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TOPIC HIGHLIGHT

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Epidemiology of fatty liver: An update

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Abstract

We provide a concise review of the main epidemiological literature on fatty liver (FL) published between January 2011 and October 2013. The findings from the literature will be considered in light of the already available knowledge. We discuss the limitations inherent in the categorization of FL into non-alcoholic and alcoholic FL, the potential relevance of FL as an independent predictor of cardiometabolic disease, and recent research addressing the role of FL as an independent predictor of mortality. This review is organized as a series of answers to relevant questions about the epidemiology of FL.

Key words: Fatty liver; Epidemiology

Core tip: We discuss the limitations inherent in the division of fatty liver into non-alcoholic and alcoholic FL, the potential relevance of FL as an independent predictor of cardiometabolic disease, and recent research addressing the role of FL as an independent predictor of mortality.

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INTRODUCTION

The aim of this paper is to provide a concise review of the main epidemiological literature on fatty liver (FL) published between January 2011 and October 2013. The findings from such literature will be considered in light of the already available knowledge[1,2]. Our main focus will be on the general population though we will also consider selected clinical studies. We have organized this paper as a series of answers to relevant questions about the epidemiology of FL. It is our hope that this format will attract the interest of practicing physicians as did our previous review on FL that was presented in this manner[3].

WHAT IS FATTY LIVER?

A liver is said to be "fatty" when its hepatocytes contain more than 5% of triglycerides[4,5].

The reference method for the diagnosis of FL is liver biopsy (LB), which is presently used to classify steatosis as light (5% to 33%), moderate (> 33% and < 66%) or severe (> 66%)[4,5]. Although LB is the reference method for the diagnosis of FL, it is an imperfect gold-standard because of sampling error[6,7]. More importantly, LB cannot be employed outside Liver Centers, and less invasive methods are needed to study the epidemiology of FL in the general population[8].

Liver ultrasonography (LUS) is the method most commonly employed to assess FL in the general population[8-11]. Compared with LB, LUS has a sensitivity of

84.8%, a specificity of 93.6%, a positive likelihood ratio of 13.3, and a negative likelihood ratio of 0.16 for the detection of moderate to severe FL[11]. LUS offers an accurate assessment of FL starting from an intrahepatic triglyceride content of 10%[11]. We have found LUS to agree well with LB for the assessment of moderate to severe FL in children[12] but there are presently not enough data to draw definitive conclusions about the interchangeability of LUS and LB in pediatric age[13,14].

Magnetic resonance spectroscopy of the liver (LMRS) has also been used to perform population studies of FL[15] but is less portable and more expensive than LUS[8]. However, a clear advantage of LMRS over LUS is that it offers a continuous rather than an ordinal measure of FL[16].

A further option to study FL in the general population is the use of surrogate markers. A discussion of such markers is beyond the scope of this article, and the interested reader is referred to a recent review on this topic[8]. We wish however to briefly mention the fatty liver index (FLI), which we developed in about 500 adult citizens of Campogalliano (Modena, Northern Italy) during the Dionysos Nutrition and Liver Study[9,17]. FLI is based on four common anthropometric and biochemical measures (body mass index, waist circumference, gamma-glutamyltransferase and triglycerides) and has gained much attention because of its association with prevalent cardiovascular disease, incident type 2 diabetes mellitus (T2DM), and liver-related mortality[18-22]. More importantly for its ability to serve as surrogate marker of FL, FLI has been successfully cross-validated in external populations[23,24].

WHAT IS NON-ALCOHOLIC FATTY LIVER (DISEASE)?

FL is usually divided into alcoholic fatty liver (AFL) and non-alcoholic fatty liver (NAFL)[3,25].

NAFL is however just one part of the spectrum of liver disease that falls under the umbrella term of non-alcoholic fatty liver disease (NAFLD)[3]. It should be noted that we are using the term NAFL in a broader sense than that recently suggested by the American Gastroenterological Association (AGA), *i.e.*, the finding of 'steatosis without steatohepatitis' at LB[26].

Besides NAFL, the NAFLD spectrum includes steato-hepatitis (NASH), fibrosis, cirrhosis and hepatocarcinoma (HCC). The idea behind NAFLD as a spectrum of liver disease was that simple steatosis might progress to NASH and then to chronic liver disease. However, this idea has been increasingly challenged in the last decade[27]. Studies performed in Liver Centers have shown that, whereas about 20% of cases of NASH will develop liver fibrosis, simple steatosis will virtually never progress to NASH[1,2,28]. There is indeed the possibility that NAFL and NASH are twin but independent conditions and that triglyceride accumulation alone is protective, at least up to a certain degree, as far as liver outcomes are concerned[27,29].

NAFL(D) and AFL(D) cannot be distinguished at LB and their differentiation is based on the assessment of ethanol intake[3,25]. After exclusion of other causes of FL (mostly hepatitis B or hepatitis C virus infection and use of steatogenic drugs), the guidelines of the European Association for the Study of the Liver (EASL) suggest that NAFLD should be diagnosed when ethanol intake is less than or equal to 20 g/d in women and less than or equal to 30 g/d in men[30]. AGA guidelines suggest that NAFLD should be diagnosed when men consume less than or equal to 21 drinks per week and women consume less than or equal to 14 drinks per week[26]. Although the EASL and AGA cut-points are roughly equivalent, the former have the advantage of focusing on actual ethanol intake, possibly avoiding the problems associated with the choice of different "drink units"[31].

