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Epidemiology of Non-Alcoholic Fatty Liver Disease

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Key Words
Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Epidemiology

Abstract
Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the most common liver disease worldwide. The prevalence of NAFLD in the general population of Western countries is 20–30%. About 2–3% of the general population is estimated to have non-alcoholic steatohepatitis (NASH), which may progress to liver cirrhosis and hepatocarcinoma. As a rule, the prevalence of NAFLD is higher in males and increases with increasing age, and it is influenced by the diagnostic method and the characteristics of the population, especially lifestyle habits. Population-based studies provide better estimates of the prevalence of NAFLD as compared to autoptic and clinical studies, but few such studies have been performed to date. 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. In these studies, 79% and 55% of patients with NAFLD had normal aminotransferase levels, showing that liver enzymes are not surrogate markers of NAFLD in the general population. Non-invasive markers such as the fatty liver index obtained from the Dionysos Study may be useful to screen for NAFLD in the general population. The most important risk factors for NAFLD are male gender, age, obesity, insulin resistance and the cardiometabolic alterations that define the metabolic syndrome. The prevalence of NAFLD is 80–90% in obese adults, 30–50% in patients with diabetes and up to 90% in patients with hyperlipidemia. 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. The incidence and natural history of NAFLD are still not well defined, but it is recognized that the majority of individuals with NAFLD do not develop NASH. The incidence of NAFLD is probably increasing in Western countries, strictly linked to lifestyle habits.

Definition and Classification of Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is operationally defined as fatty liver (FL), i.e. an accumulation of lipids inside the hepatocytes exceeding 5% of the weight of the liver, without hepatitis B virus or hepatitis C virus infection and in the absence of 'excessive' ethanol intake (conventionally defined as an intake of ethanol >20 g/day) [1, 2]. Other non-alcoholic and non-viral causes of FL that should be excluded are listed in table 1. NAFLD

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Table 1. Classification of secondary causes of non-alcoholic fatty liver (NAFL)

Genetic/metabolic diseases
Wilson's disease
Lypodystrophic diseases
Hypobetalipoproteinemia
Weber-Christian disease
Wolman's disease
Cholesterol ester storage disease
Hemochromatosis
Drugs
Corticosteroids
Estrogens
NSAID
Calcium antagonists
Amiodarone
Tamoxifen
Tetracycline
Clorochine
Perhexiline-maleate
Anti-retrovirals
Environmental toxins
Extrahepatic conditions
Cardiac failure
IBD and others intestinal diseases
Intestinal bacterial overgrowth syndrome
Hypothyroidism
Polycystic ovarian disease
Pregnancy
Other neoplastic diseases
Nutritional
Jejuno-ileal bypass
Total parenteral nutrition
Prolonged starvation
Protein malnutrition
High carbohydrate diet
Infective
Hepatitis C virus
Hepatitis B virus (?)

encompasses a wide spectrum of liver abnormalities, ranging from steatosis to steatohepatitis (NASH, non-alcoholic steatohepatitis) and fibrosis [1, 2]. While steatosis is usually associated with a benign prognosis, steatohepatitis and fibrosis may progress to cirrhosis and possibly hepatocarcinoma.

During the last decade, the number of studies on NAFLD has grown exponentially, and new concepts have been acquired by the scientific community. We now know that NAFLD is often associated with insulin resistance, obesity, diabetes mellitus, hyperlipidemia, visceral adiposity and other cardiometabolic alterations [3–7]. Population and clinical studies have increasingly shown that most cases of NAFLD are associated with the metabolic syndrome (MS), so that NAFLD is presently considered the hepatic manifestation of MS [8, 9]. In support of this idea, subjects with genetic alterations of the insulin receptor and others with various kinds of lipodystrophy often have NAFLD [10–12].

We think that now is the time to develop a 'positive' operational definition of NAFLD [13, 14] and to reach an international consensus as to whether simple non-alcoholic fatty liver (NAFL) is or is not a 'disease'. A disease is a morbid entity that satisfies at least two of the following three criteria [15]: (1) recognized etiological agent(s), (2) identifiable group of signs and symptoms, and (3) consistent anatomic alterations. NAFL(D) has no recognized etiological agents and does not have an identifiable group of signs and symptoms (one may add that its histopathological alterations are not pathognomonic). We propose to use the term NAFLD as a part of the spectrum of NAFL. NAFL should not be considered a disease owing to the available data obtained in the general population that show it has a benign course. NAFL is a condition that might stabilize, regress or evolve into NAFLD, including cirrhosis and hepatocarcinoma [16–18], depending on many factors (whose identification should be a priority of applied, clinical and epidemiological research). The time that NAFL takes to evolve into frank NASH, cirrhosis and hepatocarcinoma is uncertain because the long-term natural history is not defined except that for clinical series, which cannot be used to infer the burden of disease in the general population.

