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# Nonalcoholic Fatty Liver Disease/Steatohepatitis: Epidemiology, Pathogenesis, Clinical Presentation and Treatment

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## Key Words

Nonalcoholic fatty liver disease · Nonalcoholic steatohepatitis · Diagnostic procedures · Treatment

## Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic hepatic disorder in Western countries, with a prevalence of 20–30%. NAFLD comprises ‘silent liver disease’, in which simple steatosis is the only histological finding and which is benign in course, and nonalcoholic steatohepatitis, which is characterized by hepatocellular injury and inflammation with or without fibrosis. NAFLD is clinically important, because even benign fatty liver can progress to steatohepatitis in many patients, which can lead to liver cirrhosis and its complications and hepatocellular carcinoma. NAFLD is a hepatic manifestation of metabolic syndrome; it is closely related to other clinical features of metabolic syndrome, and thus to cardiovascular morbidity. There are several different noninvasive techniques for formal diagnosis and follow-up, but liver biopsy remains the gold standard. The most important therapeutic strategies include lifestyle changes, including changes in dietary habits aimed at weight loss and blood pressure regulation, with a consequent decrease in insulin resistance. For some patients with NAFLD/nonalcoholic steatohepatitis, pharmacological treatment is the best option, although further studies are needed to confirm its efficacy and tolerability.

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## Introduction and Epidemiology

The term nonalcoholic fatty liver disease (NAFLD) is used to cover a spectrum of disorders that are characterized by predominantly macrovesicular steatosis of the liver and occur in people who do not consume significant amounts of alcohol [1]. Among the disorders included in NAFLD, it is possible to distinguish between ‘silent liver disease’, in which the only histological finding is the presence of steatosis and which has a benign course, and nonalcoholic steatohepatitis (NASH), which is characterized by hepatocellular damage and inflammatory reactions, with or without fibrosis [1, 2].

Insulin resistance (IR) plays an important role in the pathogenesis of NAFLD and is closely linked to metabolic syndrome and its manifestations: obesity, diabetes mellitus type II, dyslipidemia, and hypertension [2, 3]. NAFLD is the hepatic manifestation of metabolic syndrome, and it is an independent predictor of cardiovascular disease [1, 2]. The likelihood of developing NAFLD increases with increasing body mass index. Patients with NASH have a reduced life expectancy, primarily due to cardiovascular disease, but also because of liver disease, which includes progression to cirrhosis and hepatocellular carcinoma [1, 2].

The prevalence of NAFLD in the general population is 20–30% [3]. Population-based studies provide better estimates of the prevalence of NAFLD as compared to

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autoptic and clinical studies. The diagnosis of NAFLD in population studies is usually obtained by ultrasonography, which is known to underestimate the prevalence of fatty liver. The Dallas Heart Study and the Dionysos Study reported that 30% of the adults in the USA and 25% in Italy have NAFLD [3, 4]. The prevalence of NAFLD is 80–90% in obese adults, 30–50% in patients with diabetes and up to 90% in patients with hyperlipidemia [4]. The prevalence of NAFLD among children is 3–10%, rising up to 40–70% among obese children. Moreover, pediatric NAFLD increased from about 3% a decade ago to 5% today, with a male-to-female ratio of 2:1 [3, 4]. It is the most common cause of chronic liver disease in Western European countries and the United States, making it a major public health problem and an economic burden [4]. The clinical significance of NAFLD lies in the fact that a certain percentage of patients (10–25%) with silent liver disease go on to develop NASH, which is a potentially progressive disorder and can lead to end-stage liver disease, including hepatocellular carcinoma [5]. 5–8% of patients with NASH will develop liver cirrhosis within 5 years. NASH is a leading cause of cryptogenic cirrhosis. Diagnosis of NAFLD/NASH requires the exclusion of all other possible causes of liver disease (e.g. viral, autoimmune, and genetic), and it is important to have data regarding either non-consumption of alcohol or consumption of quantities that do not lead to alcohol-induced steatosis (<20 g/day for women and <30 g/day for men) [6]. NAFLD and NASH can coexist with other chronic liver diseases (e.g. chronic hepatitis C, hemochromatosis, and alcoholic liver disease), and may exacerbate liver damage and disease progression [1, 2].

