Pathogenesis and Significance of Restricted Diet and Exercise Therapy in Nonalcoholic Steatohepatitis (NASH)

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Summary. The risk factors that are most strongly associated with nonalcoholic fatty liver disease (NAFLD) are: age greater than 40 to 50 years, and severe obesity, diabetes mellitus (DM), or hyperlipidemia (especially hypertriglyceridemia). The pathogenesis of nonalcoholic steatohepatitis (NASH) is multifactorial. Insulin resistance, fatty acids, and oxidant stress may be important pathogenic factors in NASH. Efforts are presently underway to define the role of these factors and to determine whether modifying them (for example, by improving insulin sensitivity) could be effective in the treatment of the condition. At present, lifestyle changes involving exercise and dietary restrictions appear to be an effective means of improving NASH. Physicians should actively check for the presence of NAFLD in those who are overweight and who have diabetes mellitus. The treatment is usually directed toward optimizing body weight. The role of pharmacological agents remains to be established, and much more work is necessary to define the pathogenesis of NASH and to develop effective treatments.

Key words. Nonalcoholic fatty liver disease (NAFLD), Nonalcoholic steatohepatitis (NASH), Insulin receptor substance 1 (IRS-1), Leptin, Restricted diet and exercise therapy

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently defined as fat accumulation in the liver exceeding 5%–10% by weight, but it is evaluated in terms of the percentage of fat-laden hepatocytes observed by light microscopy. In NAFLD, an age greater than 40 to 50 years and severe obesity, diabetes mellitus (DM), or hyperlipidemia (especially hypertriglyceridemia) are the most reliable risk factors [1]. When the fat content in the liver is above 10%, fat droplets begin to appear in many hepatocytes. By the time the amount of fat exceeds 30% of the liver weight, almost all of the hepatocytes contain a large drop of fat. In addition, the degree of NAFLD correlates with increased body weight [2]. Some investigators have reported that NAFLD progresses to liver cirrhosis [3–7] or to hepatocellular carcinoma [8, 9].

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On the other hand, the development of steatosis, steatohepatitis, progressive hepatic fibrosis, and cirrhosis is most likely the result of multiple metabolic abnormalities, such as insulin resistance, oxidant stress, fatty acids, and inflammatory cytokines [1].

In this chapter, we would like to review the significance of NAFLD, and we will discuss the management of nonalcoholic steatohepatitis (NASH), including restricted diet and exercise therapy, in relation to the pathogenesis of NAFLD.

Pathogenesis and Complications of NAFLD

Insulin Resistance

Insulin resistance is common in patients with NAFLD and NASH. Insulin modulates intracellular signaling through the tyrosine kinase activity of the insulin receptor. A major mechanism regulating insulin receptor substance-1 (IRS-1) signaling involves excess free fatty acids (FFAs). FFAs impair the tyrosine phosphorylation of IRS-1 [10]. Insulin sensitivity is also regulated by peptide mediators. In the normal human liver, IRS-1 is mainly localized in hepatocytes (Fig. 1a). Adipose tissue, especially mesenteric fat with its venous blood flowing directly to the liver, is a rich source of cytokine and peptide hormone production that regulates downstream metabolic activity. These

