Treatment of non-alcoholic fatty liver disease : Can we already face the epidemic ?

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disorder in the Western world. It comprises a disease spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), which may progress to fibrosis, cirrhosis and its complications like hepatocellular carcinoma and liver failure. In addition, evidence is accumulating that NAFLD is an independent risk factor for cardiovascular diseases. Progress has been made in unraveling the pathogenesis, which paved the way for several clinical trials for the treatment of NAFLD. Life style intervention consisting of increased physical activity and dietary modifications, remain the cornerstone of the treatment. Some pharmacological agents show promising results, although on the basis of recent clinical trials no firm conclusions can be drawn. Suggestions for treatment in some particular groups of patients can be made. Further research is required to face the burden of NAFLD, which is already present in epidemic proportions. (Acta gastroenterol. belg., **2013**, 76, **200-209**).

Key words : non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, NAFLD, NASH, clinical trials, treatment.

Introduction

In the Western society non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disorder. It encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol use, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis with its complications like hepatocellular carcinoma and liver failure. Steatosis is defined as triglyceride accumulation in at least 5% of hepatocytes, whereas NASH is hallmarked by the presence of steatosis, together with hepatocellular ballooning and inflammation (1).

It is estimated that NAFLD is present in 20 to 30% of the general population (2). NAFLD is mainly associated with obesity, insulin resistance, dyslipidemia and hypertension and thus not surprisingly NAFLD is considered as the hepatic manifestation of the metabolic syndrome (3). Even in the pediatric population NAFLD is a growing medical problem, with an overall prevalence of at least 3% (4). The prevalence of NASH in the general population is more difficult to determine. The diagnosis of NASH requires a liver biopsy, unlike steatosis, which can be detected noninvasively by imaging modalities such as an abdominal ultrasound. According to the available data, it is estimated that 2 to 3% of the general population is affected by NASH (5).

The clinical significance of NAFLD is, besides its high prevalence, determined by its complications. Several long-term follow-up studies demonstrated a higher mortality in patients with NAFLD compared to the general population, attributable to both cardiovascular and liver-related causes (6-8). Evidence is accumulating that NAFLD is associated with an increased risk of cardiovascular disease, independently of the traditional risk factors such as the components of the metabolic syndrome (9). Liver disease is another important contributor to death among patients with NAFLD, being the third most common cause and accounting for 13% of all deaths in the study of Adams and colleagues (8). In the general population liver disease is only the 13th leading cause of death, accounting for less than 1% of all deaths (8). The high prevalence of NAFLD also limits the availability of donor livers. Liver grafts with severe steatosis have higher rates of primary non-functioning and poorer graft survival, possibly as a result of the inability to initiate repair and regeneration mechanisms after liver transplantation (10).

Simple steatosis is considered to be a relatively benign condition with only a limited risk of progression (11). Among patients with simple steatosis 12 to 40% will develop NASH with some fibrosis after 8 to 13 years. In contrast, of the patients with NASH and early fibrosis, about 15% will develop cirrhosis over the same time period (5). Therefore discrimination between those two disease stages has major prognostic implications. However, besides the practical issue of the invasiveness, the result of liver biopsy (the so-called gold standard to diagnose NASH) is subject to sampling variability, interpretation error and the frequent disappearance of histological features of NASH in progressive liver disease (12,13). Therefore, there is an extensive search for non-invasive biomarkers and diagnostic tools, such as transient elastography, to estimate disease stage (14,15). The risk factors for fibrosis progression in NASH remain unclear. The presence of several metabolic disorders (amount of visceral fat estimated by waist circumference, a lowered high-density lipoprotein (HDL), increased triglycerides, arterial hypertension and insulin resistance), abnormal

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transaminases and older age are all reported to be associated with progressive, severe liver disease (3,16). A recent systematic review including 10 studies with a total of 221 patients with NASH, found that the only independent predictors of progression to advanced fibrosis were the presence of inflammation on initial liver biopsy and older age (17). It is noteworthy that hepatocellular carcinoma (HCC) can be present even in the absence of severe fibrosis in patients with metabolic syndrome, which might have implications for screening strategies in these patients (18).