Any attempt to modify the natural history of NAFLD should begin with the prevention and treatment of clinical conditions that promote its formation and progression. Diabetes mellitus type II and obesity are two metabolic conditions that are closely associated with NAFLD and its progression to advanced liver disease [1, 2]. In addition to basic therapy, which involves lifestyle changes with an emphasis on nutrition and physical activity, some pharmacotherapeutic measures may be effective [1]. Given the high prevalence of NAFLD (particularly its benign form), and its tight association with other manifestations of the metabolic syndrome and thus cardiovascular and other risks and complications, it is important to recognize and aggressively treat this condition, primarily by seeking to change the harmful habits of patients [2].

Nonalcoholic Fatty Liver Disease/  
steatohepatitis

## Pathogenesis

Despite the high prevalence of risk factors leading up to IR, only a certain percentage of people with IR develop NAFLD, and even fewer progress to NASH and associated complications [6]. This suggests that genetic predisposition coupled with environmental factors plays an important role in the development of NAFLD. The most important NASH-predisposing genetic polymorphism that has been studied over the last few years occurs in patatin-like phospholipase domain-containing 3, which encodes the enzyme triacylglycerol lipase, which hydrolyzes triacylglycerol in adipocytes [6–8]. Recent studies confirmed that this genetic variant is associated with NAFLD [6]. Other genetic variants reported to be associated with susceptibility to NAFLD have been identified in the macrophage migration inhibitory factor gene, adiponectin, methylenetetrahydrofolate reductase, PPAR- $\gamma$  coactivator 1 $\alpha$ , haptoglobin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) gene, and the ATP-binding cassette gene [6]. In patients with NAFLD, fat sources, especially triglycerides in the liver, are enhanced by the entry of free fatty acids caused by lipolysis of visceral adipose tissue and de novo lipogenesis. These two phenomena are closely related and associated with IR [8]. The influx of free fatty acids from adipose tissue in the liver comprises 60–80% of intrahepatic fat sources. A study that monitored the eating habits of patients with NAFLD revealed that their diet tends to be high in saturated fat and cholesterol and low in unsaturated fats, fiber, and antioxidants [9]. There is a correlation between saturated fat intake and insulin sensitivity. This indicates that dietary habits can induce steatohepatitis directly, by modulating the accumulation of triglycerides in the liver and inflammatory activity, as well as indirectly, by influencing insulin sensitivity. Increased body weight and obesity are clearly associated with NAFLD [8–10]. IR, a key pathophysiological mechanism in metabolic syndrome and associated diseases, is closely associated with NAFLD development and progression [8, 9]. Peripheral IR is characterized by a decreased uptake of glucose in skeletal muscles and in adipose tissue is manifested by reduced suppression of lipolysis, while IR in liver disorders is characterized by increased gluconeogenesis and glycolysis [8–10]. IR is a key factor in increased fat accumulation in the liver, not only because it leads to hyperinsulinemia, but also because it boosts the activity of enzymes involved in de novo lipogenesis. It should be noted that IR is associated with the progression of simple steatosis to NASH and fibrosis [7–10]. Experimental studies revealed that high glucose levels and hyperinsulinemia in-

crease the activity of connective tissue growth factor, and that hyperinsulinemia may induce oxidative stress and stimulate hepatic stellate cells to proliferate and secrete extracellular matrix [9].

Numerous experimental and clinical studies have shown a strong link between the severity of NASH and the degree of oxidative stress [9]. There was an increase in serum oxidative markers and a decrease in antioxidant molecules in patients with NASH. The levels of these markers correlate with the severity of liver disease and IR [9]. Mitochondrial  $\beta$ -oxidation is the oxidative path of fatty acids under normal physiological conditions; however, in patients with NAFLD, this process is enhanced, and it is the main source of reactive oxidative markers [7–9]. The significance of the increase in these molecules lies in their ability to influence the synthesis of nucleotides and protein, and to increase proinflammatory cytokine levels and activate stellate cells, which ultimately leads to liver inflammation and fibrosis, features of the progression from simple fatty liver to NASH [7, 8].

