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Special Article

Epidemiological modifiers of non-alcoholic fatty liver disease: Focus on high-risk groups

The non-alcoholic fatty liver disease (NAFLD) study group, dedicated to the memory of Prof. Paola Loria

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This work is dedicated to the memory of the late Professor Paola Loria.

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ABSTRACT

An improved understanding of non-alcoholic fatty liver disease epidemiology would lead to identification of individuals at high risk of developing chronic liver disease and extra-hepatic complications, thus contributing to more effective case finding of non-alcoholic fatty liver disease among selected groups.

We aimed to illustrate the epidemiology of non-alcoholic fatty liver disease in high-risk groups, which were identified based on existing literature. To this end, PubMed was searched to retrieve original articles published until May 2015 using relevant and pertinent keywords "nonalcoholic fatty liver disease" and "diabetes", "obesity", "hyperlipidaemia", "familial heterozygous hypobetalipoproteinaemia", "hypertension", "metabolic syndrome", "ethnicity", "family history" or "genetic polymorphisms".

We found that age, sex and ethnicity are major physiological modifiers of the risk of non-alcoholic fatty liver disease, along with belonging to "non-alcoholic fatty liver disease families" and carrying risk alleles for selected genetic polymorphisms. Metabolic syndrome, diabetes, obesity, mixed hyperlipidaemia and hypocholesterolaemia due to familial hypobetalipoproteinaemia are the major metabolic modifiers of non-alcoholic fatty liver disease risk. Compared with these metabolic conditions, however, arterial hypertension appears to carry a relatively more modest risk of non-alcoholic fatty liver disease.

A better understanding of the epidemiology of non-alcoholic fatty liver disease may result in a more liberal policy of case finding among high-risk groups.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD), the most common liver disease worldwide [1], includes simple steatosis and non-alcoholic steatohepatitis (NASH), which is associated with or precedes the metabolic syndrome (MetS) and its individual features [2–6]. NAFLD carries an increased risk of hepatic (*e.g.* cirrhosis and hepatocellular carcinoma [HCC]) and extra-hepatic (*e.g.* type 2 diabetes mellitus [T2DM], cardiovascular disease [CVD], chronic kidney disease and cancer) [7,8] complications, and therefore tends to be associated with excess morbidity/mortality and health expenditure [9–11].

Currently, the majority of hepatological scientific societies do not suggest a policy of case finding for NAFLD given that no specific drug treatment is available [2,12]. However, NAFLD care exceeds drug therapy, comprising both diagnostic procedures and tailored follow-up schedules [7,12]. Clearly, the high prevalence of NAFLD worldwide [1] makes it illogical to propose any screening campaigns to identify cases of NAFLD in the general adult population. Therefore, we hypothesise that a better understanding of NAFLD epidemiology would improve the characterisation of those groups of individuals at a high risk of developing chronic liver disease and extra-hepatic complications.

This clinical review aims to specifically illustrate the epidemiology of NAFLD in high-risk groups, which were identified according to literature data [1,6,13,14]. To this end, PubMed was searched for articles published between 1990 and May 2015 in peer-reviewed journals using the pertinent keywords: "nonalcoholic fatty liver disease" or "fatty liver" AND "diabetes", "obesity", "dyslipidaemia", "hyperlipidaemia", "familial hypobetalipoproteinaemia", "hypertension", "metabolic syndrome", "ethnicity", "family history" or "genetic polymorphisms".

Our findings identify both physiological (*i.e.* age, sex, ethnicity, families and genetics) and metabolic modifiers of NAFLD

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(*i.e.* MetS and its individual features) which may change current clinical attitudes in the diagnosis and management of NAFLD.

2. Age, sex and ethnicity

Age, sex and ethnicity modulate NAFLD risk in high-risk individuals and in the general population [14,15].

NAFLD is more common in men, increases with age and shows sex-specific differences [16–19]. In men, NAFLD increases from younger to middle age and, forming an "inverted U shaped curve", starts to decline after the age of 50–60 years [16,19]. Conversely, pre-menopausal women are relatively spared by NAFLD, however its prevalence rises after the age of 50, peaking at 60–69 years and declining after the 7th decade of life [16,18,19]. Accordingly, after the 5th decade, the prevalence of NAFLD is similar in both sexes or possibly lower in men [16,20].

Most, though not all, studies have shown that advancing age and male sex affect the risk of NAFLD, independently of coexisting MetS features [21–26]. Other studies, although confirming that men are at a higher risk of NAFLD, have shown an inverse association between NAFLD and age [27–30]. Conversely, in women, advancing age, menopausal status and MetS features are all independent predictors of NAFLD [31,32]. The lower prevalence of NAFLD, which has been reported with advancing age in the elderly [33], is potentially attributable to either selective mortality or the development of cirrhosis (which generally leads to the disappearance of steatosis). "Lean NAFLD" is associated with younger age, but findings regarding the role of sex are conflicting [29,34].

Increasing age may also have an impact on the risk of NASH and fibrosis, but data on sex are, again, inconsistent. Middle-aged and elderly individuals have a higher prevalence of fibrosing NASH [35,36]. Most studies [20,32,37–39], except for one [40], have reported that NASH is histologically more severe in women than in men. However, a systematic review shows that only age and hepatic necro-inflammation are independent predictors of the development of advanced fibrosis in NASH patients, whilst MetS features and sex are not [41]. Finally, a recent study reports that men are at a higher risk of more severe liver fibrosis compared with premenopausal women; however, post-menopausal women experience similar severity of liver fibrosis as men, suggesting that oestrogens may protect against fibrosis [42].