Progress has been made in unraveling the pathogenesis of NAFLD/NASH (19,20). It revealed a complex interplay between different pathogenic mechanisms like lipotoxicity, oxidative stress, insulin resistance, endoplasmic reticulum-stress, local vascular mechanisms (hepatic vascular flow changes and endothelial dysfunction) and adipocyte and gut mediated inflammatory pathways. Taken together with the current lack of evidence-based treatment options, this explains the abundance of potential therapeutic strategies which are currently under investigation consisting life style intervention, pharmacological treatment and bariatric surgery. In this review, we will focus on several recently published clinical trials.

Treatment

Life style intervention : physical activity, diet modification and substance use

The beneficial effect of life style intervention, focused on both dietary and exercise habits, is mainly demonstrated in patients with impaired glucose tolerance or diabetes (21,22). NAFLD is considered the hepatic manifestation of the metabolic syndrome and insulin resistance is a key mechanism in its pathogenesis. Therefore it is believed that life style intervention might have favorable effects in patients with NAFLD.

Recently Promrat *et al.* (23) randomized 31 overweight or obese patients with biopsy-proven NASH to receive intensive lifestyle intervention (aimed at changing both eating and exercise behavior) or structured education (control). After 48 weeks, patients in the intensive life style intervention arm lost significantly more weight and a higher proportion of these patients had improvements in liver histology, particularly those who achieved the study weight loss goal of at least 7%. However, there was no improvement in fibrosis.

Although weight loss remains fundamental to the management of NALFD, recent data showed beneficial effects of aerobic exercise and resistance training independent of weight loss (24-27). In a randomized controlled trial (RCT) with a study time of 3 months, life style counseling interventions in patients with NAFLD (diagnosis based on abnormal liver enzymes) were effective in improving physical activity behavior, liver enzymes and other metabolic indices independent of weight loss ; especially in patients increasing or maintaining their reported physical activity to ≥ 150 minutes/week (24). This is an important finding because weight loss via diet and/or physical activity is typically modest (1-8 kg) and returns to baseline within 1-3 years (28,29). Exercise per se enhances insulin sensitivity, modifies serum lipids, improves mitochondrial biogenesis and increases whole-body fatty acid oxidation (28). One retrospective study showed that exercise intensity may be more important than duration or total volume (30). Furthermore, exercise – in particular resistance training – may beneficially influence body composition (increase fat-free mass and decrease fat mass), which is not always reflected in a decrease of total body weight (31). Weight loss is considered as safe, although attention must be paid for too rapid weight loss because this has been associated with worsening of liver disease (32,33). In particular after bariatric surgery, too rapid weight loss even can lead to hepatic decompensation (34,35). Weight loss should not exceed approximately 1.6 kg per week in adults.

Diet modifications consist of lowering total calorie intake and altering diet composition with respect to dietary lipids and carbohydrates (36). Sources of saturated fatty acids (SFA) (butter fat, pork meat, lard, sausages, chicken skin) should be avoided. The intake of fish, nuts, seeds and grains should be promoted to increase the n-3 poly-unsaturated fatty acids (PUFA) intake and the n-3 PUFA/n-6 PUFA ratio. Olive oil (rich in mono-unsaturated fatty acids) should be preferred to safflower-derived oils (rich in SFA and n-6 PUFA) (36).

Fructose consumption (the two major dietary sources are table sugar (sucrose) and high-fructose corn syrup primarily in the form of soft-drinks) has been identified as a modifiable environmental risk factor for NAFLD and thus should be limited (37,38). Factors contributing to fructose-induced NAFLD are the induction of insulin resistance, hepatic de novo lipogenesis and oxidative stress, the formation of advanced glycation end products (AGE's) and the promotion of intestinal translocation of endotoxin (39,40). The effect of alcohol intake on the pathogenesis of NAFLD appears to be ambiguous. Alcohol consumption deteriorates the natural course of NAFLD. In patients with NASH-cirrhosis, alcohol intake is identified as a risk factor for HCC-development (41). But in contrast – as is known for cardiovascular diseases – moderate alcohol intake may be protective against NAFLD/NASH, possibly due to its beneficial effect on insulin resistance (41,42). However, the latter was shown in a healthy cohort and the diagnosis of NAFLD was based only on elevation of transaminases. In addition, coffee intake might also have favorable effects (43). Recent studies showed that cigarette smoking is an independent risk factor for onset of NAFLD and is associated with increased fibrosis severity, suggesting it may accelerate disease progression (44,45). This is in contrast with former studies, which found no correlation (46,47). Nonetheless, smoking should be strongly discouraged in all NAFLD patients because of their increased cardiovascular risk.

