Liver Disease (NAFLD), defined as a picture of chronic liver damage of emerging and increasing clinical relevance. NAFLD is frequently associated to overweight, an increasing condition in all industrialized countries and may be present alone or associated with other known causes of chronic liver damage, such as hepatitis viruses infection or ethanol and drugs use. The histological pattern of NAFLD ranges from liver steatosis to cirrhosis and hepatocellular carcinoma and the prevalence of non-alcoholic steatohepatitis (NASH) in NAFLD is estimated about 20%. Cirrhosis has been reported to develop in 15-30% of individuals with NAFLD within a 10-year period of follow-up. The metabolic steps involved in the induction and progression of this chronic liver damage are very complex and they include as substrate the metabolic syndrome or associated metabolic alterations (particularly overweight, insulin resistance, diabetes, hyperlipemia), as mediators a large series of peptides, hormones, cytokines (particular TNF-α, adiponectin, leptin, etc.) and, finally as cellular messengers, reactive oxygen and nitrosative species that are capable of induce lipid peroxidation of cellular membranes.

A large number of studies were aimed to discovery the treatment of this syndrome, but the number of well controlled trials is low. An ideal treatment of NAFLD should improve the liver damage and or its progression, both directly or trough the modulation of its pathophysiological events. Therefore drugs should ameliorate body weight, insulin resistance and other metabolic associated alterations, reduce the linkage between adipose tissue and liver by acting as anti-inflammatory and/or immunomodulatory agents, modulate the progression of liver steatosis to inflammation and fibrosis by blocking the oxidative and nitrosative species.
Correction and Management of Associated Conditions

Modification of Body Weight

Diet and life-style modification. NAFLD in the majority of cases is associated to overweight a condition of increasing importance in the industrialized populations. Physical exercise and a well balanced hypocaloric diet are common recommendation in these countries. In patients with NAFLD, weight loss was accompanied by a significant improvement of all parameters of metabolic syndrome as well as of liver function tests. Scores for steatosis, lobular inflammation, centrolobular fibrosis, Mallory bodies, and ballooning degeneration were all significantly improved with weight loss. The improvement of liver tests with weight loss was obtained in about 40% of overweight patients with NAFLD. Two main problems are related to weight management. The first is that the adherence to an hypocaloric diet is generally discontinuous; secondly a very rapid weight loss may cause a worsening of steatohepatitis. The NHLBI-NIDDK guidelines suggest that weight loss should proceed at a rate of 1-2 lb/wk. The panel recommends an initial target for weight loss of 10% of the baseline in the first 6 months until the achieve the ideal body weight. Diet is an important component of any weight-loss regimen. Saturated fats in the diet worsen insulin resistance, whereas dietary fibers can improve insulin resistance. There are no controlled studies on the value of diet in the management of NAFLD. Dietary supplementation with polyunsaturated fatty acids may improve insulin sensitivity and cardiovascular risk profile. Weight reduction regimens should be individualized in each patient. These regimens include diet, exercise, anti-obesity medications, psychotherapy, and surgery for obesity, alone or in combination. Exercise has been shown to increase the oxidative capacity of muscle cells and the utilization of fatty acids for oxidation. Exercise decreases fatty acid and triglyceride accumulation in the myocytes and thereby improves insulin sensitivity. The degree of improvement in insulin sensitivity is related to the intensity of the exercise.

Drugs for obesity. The role of weight-reducing pharmacologic regimens in NAFLD remains to be elucidated. At the moment, the drugs approved for weight reduction are sibutramine and orlistat. The guidelines for management of obesity recommend that pharmacotherapy must be considered as an adjunct to lifestyle modification for patients with a BMI > 30 kg/m² and no concomitant obesity related risk factors or diseases. Pharmacotherapy may also be considered in those with a BMI > 27 kg/m² with concomitant risk factors or diseases such as hypertension, dyslipidemia, coronary artery disease, type 2 diabetes mellitus, and sleep apnea.

A recent study evaluated the efficacy of orlistat, given for 6 months to patients with obesity and biopsy confirmed NASH. Data suggest that when combined with dietary counselling, approximately 40% of patients treated for 1 year were able to lose up to 10% of their body weight and weight loss significantly improved aminotransferase levels and liver histology.

