Is there any progress in the treatment of non-alcoholic fatty liver disease?

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Abstract

Despite the fact that non-alcoholic fatty liver disease (NAFLD) and its severe clinical form, non-alcoholic steatohepatitis (NASH), are becoming increasingly prevalent in industrialised countries, there are no licensed pharmacological treatments for them. Weight loss and life modifications, antioxidant therapies and insulin-sensitising agents are the current treatment strategies and have all been tested with inconclusive results. Low sample numbers, inadequate treatment duration and use of markers for treatment response other than histology might all account for these results. As NAFLD is a systemic rather than a liver disease, future trials should address the patient as a whole and also address cardiovascular risk factors.

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Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Weight loss; Pioglitazone; Metformin

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and its severe clinical form, non-alcoholic steatohepatitis (NASH), are becoming increasingly prevalent in industrialised countries, along with the epidemic of obesity. The prevalence of NAFLD is estimated to be 10%-25% in the Western world, while the corresponding prevalence of NASH ranges from 2%-7% (Table 1). Insulin resistance and metabolic syndrome have been implicated both in the pathogenesis and disease progression of NAFLD, causing, among other symptoms, increased free fatty acid influx to the liver, oxidative stress, mitochondrial toxicity, deregulation of adipokines and subsequently inflammation and fibrosis (Figure 1). It has become clear that NAFLD is not a benign non-progressive disease, as originally suggested, but results in increased morbidity and mortality, as shown in several studies with longitudinal follow-up. It is notable that cardiovascular events and non liver-related deaths were the main cause of mortality in patients studied. This is not surprising given the high prevalence of metabolic syndrome and its components in NAFLD patients. Currently, there are no licensed therapies for NAFLD, despite the abundance of clinical trials. In this review we will explore the current status of such treatments and propose a future research agenda.

TREATMENT STRATEGIES FOR NAFLD

The existing treatment strategies for NAFLD can be divided into three main categories: weight loss and lifestyle modifications, insulin-sensitising agents and antioxidant therapies. As a general comment, most studies suffer from inadequate patient numbers, lack of randomisation and use of markers for treatment response other than histology.
Bariatric surgery is normally limited to morbidly obese patients and is considered as a therapeutic option in selected patients with NASH [33]. However, the recent Cochrane metaanalysis found that evidence on the potential benefits and risks of bariatric surgery is derived from cohort studies and is, therefore, not conclusive [34].

It should be also underlined that in addition to food quantity, quality also matters. Results from cohort studies suggest that patients with NAFLD have higher consumption of saturated fatty acids and cholesterol, higher consumption of soft drinks that contain fructose and lower consumption of vitamins A and E [15-18]. Therefore, counselling regarding the quality of calories consumed should also be offered. Lipid lowering therapies are safe in patients with liver disease [9] and preliminary evidence suggests that they might prove beneficial in patients with NAFLD [35].

Table 1  Prevalence of non-alcoholic fatty liver disease in different countries

| Author | Country | Population | n  | Prevalence of NAFLD (%) | Methods of diagnosis |
|--------|---------|------------|----|-------------------------|---------------------|
| Fan et al [6], 2007 | China | Normal | 14446 | 14 | US |
| Papahuedoridis et al [8], 2007 | Greece | Normal | 30503 | 18 | Liver enzymes |
| Zelbers-Sagi et al [9], 2006 | Israel | Normal | 326 | 30 | US |
| Bedogni et al [10], 2007 | Italy | Normal | 598 | 20 | US |
| Tarhier et al [11], 2007 | Italy | T2DM | 2839 | 70 | US |
| Sorrentino et al [12], 2004 | Italy | Bariatric surgery | 80 | 72 | Biopsy |
| Hamaguchi et al [13], 2005 | Japan | Normal | 4401 | 18 | US |
| Yamamoto et al [14], 2007 | Japan | Normal | 263 | 18 | US |
| Park et al [15], 2006 | Korea | Normal | 6648 | 19 | US |
| Roesch-Dietlen et al [16], 2006 | Mexico | Metabolic syndrome | 337 | 16 | US |
| Browning et al [17], 2004 | USA | Normal | 2287 | 31 | MRS |
| Tran et al [18], 2006 | USA | Living donors | 70 | 38.5 | Biopsy |
| Kunde et al [19], 2005 | USA | Bariatric surgery | 233 | 97 | Biopsy |
| Weston et al [20], 2005 | USA | Chronic liver disease | 742 | 39 | US/CT |