Among the adipokines and cytokines involved in NAFLD, adiponectin, leptin, TNF- $\alpha$ , and interleukin-6 (IL-6) have a critical role [7–9]. Expression of these mediators is strongly associated with visceral obesity, and they have a decisive role in the modulation of insulin signaling and inflammatory cascades, two processes that are crucial not only in the accumulation of fat in the liver, but also in the progression of the disease [6, 8, 9]. Furthermore, leptin is elevated in obese persons and can trigger inflammation and fibrogenesis [9]. TNF- $\alpha$  levels play a key role in the pathogenesis of IR, the inflammatory response, apoptosis, and steatosis and NASH. Expression of TNF- $\alpha$  in the liver is associated with the severity of fibrosis. IL-6 is also elevated in patients with NASH and IR. Clinical studies have found a linear correlation between serum and hepatic IL-6 levels and the severity of steatosis, necroinflammatory processes, and fibrosis [9].

In addition to the pathogenic factors described above, recent studies have also investigated the roles of new potential mediators of NASH pathogenesis. These include substances that can lead to increased accumulation of fat in the liver and contribute to the development of NASH, such as endocannabinoids, retinol-binding protein, and dehydroepiandrosterone, as well as molecular mediators such as Toll-like receptor 4, the serotonin and renin/angiotensin systems, which may influence the inflammatory response and fibrogenesis, and represent a potential target for pharmacotherapy [6, 8].

In 1998, Day and James [11] attempted to explain the progression of simple steatosis, which is essentially be-

nign and reversible, to steatohepatitis using a model of 'two hits'. Insulin resistance is responsible for the reduced hydrolysis of triglycerides, which leads to increased intracellular accumulation of triacylglycerol; this is a reversible process and comprises the 'first hit' [10, 11]. This condition increases the likelihood of developing molecular and metabolic liver disorders after a 'second hit' of oxidative stress and cytokine-induced damage [11].

### Clinical Presentation and Diagnostic Methods

NAFLD is usually diagnosed in asymptomatic patients based on the accidental discovery of elevated liver enzymes or steatosis identified by ultrasound [1, 2]. Prior to initiating treatment for NAFLD, a detailed personal and family history of the patient should be collected with an emphasis on lifestyle and alcohol consumption. In addition, a complete physical examination should be performed, as well as screening for viral, genetic, and autoimmune causes of liver disease and a series of laboratory tests. In the initial evaluation, it is very important to exclude alcohol consumption [1, 2, 12]. It is necessary to perform a complete physical examination, including measurement of height, weight, waist-to-hip ratio, and blood pressure [12, 13]. Other clinical parameters such as the medications leuprorelin acetate and tamoxifen and frequent nocturnal hypoxia in obstructive sleep apnea were previously reported to lead to reversible acute transaminitis and the histological features of NASH in patients who had not been previously diagnosed with liver disease [12]. Most patients have no clinical symptoms, whereas a smaller number of patients may experience of nonspecific symptoms like fatigue, malaise, and pain below the right costal margin. Physical examination often finds hepatomegaly, and splenomegaly is a rare finding. Increased serum aspartate aminotransferase and alanine aminotransferase (ALT) levels are used as a marker for liver damage [13]. It is important to note that normal ALT values are found in almost half of all patients with NASH, and therefore do not exclude NASH and fibrosis [13]. NASH is very often unrecognized in clinical practice, and too little attention is given to the fact that the final stage of this disease may be the most common current cause of cryptogenic liver cirrhosis. It is therefore very important to perform a thorough patient history and physical examination to uncover metabolic risk factors that may be key to diagnosis [12, 13].

Noninvasive imaging methods (abdominal ultrasound, computed tomography, magnetic resonance imaging, and proton magnetic resonance spectroscopy) can

be used to diagnose steatosis (sensitivity 93–100%), but not steatohepatitis and fibrosis [12, 13]. While all of these techniques yield information about fat distribution in the liver, magnetic resonance imaging and proton magnetic resonance spectroscopy can actually quantify the total amount of fat in the liver [13].