The NAFL(D) *vs* AFL(D) categorization is vulnerable to many criticisms[25]. Besides the obvious loss of information[32], the most important criticism is that such categorization hides the fact that obesity and alcohol interact in determining the prevalence and incidence of FL[25,33,34]. From a public health perspective, it is more useful to study the effect of alcohol intake on FL-related outcomes independently from other risk factors rather than dividing FL more or less arbitrarily into NAFL and AFL[10,17,25]. Another problem is that such a categorization assumes the use of an instrument accurate enough to detect small differences in ethanol intake. Even the 7-d weighted food record method that we employed in the Dionysos Nutrition and Liver study may not be accurate enough to detect such differences[9].

WHAT IS THE PREVALENCE OF FATTY LIVER?

FL is the most common liver disease in Western countries, and NAFLD is the most common reason for altered liver enzymes in primary care[30].

In the general population of the Dionysos Nutrition and Liver Study, 45% of individuals had any degree of FL at LUS[9,17]. Using a cut-point of 20 g/d for ethanol intake, 25% had NAFLD and 20% had AFLD[9]. A recent study performed in a large primary care practice has shown that nearly one in every three patients with persistently elevated alanine transaminase has NAFLD[35,36].

Systematic reviews estimate that about 20%-30% of individuals in Western countries have NAFLD[26] and similar figures are being increasingly provided for Eastern countries[37]. The prevalence of NAFLD increases with age, is highest in males between 40 and 65 years and is higher in Hispanics and lower in African-Americans[26,30,38]. The prevalence of NAFLD is increasing rapidly among children in parallel with the current epidemic of obesity[39].

LUS data from the third edition of the National Health and Nutrition Examination Survey (NHANES Ⅲ) (1988-1994) have recently been used to provide an estimate of the prevalence of FL in the general United

States population[40]. Although these data were collected more than 20 years ago and may underestimate the present prevalence of FL, they are unique because they were obtained in a representative sample of the general population. The age-adjusted prevalence of FL in NHANES Ⅲ, defined as moderate to severe FL at LUS, was 21% while that of NAFLD was 20%[40].

Because LB can be performed only in Liver Centers, it is unknown how many individuals in the general population have NASH or liver fibrosis. Projections made mostly on the basis of autopsy data suggest that 3%-5% of individuals in the general population might have NASH[2,41]. Using surrogate markers of liver fibrosis, it has been postulated that about 3% of individuals in the general population might have liver fibrosis[42].

WHAT IS THE INCIDENCE OF FATTY LIVER?

The incidence of LUS-determined FL (any degree) in the Dionysos Study was 2 per 1000 person-years[10] but values of up to 10 per 1000 person-years have been reported by other studies employing the same method[2,30].

WHAT IS THE NATURAL HISTORY OF FATTY LIVER?

Systematic reviews of studies performed in tertiary care centers have clearly shown that NASH is a risk factor for liver fibrosis, cirrhosis and HCC[1,2,28]. However, as determined by LUS, most cases of FL in the general population regress, especially in the presence of weight loss[10,43,44].

A recent longitudinal analysis of about 11000 individuals from NHANES Ⅲ has shown that LUS-determined NAFLD alone is not an independent predictor of mortality[45]. However, when considered together with advanced fibrosis - as detected by surrogate markers - NAFLD was associated with increased mortality independently of known risk factors[45]. Another recent analysis of the same NHANES Ⅲ data (with a different number of subjects because of different inclusion criteria) has shown that NAFLD may be an independent predictor of liver-related mortality in Whites[46]. Considering the different effect measures and statistical methods employed by these studies[45,46], their results are not necessarily at odds if one considers that the effect size of the 'positive' study was highly variable (relative risk of death attributable to NAFLD = 10.74, 95%CI: 1.17-98.54).

WHAT IS THE RELATIONSHIP BETWEEN FATTY LIVER AND METABOLIC SYNDROME?

There is no doubt that NAFLD is more common among obese individuals and those with metabolic syndrome (MS)[26,30]. Because of this association, it has become common to state that NAFLD is the "hepatic component" of MS[46]. However, this hypothesis has not undergone formal testing until very recently[47]. A confirmatory factor analysis of NHANES III cross-sectional data has indeed shown that NAFLD is more likely to be a separate entity rather than an additional component of MS[47]. Even if NAFLD is not the "hepatic component" of MS, however, it remains to be tested whether MS and NAFLD contribute independently to 'hard outcomes' in the general population. This is important also in view of the ongoing controversy about the clinical relevance of the MS concept[48-50].

Although NAFLD is most commonly associated with obesity, it is by no means uncommon in lean individuals. A recent analysis of NHANES Ⅲ data has shown that the prevalence of NAFLD in lean individuals, defined as those with body mass index $\leqslant$ 25 kg/m^2, is a quarter of that observed in overweight-obese individuals (7% *vs* 28%)[35]. Compared with its overweight-obese counterpart, 'lean NAFLD' is characterized by younger age, higher insulin sensitivity and lower frequency of MS[35].

WHAT IS THE RELATIONSHIP BETWEEN FATTY LIVER AND CARDIOMETABOLIC DISEASE?

Much of the interest in NAFLD among researchers and clinicians outside the field of Hepatology stems from its association with cardiometabolic disease[51-53].

In the last few years, an increasing number of cohort studies performed in the general population of Western and Eastern countries has shown that NAFLD, diagnosed by LUS or by surrogate markers such as FLI, is independently associated with incident T2DM[18,21,54,55]. The available evidence pointing to an association between NAFLD and incident cardiovascular disease (CVD) is presently of lower quality than that available for incident T2DM[54]. In a recent study performed in a tertiary CVD care center, NAFLD was associated with coronary artery disease but not with cardiovascular mortality[56]. Likewise, a recent analysis of NHANES Ⅲ cohort data showed that NAFLD was associated with incident CVD but not with CVD mortality[57].

The availability of long-term follow-up data in more or less representative samples of the general population will be central in coming years to improve our understanding of the NAFLD-CVD relationship.

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