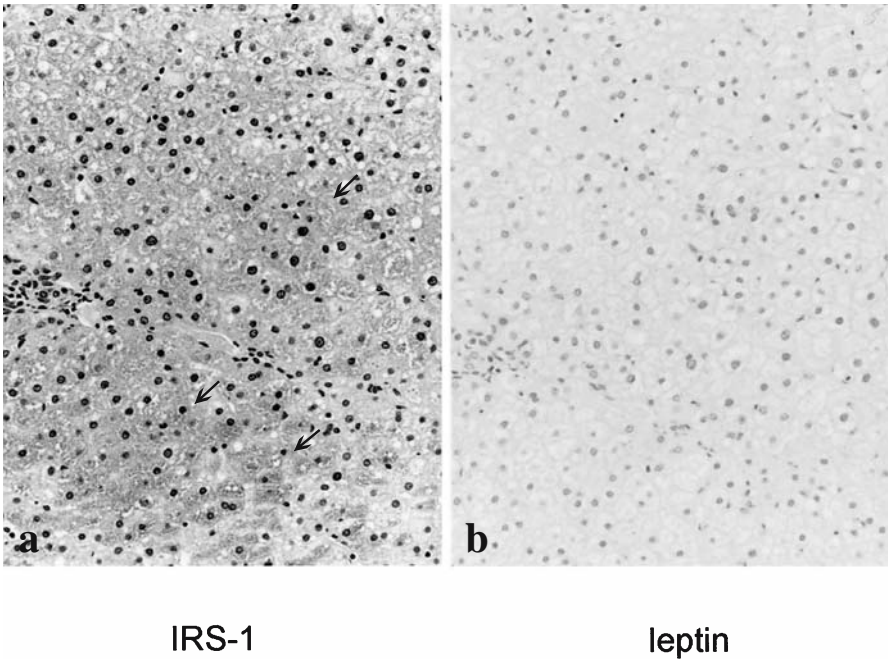

Fig. 1a,b. Immunolocalization of **a** insulin and **b** leptin receptor substance-1 (*IRS-1*) in normal liver tissues. The immunoreactive products of leptin are very scarce in the normal liver, but those of IRS-1 are mainly localized in the hepatocytes (*arrows*). × 100.

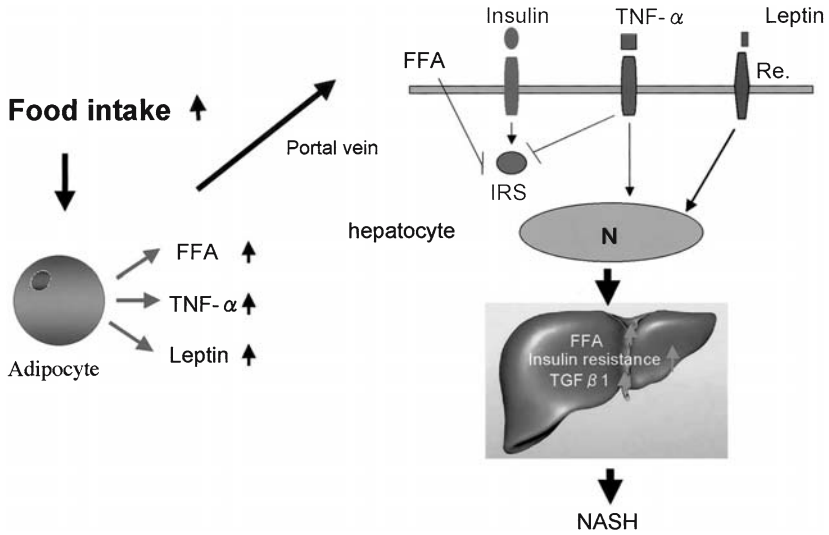

Fig. 2. Overeating and nonalcoholic steatohepatitis (*NASH*). With an increase of food intake, agents containing free fatty acid (*FFA*), tumor necrosis factor-α (*TNF-α*), and leptin are overproduced by adipocytes, and arrive at the liver by way of the portal vein. In the liver, IRS-1 is influenced by FFA, TNF-α, and other agents. The expression and function of IRS-1 appears to be suppressed. On the other hand, leptin seems to be upregulated. Eventually the liver metabolism is disturbed and NASH may occur. *N*, nucleus; *Re.*, receptor; *TGFβ1*, transforming growth factor β1.

agents include tumor necrosis factor-α (TNF-α), leptin, adiponectin, and plasminogen activator inhibitor-1 [1] (Fig. 2).

TNF-α knockout mice fail to develop insulin resistance after induction of obesity [11]. TNF-α appears to stimulate the serine phosphorylation of IRS-1, and I kappa B kinase β (IKK β) may play an important role in this process.

Leptin may also be important in regulating the partitioning of fat between mitochondrial β-oxidation and triglyceride synthesis. In the normal human liver, very little leptin is present (Fig. 1b). Defects in leptin signaling are associated with the preferential accumulation of fat and impaired β-oxidation of fat in the liver. In NASH, it was suggested that leptin is necessary for the development of fibrosis [12, 13]. On the other hand, Chitturi et al. [14] reported that circulating leptin in patients with NASH correlated with hepatic steatosis, but not with hepatic fibrosis.