Bariatric surgery

Effect of bariatric surgery on NAFLD was evaluated in a systematic review and meta-analysis in 2008, concluding that steatosis, steatohepatitis, and fibrosis appear to improve or completely resolve in the majority of patients after bariatric surgery-induced weight loss (48). This conclusion was not confirmed in a recent Cochrane review due to the lack of high-quality randomized clinical trials and the concern that some patients with NAFLD treated with bariatric surgery even showed a deterioration of fibrosis scores (49). The possible association of worsening of fibrosis with weight loss by bariatric surgery is also suggested in a recent 5-year prospective study in severely obese patients after bariatric surgery (50). Among histologic features of NASH, ballooning and steatosis improved, whereas inflammation remained unchanged and fibrosis worsened at 5-year period. Whether this worsening represented the natural history of NASH possibly related to the patient characteristics at time of inclusion or was due to the (too rapid) weight loss induced by bariatric surgery remains unclear (Table 1). However, the same research group recently showed improvement of steatosis, inflammation and fibrosis between 0 and 1 year after bariatric surgery with no aggravation between 1 and 5 years (51).

Although results of bariatric surgery may be promising in the treatment of NAFLD – in addition to its beneficial effects on the other components of the metabolic syndrome – and seems reasonable to use in a selected subpopulation, high-quality randomized clinical trials are still needed to draw a definitive conclusion.

Insulin-sensitizers

Metformin

Marchesini *et al*. (52) showed in a pilot study that metformin improved insulin sensitivity, reduced transaminase levels and decreased liver volume in patients with NASH. In 2004 the first study evaluating the effect of metformin treatment on hepatic histopathology in NASH patients was performed (53). Six-month therapy with metformin (1700 mg/d) and diet led to a greater improvement in insulin resistance and liver enzymes than dietary treatment alone. More patients in the metformin group had improvement in necroinflammation, but no statistical significance was achieved. Another RCT in non-diabetic NAFLD patients (metformin max. 2 g/d versus vitamin E 800 international units (IU)/d or prescriptive, weight reducing diet for 12 months) showed an improvement of aminotransferase levels in all groups, in association with the weight loss, but the effects in the metformin arm were larger (54). A control biopsy (performed in only the minority of metformin-treated cases) showed a significant decrease in liver fat, necroinflammation and fibrosis. However, these histological improvements were not compared to either of the controls. In contrast with these studies, a recent randomized double-blind, placebo-controlled trial in patients with NAFLD comparing metformin (max. 3000 mg/d) with placebo for 6 months, demonstrated no improvement in liver steatosis either assessed histologically or by CT (55). Moreover, there were no significant differences in serum transaminases and markers of insulin resistance. Nevertheless, metformin was associated with favorable effects on glucose and cholesterol levels and significant weight loss.

In conclusion, metformin trials for the management of NASH provided conflicting results and therefore further studies are needed (Table 2).

Thiazolidinediones : selective ligands of the nuclear transcription factor peroxisome-proliferator-activated receptor gamma (PPAR-gamma-agonists)

Pioglitazone

Belfort *et al*. (56) randomly assigned 55 patients with impaired glucose tolerance or type 2 diabetes and histologically proven NASH to 6 months of treatment with a hypocaloric diet plus pioglitazone (45 mg/d) or a diet plus placebo for 6 months. Pioglitazone compared to placebo was associated with improvement in histological findings with regard to steatosis, ballooning necrosis and inflammation. Fibrosis progression did not differ significantly. More recently, 74 nondiabetic patients with histologically

Table 1. — **Studies on the effect of life style intervention and bariatric surgery in NAFLD**

