Non-alcoholic fatty liver disease (NAFLD) includes a spectrum of liver injuries that mimics alcohol-induced liver disease, yet affects individuals who are not heavy drinkers. NAFLD is likely to be the most common cause of chronic liver disease in many countries and may also potentiate liver damage induced by other agents, such as alcohol or the hepatitis virus. The natural history of NAFLD is uncertain, and there is skepticism as to its clinical importance, given the discrepancy between the high prevalence of NAFLD in the population and the low prevalence of clinically significant liver disease.
1. Definition

Seen in the majority of patients with the metabolic syndrome, NAFLD—or metabolic steatosis—is now considered a manifestation of the syndrome [1]. Liver biopsy remains the gold standard for detecting and staging fatty liver disease as steatosis alone, which has a benign course and steatohepatitis or non-alcoholic steatohepatitis (NASH), which may be associated with fibrosis, and progression to cirrhosis and hepatocellular carcinoma (HCC). NASH was first described in 1980 by Ludwig et al. in 20 patients at the Mayo Clinic over a 10-year period [2]. These patients had histological evidence of alcoholic hepatitis on liver biopsy, but no history of alcohol abuse.

Classically, patients with NAFLD have slightly elevated liver enzyme values, deny excessive alcohol consumption, and have negative serological tests for viral hepatitis, autoimmune liver disease and congenital causes of chronic hepatitis. NAFLD is strongly associated with the metabolic syndrome, especially obesity and type 2 diabetes. In obese patients, the prevalence of NAFLD has ranged from 50% to 90% [3,4]. Obesity may also increase the risk of NAFLD after exposure to particular insults, such as alcohol-related liver problems. Bellentani et al. found ultrasound evidence of fatty liver in 46% of non-obese and 95% of obese heavy drinkers, demonstrating that obesity doubles the prevalence of alcohol-induced fatty liver disease [5]. As for diabetes, it is now established that insulin resistance may play a major role in the pathogenesis of NAFLD [1]. Consistent with this hypothesis, mild insulin resistance is very common in the earliest stages of NAFLD, and more severe insulin resistance (as in type 2 diabetes) correlates with more advanced stages of NAFLD [1].

2. Prevalence

Epidemiological studies are difficult to carry out as no single blood test, imaging study or histological parameter is 100% sensitive or specific for NAFLD. The prevalence of NAFLD in European and Japanese population-based studies is estimated to range from 14% to 21% [5,6]. In a US population-based study, NAFLD was the most likely cause of unexplained abnormal liver enzymes: 27% of adults had elevated AST, ALT or GGT levels, and 79% of those cases could not be explained by other common causes of liver disease, suggesting that NAFLD could represent approximately 30 million people in the US alone [7].

In patients with unexplained elevated liver enzymes, fatty liver was demonstrated in 20-30%, and steatohepatitis with varying degrees of fibrosis was seen in an additional 15-30% [5,8,9]. Thus, NAFLD accounts for around 70% of cases of 'cryptogenic' chronic hepatitis in the general population. The prevalence of NAFLD is even higher in obese and diabetic populations, demonstrated by liver biopsy in up to 90% of patients with cryptogenic hepatitis [3,4]. However, these diagnostic criteria probably underestimate the true prevalence of NAFLD. It has been shown that some patients with NAFLD have normal aminotransferase levels [10]. Moreover, patients with other types of liver disease may also have NAFLD, which can influence the outcome of those other diseases. It is now established that steatosis and steatohepatitis are frequently seen in chronic hepatitis C infection, and are major independent risk factors for progression to cirrhosis [11]. Therefore, positive tests for viral hepatitis do not entirely exclude a diagnosis of NAFLD.

3. Clinical impact

Only limited data are available on the natural history of NAFLD. Several distinct histological appearances have been identified in the natural course of this chronic liver disease: fatty liver alone; steatohepatitis; steatohepatitis with fibrosis; and cirrhosis [12]. It has also been noted that the development of cirrhosis is associated with fatty disappearance.