Epidemiology of NAFLD

Prevalence

The prevalence of NAFLD is rapidly increasing worldwide in parallel with the increase in obesity and type 2 diabetes [19]. It is important to note that this prevalence is partly dependent upon the method used to diagnose FL, the method used to assess alcohol intake and the cut-off point used to exclude 'relevant' alcohol intake, see table 2, with respective references [20–44]. The prevalence of NAFLD in the general population is estimated to be 20–30% in Western countries [33–35, 42] and 15% in Asian countries [45–50]. In Saudi Arabia, the prevalence of NAFLD as evaluated by computed tomography is about 10%.

Liver ultrasonography is the technique most commonly used to diagnose FL in the general population. Although it is virtually the only technique that can be used in the general population for ethical and logistic reasons,

Table 2. Prevalence of NAFLD and NASH worldwide according to different types of study and population

Type of study	Country and type of population	Prevalence of NAFLD (%)	Prevalence of NASH (%)
Autopsy random series			
Hilden [20]	Sweden	24	n.r.
Ground [21]	USA	16	n.r.
Autopsy hospitalized deaths			
Wanless [22]	Canada	7	3
Hospital series – liver biopsy			
7 studies summarized by McCullough [23]	USA, Japan, Europe	15–84	n.r.
Berasain [24]	Spain	n.r.	16
Hospital series – surgical patients			
Living donors			
Marcos and Hwang [25, 26]	USA	20	n.r.
Bariatric surgery			
Dixon, Marceau, Del Gaudio, Luyckx, Silverman and Kral [27–32]	USA, Europe	56–86	n.r.
General population study imaging ultrasound			
Bellentani [33]	Italy	58	n.r.
	Lean	16	n.r.
	Obese	76	n.r.
Bellentani [34]	Italy	24.5	n.r.
Bedogni [35]	Italy	25	n.r.
Nomura [36]	Japan	14	n.r.
Lonardo [37]	Italy	20	n.r.
Omagari [38]	Japan	9	n.r.
Araujo [39]	Brazil	33.5	n.r.
Radu [40]	Romania	20	n.r.
Imaging CT scan		10	n.r.
El-Hassan [41]	Saudi Arabia	34	n.r.
Imaging PMRS			
Browning [42]	USA		n.r.
	Hispanic	45	n.r.
	White	33	n.r.
	Black	24	n.r.
Extrapolation based on alteration of ALT			
Patt [43]	USA	14–21	n.r.
NHANES III [44]	USA	3–23	n.r.

n.r. = Not reported.

liver ultrasonography is known to underestimate the prevalence of FL. The Dallas Heart Study [50] and our Dionysos Nutrition and Liver Study [35] reported that 30 and 25% of US and Italian adults have NAFLD. In these studies, 79 and 55% of patients with NAFLD had normal aminotransferase levels, showing that liver enzymes are not surrogate markers of NAFLD.

The prevalence of NAFLD varies according to age, gender and weight status. NAFLD and the NASH have been reported in subjects of all ages, including children, where the prevalence of steatosis is smaller than in adults (13–15%), but increases in presence of obesity (30–80%) [47–49]. As a rule, the prevalence of NAFLD increases with age, with higher values in males between 40 and 65 years [41, 51–53]. Contrary to studies pub-

Table 3. Causes of death (absolute value) in the Dionysos cohort (year 2002) after a median follow-up of 8.5 years

Etiology	Alcoholic FL	NAFL
Cardiovascular diseases	9 (26%)	3 (38%)
Cancer	11 (31%)	3 (38%)
Cirrhosis/HCC	6 (17%)	1 (12.5%)

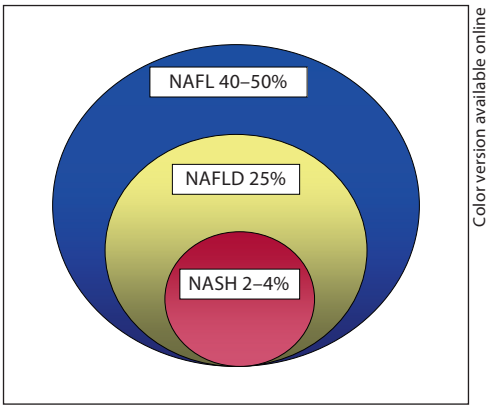

Fig. 1. Estimated prevalence of NAFL, NAFLD and NASH.

lished before 1990, which showed that NASH was more common among middle-aged women [50, 54–57], recent studies show that NAFLD is more frequent in males than in females [58]. A recent study conducted with magnetic resonance spectroscopy has shown that Hispanics have a higher prevalence of FL than other ethnic groups in the USA [20]. In obese patients, the prevalence of FL ranges between 30 and 100%, in those with type 2 diabetes mellitus between 10 and 75%, and in those with hyperlipidemia between 20 and 92% [3]. A recent study showed that 27% of US adults have raised levels of liver enzymes and that 79% of these values cannot be explained by the most common causes of liver disease [59]. It was concluded that NAFLD is the most common cause of hypertransaminasemia in the USA, being present in 31% of men and 16% of women [59]. These estimates, however, do not take into account the fact that almost 50% of the cases with NAFLD have normal levels of liver enzymes [35, 50, 60–69].