Ultrasound-based transient elastography and magnetic resonance elastography are currently being investigated for their ability to assess the stage of liver fibrosis [14]. However, transient elastography has been shown to fail at body mass index >28, and magnetic resonance elastography remains experimental [14]. Although algorithm-based assays like FibroTest, BARD score, NAFLD fibrosis score, NASH test, which combine biochemical markers and patient variables have been developed for predicting steatosis, steatohepatitis, and fibrosis in patients NAFLD, they require independent population validation and still lack the sensitivity and specificity required for widespread use [13]. Despite the invasiveness and potential complications of the procedure, liver biopsy remains the gold standard in the diagnosis and prognosis of NASH [12]. For now, liver biopsy and histopathological analysis of tissues are the only methods that can definitively distinguish steatosis from NASH and to assess the severity of disease [13].

## Treatment

Effective treatments for NAFLD should be directed toward decreasing IR and metabolic risk factors. Treatments for individual patients should begin by strongly encouraging them to radically change their previous harmful habits. Histological improvement has been reported in NAFLD patients who achieve weight loss, and there is often a reversal of metabolic syndrome complications after bariatric surgery and/or lifestyle intervention [15]. Because there is still no adequate pharmacotherapy, we should not expect patients to recover without lifestyle interventions. Moreover, we should be alert to the fact that in a fraction of patients, mild NAFLD may progress to cirrhosis and associated complications. Thus, treating patients even for relatively asymptomatic NAFLD is very important due to the cardiovascular morbidity that may accompany cirrhosis and contribute to mortality [15]. Pharmacological treatment of this patient group primarily focuses on treating accompanying metabolic disorders, and includes the use of statins, antihypertensive drugs, and antidiabetic agents (biguanides, thiazolidinediones, incretin mimetics) [15–17]. Ursodeoxycholic

acid is not significantly superior to placebo in improving histologic findings [18]. Patients should be treated for metabolic disorders whenever it is appropriate, since NAFLD is not associated with increased hepatotoxicity of these drugs. Data regarding the efficacy and safety profiles of pharmacotherapy agents used specifically to treat NAFLD remain incomplete. The pioglitazone or vitamin E for NASH Study is a recent randomized controlled trial that has yielded some promising results [19]. As corroborated by multiple other studies, pioglitazone improves steatosis, inflammation and biochemical parameters, although its effect on fibrosis is less clear. However, pioglitazone is associated with notable side effects, specifically weight gain, fluid retention, heart failure and osteopenia. Vitamin E was found to be superior to placebo with regard to the resolution of NASH [19].

## Conclusion

The increase in the prevalence of IR and its clinical manifestations led to the identification of NAFLD and its severe and progressive form, NASH [1, 2]. NAFLD is the most common chronic liver disease, and NASH is the most common cause of cryptogenic cirrhosis, making it a serious public health concern [1–3]. In recent years, significant progress has been made in identifying the molecular changes that lead to hepatic steatosis and the progression of steatohepatitis, thus revealing pathways that may be important therapeutic targets for new drugs [6]. NAFLD-related disorders may be diagnosed based on patient history, physical examination, and a series of initial laboratory tests, which primarily seek to exclude other causes of chronic liver diseases (e.g. viral, genetic, and autoimmune); thus, diagnosis of NAFLD/NASH is largely a matter of excluding other possible causes [1, 2, 13]. A number of noninvasive diagnostic methods (e.g. elastography and proton magnetic resonance spectroscopy) have been developed, but these should primarily play a role in monitoring the success of therapy in patients with NAFLD/NASH, and identifying those at risk for developing progressive forms of the disease [12, 14]. Liver biopsy, although invasive and with potential complications, remains the gold standard for diagnosing and monitoring patients [13]. Further studies are needed to find affordable noninvasive markers of fibrosis [13]. Basic treatment of patients with NAFLD/NASH consists of a change in lifestyle and eating habits, exercise, controlled weight loss, and, in some cases, pharmacotherapy, but regarding the latter there is no consensus on the best way to manage NAFLD/NASH [15].

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