Author, Year	n	Intervention	Duration	Outcome
Promrat *et al*., 2010 (23)	31	Intensive life style intervention (diet + physical activity)	48 wk	↓ NAS, ↓ steatosis, ↓ bodyweight, ↓ ALT; in addition ↓ inflammation and ↓ ballooning when ≥ 7% weight loss; no reduction fibrosis
St. George *et al*., 2009 (24)	141	Low- or moderate-intensity lifestyle intervention	3 mo	↓ liver enzymes, ↓ ferritin and ↓ other metabolic parameters especially when increasing/maintaining reported physical activity to ≥ 150 minutes/week; independent of weight loss
Johnson *et al*., 2009 (25)	19	Aerobic exercise Training	4 wk	↓ visceral adipose tissue volume, ↓ hepatic TG, ↓ plasma FFA, no change body weight nor HOMA-IR
Mathurin *et al*., 2009 (50)	381	Biliointestinal bypass, gastric bypass, gastric band surgery	5 yr	↓ steatosis, inflammation unchanged, ↑ fibrosis, ↓ weight, ↓ transaminases, ↓ diabetes, ↓ blood pressure, ↓ plasma lipids, ↓ IR

NAS, NAFLD Activity Score ; ALT, alanine aminotransferase ; TG, triglycerides ; FFA, free fatty acids ; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance ; IR, insulin resistance.

Table 2. — **Studies on the effect of insulin-sentitizers in NAFLD**

Author, Year	n	Intervention	Duration	Outcome
Metformin				
Marchesini *et al*., 2001 (52)	26	metformin (1500 mg/d)	4 mo	↓ ALAT, ↓ IR, no follow-up biopsy sampling
Uygun *et al*., 2004 (53)	36	metformin (1700 mg/d)	6 mo	↓ transaminases, ↓ insulin, ↓ IR, (↓ necroinflammation although NS)
Bugianesi *et al*., 2005 (54)	110	metformin (2 g/d)	12 mo	↓ steatosis, ↓ necroinflammation and ↓ fibrosis, ↓ transaminases
Haukeland *et al*., 2009 (55)	48	metformin (max. 3000 mg/d)	6 mo	no significant changes in liver steatosis, NAS, transaminases nor markers of IR
Pioglitazone				
Belfort *et al*., 2006 (56)	55	pioglitazione (45 mg/d)	6 mo	↓ steatosis, ↓ ballooning and ↓ inflammation, ↓ transaminases, ↓ glycemic parameters, no significant change in fibrosis
Aithal *et al*., 2008 (57)	74	pioglitazone (30 mg/d)	12 mo	↓ fibrosis, ↑ weight, ↓ glucose, ↓ HbA1C, ↓ insulin C, ↓ ALT, ↓ g-GT, ↓ ferritin, no significant change in steatosis nor inflammation
Sanyal *et al*., 2010 (58)	247	pioglitazone (30 mg/d)	96 wk	no significant overall histological improvement (although p = 0,04), ↓ steatosis, ↓ inflammation and ↓ ballooning, ↓ transaminases, no ↓ fibrosis
Rosiglitazone				
Ratziu *et al*., 2008 (59)	63	rosiglitazone (8 mg/d)	12 mo	↓ steatosis, ↓ transaminases, no change other histologic lesions
Ratziu *et al*., 2010 (60)	53	rosiglitazone (8 mg/d)	2 yr	↓ insulin, ↓ HOMA-IR, ↓ ALT, no significant change NAS, ballooning nor fibrosis
Torres *et al*., 2011 (61)	137	rosiglitazone (8 mg/d)	48 wk	↓ steatosis, ↓ necroinflammation, ↓ ballooning, ↓ fibrosis, ↓ NAS, ↓ transaminases, ↑ glycemic control

ALT, alanine aminotransferase ; IR, insulin resistance ; NS, not significant ; NAS, NAFLD Activity Score ; g-GT, gamma-glutamyl transpeptidase ; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance.

proven NASH were randomized to 12 months of standard diet, exercise, and either placebo or pioglitazone (30 mg/d) (57). Treatment with pioglitazone was associated with a reduction in hepatocellular injury and fibrosis. Sanyal *et al*. (58) showed no improvement in fibrosis with pioglitazone in a large trial (n = 247) comparing pioglitazone (30 mg/d) with vitamin E and placebo for 96 weeks. However, treatment with pioglitazone was associated with highly significant reductions in steatosis, inflammation, and hepatocellular ballooning, as well with improvements in insulin resistance and liver-enzyme levels.