Partly because of selection bias, bioptic and autoptic studies give a different estimate of the prevalence of NAFLD (3–15%) and NASH (1–7%) [45, 62–68]. When selected patients followed at tertiary care centers undergo liver biopsy, the prevalence of NAFLD is 39–51% and that of NASH is 32–34% [67–69]. Nowadays, the most reliable values for the prevalence of NAFLD and NASH in the general population are 20–30% and 2–3%, respectively. Owing to the increased prevalence and incidence of obesity and diabetes, in the next few years NAFLD may represent the principal cause of liver disease worldwide and possibly the first cause of liver transplantation [69].

We suggest to expand the number of prospective cohort studies in the general population, even if they are more expensive and difficult to handle, because they give more reliable results about the burden of disease attributable to NAFLD. The most simple, noninvasive and practical method for diagnosing FL in population studies is presently liver ultrasonography. Liver enzymes, especially ALT, should not be used because they miss most cases of NAFLD in the general population. Noninvasive tests such as the Dionysos 'fatty liver index' (FLI) might prove to be useful in predicting FL in the general population [70, 71]. FLI is a continuous score based on four variables that are simple and cheap to collect: BMI, waist circumference, serum triglycerides and γ-glutamyl-transferase. FLI was recently studied by the RISC group on 1,300 apparently healthy non-diabetic subjects from different European countries and found to be a predictor of insulin resistance and cardiovascular risk factors [71]. This adds to the potential value of FLI as predictor of FL in the general population.

Risk Factors

As reported above, NAFLD is more prevalent in patients with obesity, diabetes and the full spectrum of the MS. Moreover, these same conditions have been identified as risk factors for NASH and liver fibrosis [67–69]. In the literature, many competing definitions of the MS are available. The definition recently put forth by the International Federation for the Study of Diabetes (IDF) [72] requires the presence of central obesity (waist circumference >94 cm for European men and >80 cm for European women) and at least two of the following factors: (1) triglycerides >1.70 mmol/l or specific treatment, (2) HDL-cholesterol <1.03 mmol/l in men and <1.29 mmol/l in women or specific treatment, (3) systolic arterial pressure >130 mm Hg or diastolic >85 mm Hg or specific treatment, and/or (4) fasting glucose >5.6 mmol/l or previous diagnosis of type 2 diabetes. The prevalence of MS in the USA, as detected by the NHANES III Study using the Adult Treatment Panel III criteria, is 20% in young subjects and 40% in adults older than 40 years. In subjects with MS, the prevalence of NAFLD varies between 36 and

63%. NAFLD is presently considered the hepatic manifestation of MS and is a predictor of the development of diabetes cardiovascular disease. According to a recent study, cardiovascular disease and cancer are the most common causes of death in patients with NAFLD [73]. We obtained the same result in our Dionysos cohort after a median follow-up of 8.5 years (table 3). In some, but not all, studies, a diagnosis of NAFLD was associated with a shorter survival than expected for the general population, with the increased mortality due mostly to cardiovascular disease. An association between elevated liver enzymes and cardiovascular risk has been reported by some population-based studies, most notably the Hoorn Study, the Framingham Study and the Valpolicella Study [74–76]. Even if it is not yet clear whether NAFLD has a causative role in cardiovascular disease, it surely is associated with its development, and as a result, hepatologists should start to evaluate the cardiovascular risk of their patients with NAFLD.

Incidence

Very few data are available on the incidence of NAFLD in the general population. In the 8.5-year follow-up of the Dionysos Study, FL detected by ultrasonography regressed in nearly 1 of every 2 patients and had a substantially benign course [77]. The incidence and remission rates of FL after a median follow-up of 8.5 years were 18.5 and 55.0 per 1,000 person-years. Importantly, every increase of 20 g/day of ethanol intake at baseline was associated with a 17% increase in the rate of incident FL [77].

Conclusion

NAFLD has become a common diagnosis in clinical practice reflecting its increased prevalence and incidence in the general population. We think that it is important to reach a 'positive' operational definition of NAFLD which can be shared by researchers worldwide. Simple NAFL is present in almost 40–50% of the general population and must be considered benign in light of the available evidence. The main task for the future is to become able to distinguish NAFL from NAFLD. Population cohort studies with long-term follow-up are essential to better define the incidence and natural history of NAFLD. Genetic studies are also needed to determine to what extent the genetic background predisposes to the development of serious liver disease and cardiometabolic disease.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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