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Prevention and treatment of nonalcoholic fatty liver disease☆

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ABSTRACT

A better knowledge of the biochemical mechanisms implicated in the development and progression of nonalcoholic fatty liver disease, linking fatty liver to insulin resistance and the metabolic syndrome, has shifted the goal of treatment from a mere clearing of fat from the liver to a systematic treatment of metabolic risk factors for fatty liver. Any attempt to modify the "unhealthy" habits responsible for fatty liver requires an integrated approach, based on the cognitive theory of behaviour by a multidisciplinary team including physicians, psychologists, dieticians and physical exercise experts, and recent data demonstrate that this is feasible and effective. Whenever this goal is not attained, a treatment based on insulin-sensitizers remains the best option, to simultaneously tackle all metabolic alterations of the metabolic syndrome. However, in individual patients, both raised blood pressure and dyslipidemia need to be controlled, in order to reduce cardiovascular risk. In these areas, any attempt should be made to use of drugs less likely to induce a deterioration of glucose control. It remains to be determined whether these treatments are able to modify the natural history of nonalcoholic fatty liver disease in the long term.

1. Introduction

Any attempt to modify the natural history of nonalcoholic fatty liver disease (NAFLD) should start from the prevention and treatment of the cultural and clinical conditions that promote its development. Type 2 diabetes mellitus (T2DM) and obesity are the two metabolic conditions more closely associated with NAFLD and its progression towards advanced liver disease. They both stem from alterations in insulin action (insulin resistance), a metabolic state in which physiologic concentrations of insulin produce a lower-than-normal biologic response, or higher-than-normal insulin concentrations are necessary to elicit a normal metabolic response. Thus, any measure able to modify overweight/obesity or a sedentary lifestyle, as well as the associated defect(s) in insulin action represents both a preventive measure and a treatment option for NAFLD. This basic treatment approach must be integrated, according to specific conditions and to the severity of liver disease, with specific interventions directly addressing the damaged liver. Treating the patients means promoting behavioural changes towards healthier lifestyles, which would result in improved liver function. Given the association of NAFLD with the metabolic syndrome (MS) [1], other features are also expected to benefit from a comprehensive lifestyle approach, and in turn a correct treatment of hypertension and dyslipidemia may be beneficial for liver disease. Insulin resistance is also associated with hypertension and dyslipidemia, and the majority of defects might be potential target for the action of insulin-sensitizers (metformin and thiazolidinediones), which are thus expected to improve the underlying metabolic abnormalities affecting the diseased liver, reducing steatosis, necro-inflammation and, possibly, fibrosis, as well as having beneficial effects on other metabolic abnormalities.

We shall review the treatment of NAFLD, with specific focus on the areas of behaviour and pharmacological treatment of insulin resistance, and the additional problems raised by the association with hypertension and dyslipidemia. NAFLD treatment must be considered as part of the general treatment of MS and of its individual components, favouring the use of drugs with beneficial effect on glucose metabolism or less likely to deteriorate glucose control.

2. Lifestyle and weight loss treatment of NAFLD

2.1. Behavioural therapy

A program of cognitive-behavioural therapy remains the most effective tool to obtain long-term adherence to lifestyle changes.

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Table 1
Potential mechanisms for the unhealthy, steatosis-producing effects of a westernized diet in the general population.

Mechanisms	Biochemical events	Effects
Fructose-derived metabolic imbalance	Rapid separation of glucose and sucrose in the fructose molecule Presence of caramel coloring, rich in advanced glycation end-products	Stimulation of lipogenesis, favouring dyslipidemia and obesity Promotion of insulin resistance and inflammation
Fructose-derived hormonal imbalance	Failure to stimulate insulin and leptin and to suppress ghrelin	Absence of satiety signals to the central nervous system and positive energy balance
Excess of red meat	Uncertain	Linked to diabetes and obesity in epidemiological studies
High levels of trans-fatty acids	Liver cell membrane damage, via reactive oxygen radical production	Increased weight gain, abdominal obesity, coronary artery disease and type 2 diabetes
Excess triglycerides	Increased hepatic free fatty acids	Cytokine-independent stimulation of necro-inflammation and fibrosis

Patients are educated to a correct self-management of their diet and to a moderate daily physical activity. Adherence to combined dietary restriction and increased physical activity result in larger and progressive weight loss that can be maintained through the years [2]. Physical activity has an independent and beneficial effect on fatty liver [3]. Physical exercise promotes both weight loss, by increasing the negative energy balance, and insulin sensitivity, the determinant of fatty liver, by promoting triglyceride consumption in the skeletal muscle tissue. A longitudinal study aimed at increasing physical activity in adults showed that cardiorespiratory fitness at baseline, independently of total adiposity, body fat distribution and exercise intensity, determines liver fat content in humans. Moreover, measurement of fitness at baseline predicts the effectiveness of a lifestyle intervention in reducing hepatic steatosis in patients with NAFLD [4]. Lifestyle counselling interventions are effective in improving physical activity behaviour. Maintaining or increasing physical activity provides health benefits for patients with fatty liver, independent of changes in weight [5]. However, strategies are needed to increase exercise uptake in NAFLD patients [6], because barriers to physical activity and fear of falling influence engagement in most NAFLD patients.