Rosiglitazone

In 2008 the FLIRT trial consisted of 63 patients with histologically proven NASH, who were randomly assigned to treatment with rosiglitazone (8 mg/d) or placebo for one year (59). There was a significant improvement in steatosis and aminotransferase levels, but no improvement in necroinflammatory lesions or fibrosis. The FLIRT 2 extension trial concluded that rosiglitazone (8 mg/d) has a substantial antisteatogenic effect in the first year of treatment without additional benefit with longer therapy, despite a maintained effect on insulin sensitivity and transaminase levels (60). This suggests that improving insulin sensitivity may not be sufficient for improving liver injury. In a recent study, 48 weeks of therapy with rosiglitazone (8 mg/d) led to improvement in steatosis, hepatocellular inflammation, ballooning degeneration, and fibrosis ; however, in order to increase the beneficial effect, combination therapy with rosiglitazone and metformin or rosiglitazone and losartan conferred no greater benefit than rosiglitazone alone with respect to histopathology (61).

In a recent meta-analysis of randomized trials, pooled results demonstrated that thiazolidinediones improved histological steatosis and inflammation but not fibrosis (32) (Table 2). Their beneficial effects disappear at discontinuation, suggesting that long-term treatment is needed (62). This is an important issue because of the not unfrequent side effects of these drugs such as weight gain and lower extremity edema. In addition, recently the European Medicines Agency (EMA) recommended the suspension of the marketing authorisations for the rosiglitazone-containing anti-diabetes drugs because of the increased risk of heart failure and myocardial ischemia (63). Concern has also risen about the increased risk of bladder cancer in patients taking pioglitazone. The EMA advises not to prescribe this drug in patients with current or a history of bladder cancer or in patients with uninvestigated macroscopic haematuria.

Ursodeoxycholic Acid (UDCA)

UDCA is mainly used in chronic cholestatic disorders, but in theory it may have numerous protective effects on pathogenic mechanisms involved in NASH (64). After a pilot study in NASH patients (UDCA 13-15 mg/kg/d for

12 months), which suggested beneficial effects of UDCA on some laboratory values and grade of hepatic steatosis, this agent was further investigated in randomized controlled trials (65). A very recent randomized placebo-controlled trial (n = 186) with high-dose UDCA (23-28 mg/kg of body weight/d) over a treatment period of 18 months, failed to improve the overall histology in patients with NASH in comparison with placebo (66). Only lobular inflammation improved significantly. This result was in accordance with an earlier study using a lower dose UDCA (13-15 mg/kg/d) over a period of 24 months (67). Another double-blind placebo controlled study, with a limited number of NASH patients (n = 48), showed an improvement of serum aminotransferase levels and liver histology only in those patients treated with UDCA (12-15 mg/kg/d) in combination with vitamin E (400 IU 2/d) (68). A recent RCT demonstrated improvement in liver function test (primary efficacy endpoint was change in serum ALT) in patients treated with high-dose UDCA (28-35 mg/kg/d) for 12 months, but no liver histology data were reported (64).

In general, the results with UDCA in the treatment of NAFLD are disappointing (Table 3). Maybe in the future better results will be achieved with non-UDCA bile acids, which are currently under experimental investigation (69).

ACE-inhibition and sartans

Angiotensin II, the main effector of the renin-angiotensin system, causes oxidative stress, insulin resistance, vascular damage (endothelial dysfunction, microthrombi, increased intrahepatic vascular resistance) and induces hepatic inflammation and fibrogenesis (70,71). These finely intertwined pathways are all identified as important players in the pathophysiology of NAFLD (72-76). Therefore, inhibiting the renin-angiotensin system via angiotensin converting enzyme (ACE)-inhibitors or angiotensin-II-receptor-blockers (ARB's), seems promising in the treatment of NAFLD.