Adiponectin has a cytokine structure and appears to improve hepatocyte insulin sensitivity.

Oxidant Stress

Oxidant stress is frequently stated to be a central mechanism of hepatocellular injury in NASH. Multiple possible sources of oxidant stress in NAFLD have been identified, and include cytochrome P450, peroxisomal β-oxidation, mitochondrial electron leak, and recruited inflammatory cells.

Treatment of NAFLD

The treatment of NAFLD, including NASH, includes modification of the clinical conditions associated with NAFLD, such as type II DM, hyperlipidemia, and obesity. Specific therapeutic interventions tested so far include weight reduction, and the use of ursodeoxycholic acid (UDCA), clofibrate, troglitazone, vitamin E, and other agents.

Exercise Therapy and Restricted Diet

Those who are overweight (body mass index [BMI] >25 kg/m^2) and have NAFLD should be considered for a weight-loss program (Figs. 3, 4). A target of 10% of baseline weight is often used as an initial weight-loss goal. Dietary recommendations generally include both caloric restrictions and a decrease in saturated fats, as well as a proportion of total fats of 30% or less of the total calories. Both intermittent and daily exercise can help achieve weight loss and improve insulin sensitivity.

We previously reported that patients with NAFLD (including NASH and fatty liver [FL]) who were subjected to dietary restriction and an exercise regimen (Fig. 3) lost weight for 3 months, and achieved a significant improvement in their serum transaminase levels compared with those before treatment (Figs. 4, 6). In addition, serial liver biopsy results (degrees of steatosis and fibrosis) in these patients showed a significant improvement after treatment (Figs. 4, 7). Moreover, in regard to BMI, steatosis, and ballooning of hepatocytes, the FL group had improved compared with the NASH group after treatment (Fig. 5).

Subjects with a BMI of more than 35 kg/m^2 and NAFLD may be considered for more aggressive weight management, including a gastric bypass. However, patients should

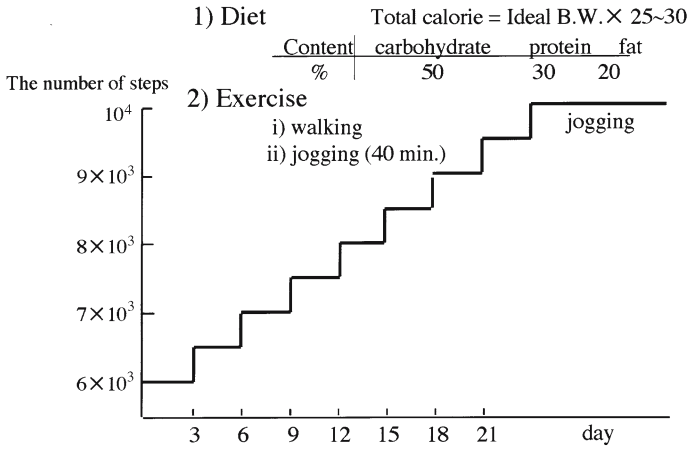

Fig. 3. Therapeutic plan for patients with nonalcoholic liver disease (NAFLD): diet and exercise. A diet that consists of total ideal body weight (*B.W.*) times 25 to 30 calories per day is designed. For exercise, a program of walking is established, in which the subject walks 1000 steps the first week. This is increased by 1000 steps per week until 10 000 steps are reached, after which jogging for 40 min is started.