Advancing age increases the risk of the hepatic and extra-hepatic complications of NAFLD [43]; it is, therefore, expected that older NAFLD patients will have a higher likelihood of overall and disease-specific mortality [44–47]. Whether sex affects NAFLD natural history and mortality is uncertain, although studies have suggested a worse outcome in men [45,48,49].

The prevalence of NAFLD follows a gradient in different ethic groups: Hispanics > Whites/Caucasians > African-Americans [50–53], and ethnicity may modulate the association among NAFLD, sex and MetS features. For example, NAFLD is more common in men than in women among Whites, but not among African-Americans or Hispanics [50]. Moreover, although they have the highest prevalence of obesity, a smaller percentage of obese/MetS African-Americans have NAFLD. In contrast, Hispanics have the highest prevalence of NAFLD, including the obese and MetS population [53]. Interestingly, among patients with NAFLD, NASH is less frequent in African–Americans than in Hispanics [54]. Finally, the adverse effect of insulin resistance (IR) on NASH risk is worsened by non-Hispanic ethnicity [38].

In summary (Fig. 1, panel A), there are complex and intertwined relationships among age, sex, ethnicity and MetS features which heavily affect the risk of development and progression of NAFLD/NASH.

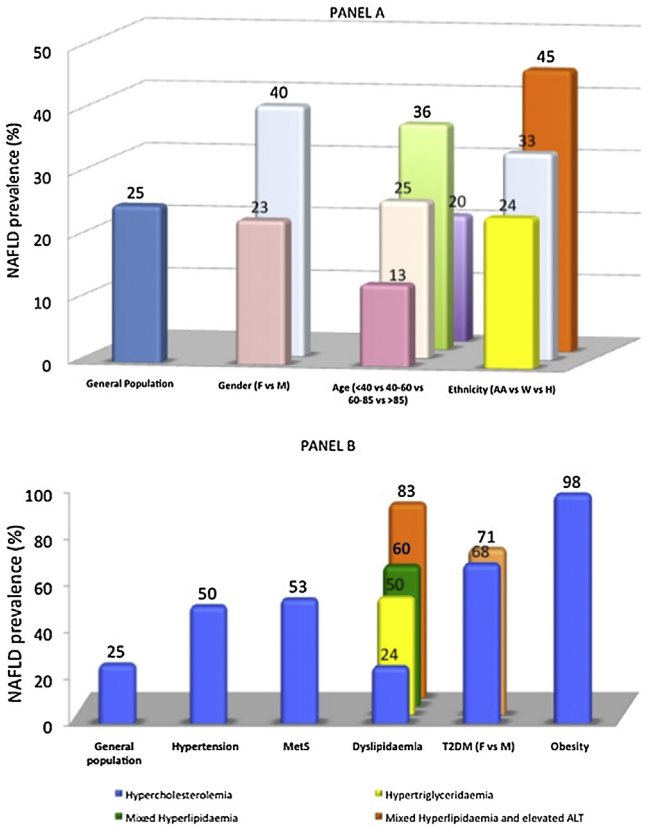

Fig. 1. Prevalence of non-alcoholic fatty liver disease in various high-risk groups compared with the general adult population. (Panel A) Chief physiological modifiers (age, sex and ethnicity). Data extrapolated from the bibliography and Supplementary Tables S1 and S2, illustrate the effect of gender (NAFLD is more common in men than in women), age ("inverted U pattern") and ethnicity (gradient Hispanics > Whites/Caucasians > African-Americans) on NAFLD prevalence. *Colour codes*: Gender: Pink, Women; Grey, Men. *Age*: Pink, <40 years; Light Pink, 40–60 years; Green, 60–85 years; Violet, >85 years. *Ethnicity*: Yellow, AA; Grey, W; Red, H. *Abbreviations*: AA, African-Americans; F, Female; H, Hispanics; M, Male; W, Whites/Caucasians. (Panel B) Effect of the metabolic syndrome and its individual features. Data from the bibliography and Supplementary Tables S1 and S2 demonstrate that type 2 diabetes seems to rescind sex differences in susceptibility to NAFLD. Indeed, type 2 diabetic patients are equally affected by NAFLD irrespective of sex, in contrast to the general population (Fig. 1 Panel A), in which men are more frequently affected than women. Moreover, the metabolic syndrome seemingly adds little to the risk of developing NAFLD conveyed by most of its individual features, except for hypertension. Among the features of the metabolic syndrome there is a gradient of risk in association with NAFLD: obesity > mixed dyslipidaemia with raised serum alanine aminotransferase (ALT) levels > type 2 diabetes mellitus > hypertension. *Colour codes*: Dyslipidaemia: Blue, Hypercholesterolaemia; Yellow, Hypertriglyceridaemia; Green, Mixed Hyperlipidaemia; Orange, Mixed hyperlipidaemia with raised serum ALT levels. *T2DM*: Red, Women; Blue, Men. *Abbreviations*: F, Female; M, Male; T2DM, Type 2 Diabetes; MetS, Metabolic Syndrome.

3. Family studies

Inheritable factors play a major role in the variety of presentations of NASH/NAFLD [55]. Family and twin studies have provided substantial support for this connection and the identification of high-risk genetic polymorphisms, such as patatin-like phospholipase domain-containing 3 (*PNPLA3*), may provide keys to uncovering a familial inheritance pattern. For example, familial patterns of NASH, frequently related to the recognition of cirrhosis in multiple generations, have been described. Differences in environmental exposure combined with genetic predisposition ("nature *plus* nurture") both likely contribute to the variance in phenotypic expression of NASH, although they can be difficult to separate because of the commonalities of both genetic and environmental factors in families.