A pilot study treating seven patients with both NASH and hypertension with losartan (50 mg/day) for 48 weeks, showed improvement of serum liver enzyme levels, hepatic necroinflammation and hepatic fibrosis (77). Georgescu *et al*. (78) compared valsartan (80 mg/d) with telmisartan (20 mg/d) for 20 months in a recent RCT in 54 patients with mild-to-moderate hypertension and biopsy-proven NASH. Both groups showed significant decrease in ALT levels versus inclusion, also HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) decreased significantly in both groups, but the decrease in the telmisartan group was significantly higher than in the valsartan group. Both agents improved steatosis, but telmisartan significantly improved ballooning, lobular inflammation and fibrosis. The improvement of fibrosis with telmisartan is possibly explained by its combination of PPAR-γ en ARB activity (32). Recently the study of Torres *et al*. (61) showed no benefit of combination therapy with rosiglitazone and losartan versus rosiglitazone and metformin or rosiglitazone alone. This may be attributable to the possible inadequate dose of losartan or the choice of ARB, in view of the superior effect of telmisartan in aforementioned study.

On the basis of these data, an ACE-inhibitor or an ARB may be considered as the first line agent in NASH patients who need pharmacological treatment of their arterial hypertension.

Endocannabinoids

The cannabinoid type 1 (CB1) receptor antagonist has multiple potential favorable effects on body weight, insulin resistance, fibrogenesis and de novo lipogenesis (79,80). The ADAGIO-Lipids trial comparing rimonabant 20 mg/d with placebo for 1 year in abdominally obese patients with atherogenic dyslipidemia (n = 799), showed that rimonabant significantly improved multiple cardiometabolic risk markers and induced significant reductions in both intra-abdominal and liver fat, assessed by CT (81). Moreover, rimonabant reversed CT-assessed steatosis in 48% of patients versus 19% on placebo and significantly decreased ALT. Liver biopsies were not obtained.

However, safety profile (in particular anxiety and depression) remains an important issue. These side effects led to the discontinuation of several trials such as the recently published Crescendo trial investigating rimonabant for prevention of cardiovascular events (82). The Food

Table 3. — **Studies on the effect of ursodeoxycholic acid (UDCA) in NAFLD**

Author, Year	n	Intervention	Duration	Outcome
Ratziu *et al*., 2011 (64)	126	UDCA (28-35 mg/kg/d)	12 mo	↓ ALT, ↓ serum fibrosis marker, ↑ glycemic control, no histological data obtained
Laurin *et al*., 1996 (65)	24	UDCA (13-15 mg/kg/d)	12 mo	↓ steatosis, ↓ ALT, ↓ g-GT
Leuschner *et al*., 2010 (66)	186	UDCA (23-28 mg/kg/d)	18 mo	no significant changes in overall histology, only ↓ inflammation, no improvement laboratory data except g- GT
Lindor *et al*., 2004 (67)	166	UDCA (13-15 mg/kg/d)	2 yr	no significant differences in steatosis, inflammation, fibrosis nor transaminases
Dufour *et al*., 2006 (68)	48	UDCA (12-15 mg/kg/d)	2 yr	↓ ALT, no significant effects on histology (only ↓ steatosis in combination with vitamin E)

ALT, alanine aminotransferase; g-GT, gamma glutamyl transpeptidase.

Table 4. — **Studies on the effect of anti-oxidants in NAFLD**

Author, Year	n	Intervention	Duration	Outcome
Sanyal *et al*., 2010 (58)	247	vitamin E (800 IU/d)	96 wk	improvement overall histological outcome, ↓ steatosis, ↓ inflammation, ↓ transaminases, no improvement fibrosis nor metabolic factors
Harrison *et al*., 2003 (83)	49	vitamin E (1000 IU/d) and C (1000 mg/d)	6 mo	↓ fibrosis, no changes in inflammation nor ALT
Abdelmalek *et al*., 2009 (84)	55	oral betaine (20 g/d)	12 mo	↓ steatosis, no changes in NAS, fibrosis nor ALT
Vilar Gomez *et al*., 2009 (87)	60	Viusid (50g)	6 mo	↓ NAS, ↓ steatosis, ↓ ballooning, ↓ inflammation, no change in fibrosis nor transaminases
Gonciarz *et al*., 2010 (88)	42	melatonin (10 mg/d)	12 wk	↓ liver enzymes

ALT, alanine aminotransferase; NAS, NAFLD Activity Score.

and Drug Administration (FDA) denied drug approval in the United States and also in Europe it is not available anymore. Because of the data supporting a beneficial role of endocannabinoids in the pathogenesis of several features of NAFLD, research efforts should be made to develop CB1 antagonists unable to cross the blood-brain barrier and thus preventing the central side effects (79).