In NAFLD patients and in the general population behavioural programs produce a remarkable weight loss, which is expected to be larger than that achieved by a prescriptive diet [7,8], but adherence to lifestyle modifications is frequently lost during follow-up with return to pre-treatment body weight [9]. Unfortunately, effective cognitive-behavioural programs require a dedicated team, which is rarely available in busy Liver Units because of time and space constraints, and referral to specific teams in diabetes or obesity settings have been proposed [10]. At present, very few trials of behaviour therapy have been reported in NAFLD patients, with beneficial results extending from liver enzymes to liver histology [7,8,11–14]. These data are now supported by a small randomized controlled trial showing that 1-year intense lifestyle intervention using a combination of diet, exercise, and behaviour modification significantly promotes weight loss (9.3% of their weight vs. 0.2% in the control group) and improves steatosis ($P < 0.001$), lobular inflammation and ballooning injury ($P = 0.03$), without differences in fibrosis [15].

The diet composition has definitely a role both in the pathogenesis and in the treatment of NAFLD. Patients with hepatic steatosis, independently of the presence of nonalcoholic steatohepatitis (NASH), are reported to consume a diet richer in refined sugars [16] or in saturated fats and cholesterol and poorer in fibres and antioxidants [17], while a low carbohydrate diet ("Atkins" diet) [18] and a low fat-diet [19] may be useful in reducing the intrahepatic triglyceride content. In the last year, a series of experimental and clinical studies have shown that specific components of the fast-food diet, namely large amounts of fructose in the form of high-fructose corn syrup present in carbonated beverages, may have a direct role in liver fat accumulation [20,21] via different potential mechanisms (Table 1). Experimental studies in animals have shown that fructose may induce a rapid increase in hepatic triglyceride content [22], responsible for hepatic insulin resistance rapidly extending into the periphery, which in turn may be a likely cause of systemic atherogenic profile [23]. Moreover, Zelber-Sagi et al. found that patients with NAFLD consume almost twice the amount of soft drinks compared to the general population [24], and the daily intake of soft drinks is associated with increased risk for NAFLD, independently of age, gender, BMI and total calories. Thus, specific dietary habits may constitute specific targets of behavioural changes, although the "healthy" diet for the liver is not remarkably different from a general "healthy" diet, independently of the presence of liver disease [25].

In general, weight loss was shown to reduce serum liver enzymes and to improve liver histology [26], whereas gradual weight reduction and increased physical activity improves liver enzymes [12,14], insulin sensitivity and quality of life [27]. Physical activity may also be beneficial for NAFLD-associated cardiovascular risk factors and for the prevention of disease progression [28]. While the optimum amount of exercise to support long-term weight loss has yet to be determined [29], weight reduction should be achieved with a calorie deficit (diet and exercise) of ~500 kcal/die, and should continue at a rate of ~0.5 kg per week. More rapid weight loss (>1.6 kg/wk) can lead to a massive mobilization of fatty acids from visceral fat depots with a paradoxical increased hepatic accumulation and exacerbation of NASH in obese patients [30]. In T2DM patients, moderate weight reduction (8%) was shown to reduce hepatic steatosis, and the removal of liver fat was accompanied by a dramatic improvement in hepatic insulin resistance, with return to normal suppression of hepatic glucose production by insulin [31].

2.2. Weight-reducing drugs

In patients who fail to lose body weight by dietary and physical interventions alone, weight-reducing drugs might be used with success. The most effective medication remains sibutramine, after the cannabinoid receptor subtype 1 (CB1) antagonist, rimonabant, was withdrawn from the market. Sibutramine is a serotonin and norepinephrine re-uptake inhibitor that acts by enhancing satiety. The combination of sibutramine and lifestyle modifications resulted in a larger reduction of body weight compared with medication or lifestyle treatment alone [32]. Its use has been associated with weight loss and improvement in serum aminotransferase levels in obese patients with NAFLD [33]. Insulin resistance and hepatic steatosis, evaluated by ultrasonography, improved as well, but there were no data on histological outcomes. Similar beneficial