NAFLD: Non-alcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus; US: Ultrasonography; MRS: Magnetic resonance spectroscopy; CT: Computerized tomography.

Figure 1  Mechanisms of progression from normal liver to non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. NASH: Non-alcoholic steatohepatitis.

is not, therefore, surprising that they are often inconclusive and fail to show any treatment effect. Currently, there is no licensed pharmacological treatment for NASH and patients are usually advised to lose weight and exercise.

Weight loss

As NAFLD is most commonly associated with obesity, weight loss is a reasonable initial step towards treating this condition. The theoretical advantages of weight loss include decreasing insulin resistance and, if combined with exercise, increasing muscle insulin sensitivity. Despite the pathophysiological evidence of such an approach, there has been only one randomised control trial (RCT) of weight loss in patients with NAFLD, with a sample size of just 31 patients [27]. Patients in the intervention group were targeted for a 7%-10% weight reduction through intensive lifestyle intervention and were monitored for a year with initial and end-of-treatment liver biopsies. Although there was significant improvement in the NASH histological activity score (NAS) in the intervention group and a significant correlation of percent weight loss with improvement in NAS, no significant improvement in fibrosis was documented [28]. All other trials have been non-randomised, with no control group and have usually comprised selected patients or case series [29]. However, improved liver biochemistry and even resolution of stigmata of liver disease have been shown with weight loss in selected overweight patients [30,31]. The main concerns with this strategy include the feasibility of maintaining weight loss over a prolonged time course. Furthermore, rapid weight loss in morbidly obese can actually worsen fibrosis [32]. Therefore, counselling should aim towards gradual weight loss with appropriate life-style modifications and behavioural therapies that would allow weight loss to be maintained over the course of time [33].

Orlistat, which is a reversible inhibitor of gastric and pancreatic lipase and thus prevents the absorption of diet triglycerides, is used for weight loss and has been tested in the management of NASH in a small RCT [34]. Although patients who achieved a weight loss of > 9% improved in biochemical and inflammation measures, there were no significant differences in weight loss between the orlistat and the placebo group.

Bariatric surgery is normally limited to morbidly obese patients and is considered as a therapeutic option in selected patients with NASH [35]. However, the recent Cochrane metaanalysis found that evidence on the potential benefits and risks of bariatric surgery is derived from cohort studies and is, therefore, not conclusive [36].
**Anti-oxidant therapies**

Ant-oxidant therapies have been tried for NAFLD on the theoretical basis that oxidative stress is involved in the pathogenesis of the disease. The results of trials are inconclusive and contradictory, probably because of the small patient numbers. A small pilot trial of pentoxifylline showed improvement in aminotransferases in the 11 patients who completed the 1-year course of medication, although no follow-up histological evaluation was available. Ursodeoxycholic acid failed to show any benefit after two years of therapy in a RCT of 165 patients. A combination of vitamins E and C taken for 6 mo improved fibrosis but not necroinflammation or liver enzymes. A recent RCT, published in abstract form, of vitamin E or pioglitazone or placebo, showed significant improvement in the NAS score of patients who received vitamin E compared to the other two groups. However, no improvement in fibrosis was documented. However, other small RCTs have failed to demonstrate any treatment effect of vitamin E.

**Insulin-sensitising therapies**

As insulin resistance is considered the main underlying mechanism and predisposing condition for NASH, treatment strategies targeting insulin resistance are a main focus of the current research agenda. Metformin and thiazolidinediones which are licensed antidiabetic medications that target peripheral and hepatic insulin resistance have been used in the treatment of patients with NASH.

