadaro 2008; Tanaka 2008).

Ethyl-eicosapentanoic acid (EPA-E), a synthetic polyunsaturated fatty acid, was recently investigated in a phase 2b multicenter, prospective, double-blind, randomized, placebo-controlled trial in 243 patients with NASH (Sanyal 2014). Subjects received placebo, low-dosage EPA-E (1800 mg/day), or high-dosage EPA-E (2700 mg/day) for 12 months.The primary efficacy end point was NAFLD activity score ≤ 3, without worsening of fibrosis; or a decrease in NAFLD activity score by ≥ 2 with contribution from >1 parameter, without worsening of fibrosis, 1 year after the last dose of EPA-E or placebo was given. A similar proportions of subjects in each group met the primary end point (40%, 37%, and 35.9% for placebo, low-dosage, and high-dosage EPA-E, respectively). EPA-E had no significant effects on steatosis, inflammation, ballooning, fibrosis scores, levels of liver enzymes or insulin resistance; however, high-dosage EPA-E significantly reduced levels of triglyceride (P=0.03). Omega-3 fatty acids are not recommended as a specific treatment for NAFLD, but may be considered as first-line agents to treat hypertriglyceridemia (Chalasani2012).

Renin-angiotensin-aldosterone systeminhibitors

The renin-angiotensin-aldosterone (RAAS) system plays a central role in blood pressure control and influences intracellular insulin signaling by several mechanisms (Baran&Akyuz 2014). Consequently, it may be an important target for treatment of the metabolic syndrome and NAFLD. Angiotensin II is a powerful pro-oxidant and pro-fibrotic factor. Animal models have demonstrated the influence of angiotensin II in hepatic steatosis and fibrosis (Morris 2013). There are few clinical studies on the efficacy of angiotensin receptor blockers (ARB) or angiotensin-converting enzyme (ACE) inhibitors in NAFLD. The ARB, losartan, was associated with a decrease in the degree of inflammation, necrosis and fibrosis based on the liver biopsy data in a small-scale study in NASH patients (Yokohama 2004).

A retrospective study in liver transplant patients observed a lower frequency of the development of NAFLD in patients prescribed ACE inhibitors (Seo 2007).Furthermore, in a recent cross-sectional study in 290 hypertensive patients with biopsy proven NAFLD, those on baseline RAAS blockers had less advanced hepatic fibrosis, potentially suggesting a beneficial effect of RAS blockers in NAFLD..Currently, treatment with ACE inhibitors and ARBs can only berecommendedinNAFLDpatientswithanestablishedindicatio nofanti-hypertensive therapy.

Anti-cytokines

Inflammatory cytokines, including

TNF-α, play an important role in the pathogenesis of steatohepatitis (Baran&Aykus 2014).A systemic review was conducted onthe effects of the anti-TNF-α agent, pentoxifylline, in patients with NAFLD (Li 2011).In total, 6 randomized controlled trials and 4 prospective cohort studies were analyzed, and it was concluded that pentoxifylline reduces AST and ALT levels and may improve liver histology in patients with NAFLD (Li 2011). However,pentoxifylline is poorly tolerated, with up to 40% of patients discontinuingtreatment because of gastrointestinal side effects (Adams 2004).

Pre- and probiotics

Experimental studies on biological models demonstrated that intestinal bacterial endotoxins damaged liver to a less degree in the presence of pre-and probiotics (Wang 2013; Rishi 2011).Small clinical studies have suggested benefits of probiotics in NAFLD patients(Aller 2011; Wong 2013; Alisi 2014).In one placebo-controlled study in obese children with NASH (n=44), fatty liver severity assessed by ultrasonography was improved with VSL#3, a mixture of eight probiotic strains(Alisi 2014). No decrease in ALT was observed, and histological studies were not performed (Alisi 2014).

CONCLUSIONS

The prevalence of NAFLD has increased rapidly in parallel with trends of obesity, type 2 diabetesand the metabolic syndrome. As the prevalence of NAFLD grows, it is expected that there will be an increasing burden of liver-related and cardiovascular mortality. Effective strategies are needed to treat NAFLD and prevent progression to NASH; however, few such approved treatments are available. Weight loss is highly recommended in the management of NAFLD. Other management strategies target additional risk factors and include insulin sensitizers, statins and renin-angiotensin-aldosterone system blockers, which may be used in NAFLD when indicated for respective co-morbidities. Hepato-protective agents, such as Vitamin E and essential phospholipids may be useful adjunctive treatments in selected patients. Further clinical studies are needed to fully confirm the effects of existing agents and to provide additional evidence-based strategies to manage NAFLD and NASH.

Conflict of Interest: None

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