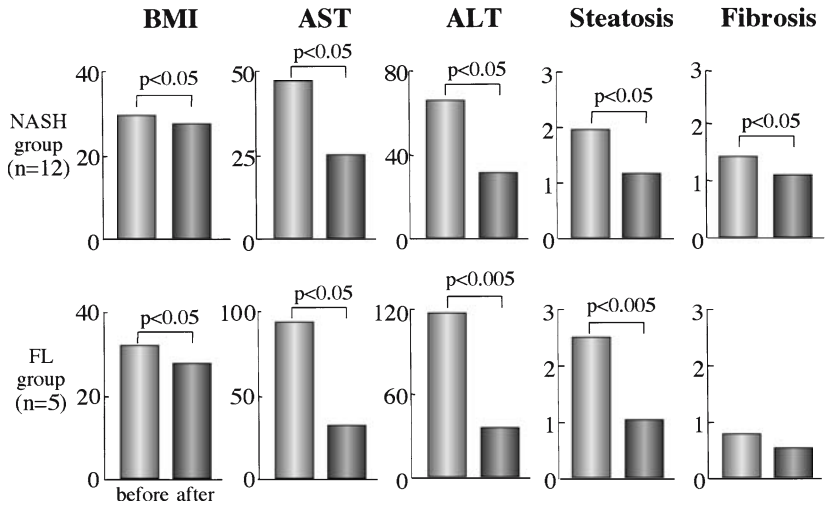

Fig. 4. Comparison of body mass index (*BMI*), aspartate aminotransferase (*AST*), and alanine aminotransferase (*ALT*) levels, and histological findings before and after treatment in NASH and fatty liver (*FL*) groups. BMI, AST, and ALT levels after treatment in the NASH and FL groups were significantly decreased compared with the levels before treatment. In addition, the degrees of steatosis and fibrosis after treatment in the NASH and FL groups tended to decrease compared with those before treatment.

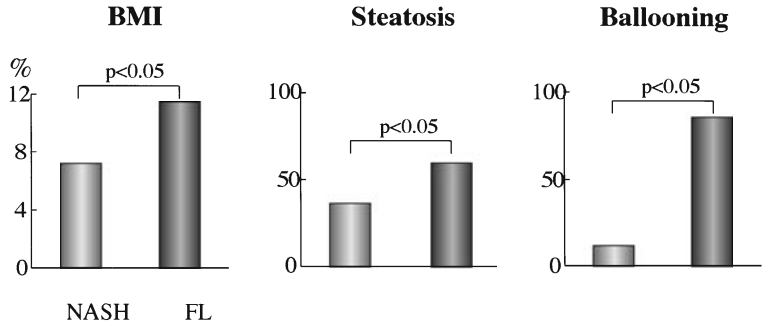

Fig. 5. Comparison of improvement rate between NASH and FL groups. The values for BMI, steatosis, and ballooning hepatocytes in the FL group were significantly improved compared with those in the NASH group.

be monitored for signs of subacute nonalcoholic steatohepatitis during weight loss, and liver function should be checked at appropriate intervals, depending on the rapidity of the weight loss.

Pharmacological Treatment

In addition to obesity, hyperlipidemia is seen in 20% to 81% of patients with NASH [5, 15, 16]. Studies of treatment strategies aimed at alleviating hyperlipidemia in

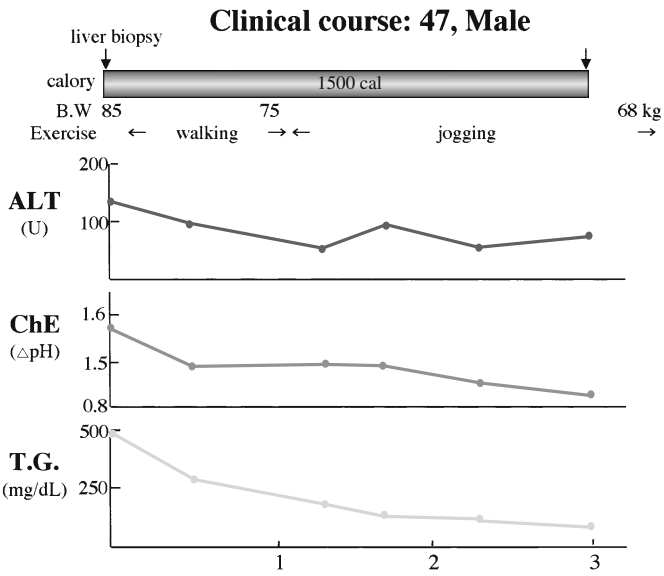

Fig. 6. Clinical course of restricted diet and exercise therapy in a patient with NASH (47-year-old man). Body weight, *ALT*, cholinesterase (*ChE*), and triglyceride (*T.G.*) levels were gradually improved by the treatment.