Correction of Metabolic Disorders

Antidiabetic and insulin sensitizing agents. Insulin resistance seems to be the common denominator in many cases of NASH that is associated with a decreased insulin-mediated suppression of lipolysis. Consequently, subjects with NASH have high serum-free fatty acid concentration, allowing greater hepatic fatty acid uptake and oxidation. Increased fatty acid delivery to the liver also may have complex effects within the hepatocytes, including interference with insulin function and preferential utilization of fatty acids for mitochondrial oxidation.

These, along with other potential intrahepatic abnormalities, culminate in the development of steatohepatitis. These considerations, along with the well-known association of NASH with obesity and diabetes, have led to attempts to treat NASH by treating insulin resistance. Two classes of drugs have been shown to correct insulin resistance: biguanides (e.g., metformin) and thiazolidinediones (e.g., rosiglitazone and pioglitazone). At the moment, the use of these
drugs remains experimental. Thiazolidinediones act via peroxisome proliferator activated receptor γ and improve insulin sensitivity. In a recent study, with rosiglitazone, the serum levels of aminotransferase, alkaline phosphatase, and γ-glutamyl transpeptidase (GGT) decreased significantly during treatment and remained at reduced levels also when the treatment was discontinued. A significant improvement of steatosis, features of necroinflammation, hepatocellular ballooning, and zone 3 perisinusoidal fibrosis was also observed.

Metformin, a biguanide introduced in late 1950, is extensively used to treat type II diabetes as it improves insulin sensitivity. Metformin decreases hepatic glucose output and enhances peripheral glucose uptake thus blunting compensatory hyperinsulinaemia. In addition, metformin can also decrease hepatic lipogenesis. Metformin activates AMP-activated protein kinase (AMPK) in hepatocytes resulting in phosphorylation and inactivation of acetyl-CoA carboxylase, a rate limiting enzyme in lipogenesis. Recently, investigators evaluated the role of metformin therapy in the obese ob/ob mouse model of NAFLD, and in patient with this syndrome. In man there was a significant decrease in weight, body mass index and waist hip ratio, which was more evident in the first 3 months. Similarly there was a decrease in serum ALT and AST by the third month of treatment. However, despite continued metformin treatment there was a rebound increase in ALT and AST at 6 months and at the 1 year. At 3 months, there was a significant correlation between changes in ALT levels and HOMA IR score. However, after 3 months there was no further improvement in insulin sensitivity and there was a gradual rise in AST and ALT. Among the 10 patients who had post-treatment biopsy at 1 year, three patients (33%) showed an improvement in steatosis, two (20%) showed an improvement in inflammation score and one patient (10%) showed improvement in fibrosis. In an excellent study, Marchesini’s group had treated 20 patients who had steatohepatitis with metformin (500 mg three times a day for 4 months). Long-term metformin significantly reduced mean transaminase concentrations, which returned to normal in 50% of actively treated patients. Also, insulin sensitivity improved significantly and liver volume decreased by 20%. Similar data have been reported in insulin resistant ob/ob mice with fatty liver.

**Lipid lowering agents.** Hypertriglyceridemia is often associated with NASH. In one controlled trial, clofibrate had no beneficial effects on liver functions or hepatic histology; in another small controlled trial, gemfibrozil improved liver chemistry. Based on the current understanding of the pathogenesis of NAFLD, there is no rationale for the use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors for the treatment of patients with NAFLD.

**Modulation of Mediators of Liver Damage**

A large series of experimental studies stressed the role of TNF-α, IL-10, IL-6 and other cytokines as mediators of the shift of steatosis to NASH and fibrosis. In this context antagonist of IL-1 receptors and of TNF-α as well as IL-10 have been proposed as a therapeutical approach to NAFLD. Data are mainly referred to experimental studies in animals and only few sporadic studies have been performed in humans. Our group published an open pilot study that demonstrated a reduction of plasma levels of TNF-α associated with an improvement of liver damage through the administration of lactobacilli in patients with NASH.