Anti-oxidants

Oxidative stress is considered to be a key mechanism in the pathogenesis of NASH. Therefore, several anti-oxidants such as vitamins E and C, betaine and Viusid have been explored (Table 4). The most investigated anti-oxidant is vitamin E, showing fairly promising results. A recent and till now the largest study, compared pioglitazone (30 mg/d), vitamin E (800 IU/d) or placebo for 96 weeks in 247 adults with NASH and without diabetes (58). Vitamin E therapy as compared with placebo was associated with a significantly higher rate of improvement in nonalcoholic steatohepatitis (43% versus 19%). An earlier randomized controlled trial in 2003 in 49 patients with NASH comparing the combination of vitamin E (1000 IU/d) and C (1000 mg/d) with placebo for 6 months, resulted in a statistically significant improvement in fibrosis score (83). Trials with other anti-oxidants such as betaine (a methyl donor : aiming at restoring reduced hepatic gluthatione stores), silybin (milk thistle), melatonin and Viusid (a nutritional supplement with different antioxidant molecules) are published with rather varying results, possibly due to the great heterogeneity in study designs (32,84-88).

Although the results of vitamin E are hopeful, it has a controversial long-term safety. A meta-analysis in 2005 demonstrated that high-dosage vitamin E supplementation (≥ 400 IU/d) may increase all-cause mortality (89).

Other agents

Orlistat is a reversible inhibitor of gastric and pancreatic lipase, which blocks absorption of approximately 30% of dietary triglycerides. Harrison *et al*. (90) showed that moderate weight loss by the use of orlistat, attainable by approximately 40% of the subjects who completed the trial, was associated with significant improvements in serum aminotransferases, insulin resistance and liver histology. It has a potential use in overweight or obese patients but its role remains elusive and larger trials are needed. Side effects such as diarrhea hamper the blinding of studies.

Pentoxifylline, an oral inhibitor of tumor necrosis factor-alpha (TNF-α) production, showed promising results in treatment of NAFLD in rather small studies (91,92). These results were confirmed in a recent study ; therapy with pentoxifylline (n = 26) for 1 year resulted in significant improvement of histological features (with a trend for improved fibrosis) of NASH compared to placebo (n = 29) (93).

Treatment with L-carnitine, a modulator of mitochondrial free fatty acid transport and oxidation, improved steatosis, NAFLD activity score and transaminases when added to lifestyle intervention for 6 months (94). Further large prospective placebo-controlled trials are warranted before any firm conclusion can be drawn on the effectiveness of lipid-lowering drugs (statins, fibrates) in NAFLD/NASH (32,95). Other therapeutic modalities that are under investigation, some in experimental phase, are new antidiabetic class glucagon-like peptide (GLP)-1-receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, iron depletion through venesection and even sunlight therapy (96-98).

Liver transplantation

NASH is nowadays the third most common indication for liver transplantation in the United States and is on a trajectory to become the most common (99). Steatosis is frequent after liver transplantation for NASH (45% after 5 years), however post-transplant NASH is unusual (7% in the 5-year period after liver transplantation for NASH) (5,100). Patients undergoing transplantation for NASH have comparable long-term outcomes with patients transplanted for other common causes (99,101). However, in the study of Malik *et al*. (101), transplant recipients with NASH who were ≥ 60 years, had a body mass index (BMI) ≥ 30 kg/m^2 and had pretransplant diabetes and arterial hypertension, had a very high 1-year

Table 5. — **Practical recommendations for the treatment of patients with NAFLD**