The first evidence of the potential effect of metformin came from a small cohort study of 20 patients with no follow-up histological evaluation, in which transaminase values and insulin sensitivity improved after 4 mo of treatment. A small Turkish RCT of 36 patients, comparing metformin with no treatment and with 6 mo follow up, confirmed the improvement in transaminases but failed to demonstrate any effect on liver histology. An RCT of metformin vs vitamin E vs no treatment in patients who were all assigned to prescriptive diet showed a significantly higher rate of transaminase normalization as well as a significant improvement in necroinflammation and fibrosis compared to baseline biopsy in the metformin group. However, liver biopsy was not performed in the control group and it is thus difficult to assess if the histological improvement was due to weight loss or metformin. Therefore, although metformin is a safe and promising medication, it has not yet been assessed in properly designed and adequately powered RCTs.

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor-γ agonists that improve insulin resistance in liver, muscle and adipose tissue. The licensed TZDs, pioglitazone and rosiglitazone, have been both tried in RCTs in patients with NAFLD. The two drugs appear to have different effects on lipid metabolism, as rosiglitazone has no effect on de novo hepatic lipogenesis and plasma triglycerides, while pioglitazone actually decreases both. An RCT of 45 mg of pioglitazone vs placebo for 6 mo, showed significant improvements in steatosis, necroinflammation and ballooning in the treatment group although improvement in fibrosis did not reach statistical significance ($P = 0.008$). These encouraging results provided the rationale for further RCTs of longer duration. A lower dose of pioglitazone (30 mg/d) improved fibrosis and hepatocellular injury compared to placebo in an RCT of 74 non-diabetic patients with NASH. However, the biggest RCT to date, with a follow-up of 2 years, failed to show any significant histological improvement in the pioglitazone group (30 mg/d) compared to the placebo group. RCTs on rosiglitazone, of one and two year duration, have shown no significant effects on liver histology.

**CRITICAL APPRAISAL AND FUTURE DIRECTIONS**

Although NAFLD is an increasingly prevalent disease, there is a lack of approved therapies for it. There are several reasons for this absence of effective therapies.

Firstly, most published studies are not adequately powered to demonstrate significant treatment effects and some of the non-significant findings that they report might actually be type II errors.

Secondly, treatment effects are assessed after 6 or 12 mo of therapy duration, which is an arbitrary time cut-off and might be inadequate. Although such treatment durations have been successfully implemented for chronic viral hepatitis B and C infections, these conditions have totally different pathophysiology of liver injury and probably a more rapid clinical course than NAFLD.

Thirdly, the NAS activity score is increasingly being used as a surrogate marker to assess therapeutic effect. However, this score is not a valid surrogate marker for NAFLD as it does not take fibrosis into account. Existing studies suggest that the presence and severity of fibrosis actually dictate long-term mortality in patients with NAFLD, while the NAS score is an untested, if not irrelevant, surrogate marker. Therefore, although improvements in the NAS score not accompanied by improvements in fibrosis would currently classify a study as having a positive result, the true value of these studies is unknown.

Fourthly, metformin remains an untested therapeutic option, despite preliminary evidence of its benefits. This may be because it is a cheap and well established drug and there is, therefore, limited interest in funding and any RCT would have to be investigator-initiated.

Lastly, and most importantly, NAFLD is a systemic rather than a liver disease. Indeed, cardiovascular disease is the main cause of death in NAFLD patients. Therefore, all risk factors should be globally assessed and therapeutic strategies should ideally target the patient as a whole rather than liver-specific disease manifestations alone.

Future trials should recruit larger number of patients for a longer treatment period. The recent pioglitazone or vitamin E for nonalcoholic steatohepatitis RCT demonstrated that insulin resistance might not be the driving force behind fibrosis progression in NAFLD patients and that combination therapy targeting different mechanisms might represent the optimal strategy for NAFLD.
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