patients with NASH have had conflicting results [17–20]. In one study, 16 patients with hypertriglyceridemia and NASH were treated with clofibrate for 12 months [17]. There were no significant changes in biochemical or histologic parameters. The only randomized controlled trial of lipid-lowering agents in the treatment of NASH examined 46 patients who were randomized to receive either gemfibrozil or no therapy, regardless of serum triglyceride levels [17]. There was a significant decrease in serum transaminases, but histologic data were unavailable [17]. As reported previously, these conditions are part of the spectrum of clinical manifestations of the insulin-resistance syndrome. Therefore, agents that improve insulin sensitivity may be of particular value in the treatment of NASH. Marchesini et al. [18] have recently reported a pilot study of 14 patients with NAFLD who were given metformin 500 mg three times a day for 4 months. Although no sequential biopsies were available, significant improvements in the aminotransferase levels were noted [18]. An open-label study of troglitazone, a peroxisome-proliferator activated receptor γ (PPAR-γ) agonist that improves insulin sensitivity, showed a significant decrease in liver volume, as measured on magnetic resonance imaging, in patients with lipoatrophic diabetes, severe insulin resistance, and NAFLD [19]. Caldwell et al. [20] treated 10 patients with biopsy-proven NASH with troglitazone for 6 months. At the end of the treatment period, serum aminotransferase levels were normalized in 7 of the 10 patients; however, this biochemical improvement was accompanied by only a minimal improvement in histology on serial liver biopsies [20].

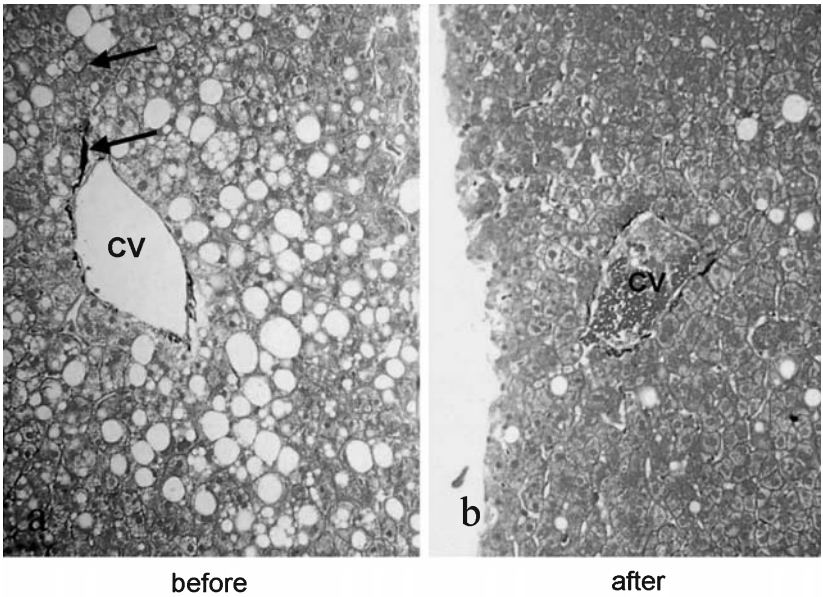

Fig. 7a,b. Light micrographs showing liver specimens before and after therapy in the patient with NASH whose clinical course is shown in Fig. 6. Steatosis and perivenular fibrosis (*arrows*) improved after treatment. *CV*, central vein. × 400.

Conclusions

NAFLD is frequently associated with the presence of obesity, insulin resistance, and hyperlipidemia. There is increasing evidence that NASH, part of the spectrum of NAFLD, can progress to cirrhosis and hepatocellular carcinoma. Physicians should actively check for the presence of NAFLD in those who are overweight and have DM. The treatment is usually directed toward optimizing body weight. The role of pharmacological agents remains to be established, and much more work is necessary to define the pathogenesis of NASH and to develop effective treatment modalities.

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