Thorough evaluation and treatment of cardiovascular co-morbidities with standard of care approaches Annual non-invasive monitoring of liver fibrosis in NASH patients Yearly or 2-yearly evaluation (with ultrasound) of HCC presence in non-cirrhotic NASH 6-monthly surveillance for HCC (with ultrasound) in cirrhotic NAFLD/NASH Lifestyle intervention : – Loss of 7 to 10% of body weight in overweight and obese patients (max. approximately 1.6 kg per week in adults) – Physical activity: moderate aerobic exercise for at least 150 minutes a week – Diet : daily calorie intake: 1,000 to 1,200 kcal/day for overweight women and 1,200 to 1,600 kcal/day for overweight men and heavier or more active women (108) composition: poor in saturated fatty acids, promote intake of n-3 polyunsaturated fatty acids and lower intake of n-6 polyunsaturated fatty acids (29), avoid soft-drinks (limit fructose intake) – Smoking cessation in all patients, avoid alcohol use, coffee intake beneficial ? Vitamin E 800 IU/d in NASH patients ?
In specific subpopulations of NASH Glucose intolerance and NASH: metformin or pioglitazone ? Arterial hypertension and NASH: telmisartan ? Severe obesity (BMI ≥ 35 kg/m.) and NASH: consider bariatric surgery

mortality of 50%, despite a low MELD score (model for end-stage liver disease score). This may have implications for selection of patients for transplantation, especially in the context of the current scarcity of donor livers.

Practical recommendations and conclusion

Since simple steatosis is considered to be a relatively benign condition, these patients can be managed by general physicians. Patients with NASH on the contrary, need a parallel follow-up by gastroenterologists/hepatologists because of their risk for disease progression to end-stage liver disease and its complications. Liver biopsy to diagnose NASH should be performed based on an individualized decision rather than rigid guidelines (102). Current data do not support routinely repeating a liver biopsy in patients with NASH, but annual non-invasive monitoring (ideally combining serum and imaging methods) of fibrosis is warranted (102,103). There is insufficient evidence to recommend HCC surveillance (liver ultrasound every 6 months) in non-cirrhotic NASH patients. However, future findings on HCC in non-cirrhotic NASH may prompt some reconsideration of cancer surveillance strategy in these patients (102-106). Therefore, we recommend a yearly or 2-yearly evaluation (liver ultrasound) of the presence of HCC in non-cirrhotic NASH. Cirrhotic NASH patients should be screened every 6 months (105-106).

Because of the close correlation with features of the metabolic syndrome, patients with NAFLD need a thorough evaluation and treatment of cardiovascular co-morbidities. Life style intervention consisting of increased physical activity and dietary modifications, remain the cornerstone of treatment for both simple steatosis and NASH. The paucity of data makes it difficult to make detailed recommendations (107). It is generally recommended that overweight and obese patients with NAFLD lose 7 to 10% of their body weight by moderate aerobic exercise for at least 150 minutes a week in combination with diet modification in total caloric intake and composition (low in fructose, saturated fatty acids and n-6 polyunsaturated fatty acids and rich in n-3 polyunsaturated fatty acids). Weight loss should not exceed approximately 1.6 kg per week in adults (108). Smoking cessation is mandatory for all patients. We discourage alcohol consumption, because of its detrimental effects on the natural course of NAFLD (Table 5).

With respect to pharmacological treatment and bariatric surgery no firm conclusions can be drawn. However, on the basis of aforementioned studies some approaches may be considered. Because of its promising results, one could consider starting vitamin E (800 IU/d) in NASH patients. But the possible advantages of vitamin E must be weighed against the unclear long-term safety. Metformin or pioglitazone could be given for NAFLD patients with glucose intolerance or diabetes. The results of trials with new class of anti-diabetics (GLP-1 agonists and DDP-4 inhibitors) are awaited. Telmisartan may be considered as the first line agent in NAFLD patients who need pharmacological treatment of their arterial hypertension. In severely obese patients (BMI ≥ 35 kg/m^2) with NASH, the indication for bariatric surgery can be explored.

In conclusion, despite the multiplicity of clinical trials, a gold therapy is still lacking ; most likely reflecting the heterogeneity of studies and the multifactorial pathophysiology. Therefore, evaluating combination therapies embedded in well-designed randomized controlled trials possibly will enrich our armory to face the clinical health burden of NAFLD, which is already present in epidemic proportions.

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