Adiponectin is a protein exclusively secreted from adipose tissue. Both in vivo and in vitro experiments demonstrated that adiponectin and TNF-α suppress each other’s production and also antagonize each other’s action in their target tissues. Administration of adiponectin to mice has been shown to produce beneficial effects on lipid metabolism, such as an enhancing lipid clearance from plasma and an increasing fatty acid β-oxidation in muscle. Recent studies from Scherer’s group suggest that adiponectin can act directly on hepatic tissue and inhibit glucose production. Adiponectin also has direct antiinflammatory effects. These results collectively indicate that adiponectin might have hepatoprotective effects. The potential mechanism of protection include the induc-
Inhibition of Lipid Peroxidation and of Fibrosis Progression

Cytoprotective and Antioxidant Drug

Ursodeoxycholic acid (UDCA), a naturally occurring bile acid with multiple hepatoprotective activities, improves liver condition in patients with a wide range of chronic liver diseases and hepatobiliary diseases. However in a recent study, UDCA was not associated with an improvement in serum liver biochemistries or histology when compared with placebo in patients with NAFLD. Vitamin E was used both in adults and child patients with NAFLD. This antioxidant was able to improve liver enzyme abnormalities, but it did not induce significant variations of liver histology. N-acetyl-L-cysteine or dietary supplementation with lecithin and other antioxidants had similar effects. Betain, glucoronate, nicotinamide, ascorbate and s-adenosil-methionine improved liver tests and in some case also liver histology.

Antifibrotic Agents

Even if no drugs are approved as antifibrotic agents in humans, at the moment many authors focused their attention on the possibility to reverse liver fibrosis or by reducing the activation of hepatic stellate cells or by promoting their apoptosis or degradation of formed collagen. The main activators of hepatic stellate cells are the reactive oxygen species and the lipid peroxidation products. Therefore also antioxidants may be considered antifibrotic agents. In addiction, an antifibrotic effect has been documented also for anti-inflammatory cytokines or proinflammatory cytokines, as well as for the classic antiviral drugs such as interferon alfa, lamivudin, adefovir. There is evidence for a causative role of TGF-β1 in fibrogenesis from in vitro and in vivo studies. Kupffer cells and stellate cells secrete TGF-β1, that accelerates the trasformation of resting stellate cells to myofibroblasts. TGF-β1 also increases the production of many extracellular matrix proteins by fibroblasts and stellate cultured cells. In animals, the inhibition of the production of TGF-β1 is associated to a decrease of liver fibrosis. The inhibition of collagen production by hepatic stellate cells may be also obtained by modulating the nitric oxide, NFkB, chemokine and endothelin systems. Oral supplementation of n-acethyl-cysteine attenuates the deposition of collagen fibers in vitro.

Pirferidone is able to inhibit both proliferation of fibroblasts and synthesis of the collagen in various experimental models of fibrosis. In rats it reduces the proliferation of activate hepatic stellate cells, the synthesis of extracellular matrix components and may have anti-inflammatory effects. The degradation of collagen may be obtained by MMPS or TIMP-1 antisense. Pioglitazone or rosiglitazone reduces collagen accumulation and therefore these drugs should be indicated also to reduce the progression of liver damage in patients with NAFLD.

The Role of Silybin

Silybin is the main component of the flavonoid silymarin. It acts as a radical scavenger, stimulates hepatocite RNA synthesis and suppresses the proliferation of hepatic stellate cells and the collagen deposition in vitro. In rats with induced fibrosis silybin reduces collagen accumulation, as well as lipid peroxidation. Conjugated with a phytosome and vitamin E, silybin is rapidly absorbed in man. Preliminary data of our group show that this compounds is able to improves liver steatosis, insulin resistance and plasma markers of liver fibrosis in patients with NAFLD.

In conclusion, NAFLD is a major cause of liver-related morbidity and is frequently associated with the presence of insulin resistance. There is an increasing evidence that NAFLD can progress to cirrhosis and liver failure. There is no an established treatment for NAFLD. The treatment usually is directed toward optimizing body weight. The role of pharmacologic agents remains to be established, and much more work is necessary to define the pathogenesis of this condition and to develop an effective treatment. The possibility of act in the modulation of both induc-
tion of liver steatosis and in progression to NASH until cirrhosis should stimulate the future research to identify what patient should be treated and to optimize the more effective therapy in each individual patient.

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