Cross-sectional studies of NAFLD indicate that most patients have a fatty liver alone, and it is now accepted that such patients rarely progress to steatohepatitis or fibrosis over time. In one longitudinal study, repeat liver biopsies in patients with fatty liver alone showed no progression to steatohepatitis over a 10-year period [13]. These data were further confirmed by other studies [14]. In contrast, progression from fatty liver alone to steatohepatitis was only noted in one patient following liver transplantation [15]. Morbidly obese individuals with a fatty liver alone who undergo rapid weight loss following bypass surgery have also been reported to develop steatohepatitis [16].

At the time of diagnosis, about 30-40% of patients with NASH have advanced fibrosis, whereas 10-15% have established cirrhosis [12]. Established risk factors for advanced fibrosis in patients with NASH are mainly age, obesity and diabetes [8]. Conversely, epidemiological surveys have clearly demonstrated an overprevalence of cirrhosis and HCC in obese and/or diabetic patients [17-20]. Indeed, a long-term follow-up involving more than 800,000 US veterans showed that type 2 diabetes doubled the risk of chronic non-alcoholic liver disease or HCC, and that HCC incidence correlated with the duration of diabetes (Fig. 1) [20].

Assessment of the rate of progression of fibrosis in NASH patients is limited by the fact that all studies are retrospective, and few patients have undergone repeat biopsies during follow-up. In one study, six out of 13 patients showed...
progression of fibrosis and one patient developed cirrhosis after a median duration of 4.5 years [14]. Similarly, five out of 13 patients developed increasing fibrosis over a mean follow-up of 3.5 years [21]. In yet another report, 132 patients with NAFLD were divided into four categories based on their liver histology: 1) fatty liver alone; 2) fat plus lobular inflammation; 3) fat plus ballooning degeneration; and 4) fat plus ballooning plus either Mallory’s hyaline or fibrosis. Cirrhosis was present in four of 19 patients in group 3 and in 14 of 26 in group 4 [22].

Cryptogenic cirrhosis, which represents around 10% of cirrhosis, is probably related to NASH progression in the majority of cases, given the significantly higher prevalence of metabolic factors such as obesity and diabetes compared with other chronic liver disease [12,23]. In patients with cryptogenic cirrhosis, longitudinal studies have shown that the rate of complications such as decompensation or HCC was similar to the rate observed in patients with HCV-related cirrhosis [24].

The precise risk of mortality in patients with NAFLD is not known. In a study of 30 patients with NASH followed-up for more than 10 years, the five-year survival was only 67% and the 10-year survival was 59% [25]. Although the overall mortality was not significantly different from that of an age-and gender-matched population, liver-related mortality was higher. In another retrospective series, liver-related mortality was 7/54 over 18 years of follow-up in those with fatty liver, ballooning degeneration and Mallory bodies or perisinusoidal fibrosis [22]. Although most patients with NASH without bridging fibrosis or cirrhosis have a very low risk of death up to 5-10 years from the time of diagnosis, those with more advanced disease are at a higher risk of death as a consequence of NASH. A recent long-term follow-up showed that, in 420 patients with NAFLD, survival was lower than that expected in the general population (standardized mortality ratio, 1.34; 95% CI, 1.003-1.76; \( p = 0.03 \)), and liver disease was the third most common cause of death, after cardiovascular disease and malignancy [26] (Fig. 2).

4. Conclusion

NAFLD, or metabolic steatosis, is likely to represent the leading cause of chronic liver disease in Western countries, given the extensive prevalence of obesity and type 2 diabetes in those populations. Progression of disease is low, and only a minority develops into cirrhosis or HCC. However, given its high prevalence in the general population, NAFLD is soon likely to become the leading cause of cirrhosis and HCC in the developed countries. At present, cryptogenic cirrhosis and its complications are the second most common indication for liver transplants in the US. When associated with other frequent causes of chronic liver disease, such as alcohol consumption or HCV infection, metabolic steatosis may be a major factor in disease progression. This highlights the urgent need for diagnostic markers and efficient treatments for patients with NAFLD [27].

Conflicts of interest: The authors have none to declare.

References


