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Is non-alcoholic steatohepatitis in lean people a risk factor for liver or cardiovascular disease?

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is commonly diagnosed in obese or overweight individuals. However, lean individuals with NAFLD represent one notable part of the phenotypic clinical cases of NAFLD. Current evidence suggests that lean and obese patients with NAFLD share different metabolic and cardiovascular disease (CVD) risk profiles. Lean NAFLD and its advanced form non-alcoholic steatohepatitis (NASH), need further investigation including epidemiology, clinical risk assessment, liver histological changes, genetic and pathophysiologic predisposing mechanisms, natural history, relation to CVD risk, and treatment strategies in this population with this under-recognized disease. However, to the extent it induces hepatic fibrosis (50% of the cases of NASH) this is as harmful as NAFLD in obese individuals and needs treatment with pioglitazone and potent statin for the reduction of liver and CVD morbidity and mortality.

Key words: non-alcoholic fatty liver disease; non-alcoholic steatohepatitis; liver cirrhosis; cardiovascular morbidity; cardiovascular mortality; treatment

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Introduction

Non-alcoholic fatty liver disease (NAFLD), characterized by accumulation of fat (>5%) in liver cells, in the absence of excessive alcohol intake, chronic viral hepatitis or other liver disease, is the most common liver disease woldwide [1-3]. NAFLD is strongly connected with metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and dyslipidemia.1 However, there is emerging evidence that NAFLD appearance in lean or normal weight individuals too and not only in overweight/obese ones [1,4].

Data from the National Health and Nutrition Examination Survey III (NHANES III) conducted between 1988 and 1994 showed that among 11,613 participants 2,185 (19% ± 0.76%) had NAFLD; of these, 307 (12% ± 1.03%) had non-alcoholic steatohepatitis (NASH), the most advanced form of NAFLD with liver inflammation and usually fibrosis [5]. Multivariate analysis showed that NAFLD in lean subjects was independently associated with younger age, female sex, and a decreased likelihood of having insulin resistance (IR), suggesting that NAFLD in these subjects might have a different prognosis [6]. In overweight/obese NAFLD patients, T2DM was the only independent predictor of NASH, leading to liver fibrosis and increased CVD risk [6]. In lean NAFLD individuals, the only variable independently associated with NASH was haemoglobin. Alanine aminotransferase (ALT) and diabetes were independent predictors of fibrosis ≥ 2 in NAFLD overweight or obese patients, whereas haemoglobin was the only independent predictor of fibrosis ≥ 2 in lean NAFLD [6].

The above suggest a different degree of CVD risk for the two forms of NAFLD, i.e. fat and lean [7]. Results from several studies have shown that lean patients with NAFLD have insignificant IR (some genetic variants are associated with NAFLD without IR), as compared to that in obese patients with NAFLD [7]. Some studies suggest that the prevalence of NASH and advanced fibrosis do not differ significantly between lean and obese patients with NAFLD; however, lean patients tend to have less severe disease at presentation [8]. In other studies young, lean subjects with NAFLD are at a significantly increased CVD risk, especially those with NASH [9].

The above are sometimes conflicting and they suggest that it is not entirely clear if lean NAFLD has the same epidemiology, pathogenesis, prognosis, or outcome with obese NAFLD.

Epidemiology of lean NAFLD

The prevalence of lean subjects with NAFLD in a sample of Iranian population was 17.5%.10 High triglycerides (TGs), higher systolic blood pressure (SBP), and higher body mass index (BMI), mainly over 23.2 Kg/m^2 were independent predictors associated with the presence of NAFLD in lean subjects [10].

South Asians have a very high prevalence of MetS [11]. According to studies from India [12,13] and Sri Lanka [14-16], the prevalence of NAFLD in South Asia varies from 9 to 45% (mean 30%). The lowest prevalence (8.7-18%) of NAFLD was observed in physically active, poor, lean persons residing in rural regions [14,16]. A study from India, a very large country, reported that 13% of NAFLD cases were lean, while 69% were obese and 18% were overweight, respectively [17]. In a study from China, an even larger country, the prevalence of lean NAFLD was as high as 18% [18]. Of note, populations of Asian countries were shown to have an elevated risk of T2DM, hyperlipidaemia and hypertension at a relatively low level of BMI [19-22]. Therefore, the recommended by WHO BMI cut-off points for Asians for defining overweight (23-25 kg/m^2) and obesity (>25 kg/m^2) are clearly lesser than those of Western populations [19]. In any case, the prevalence of lean NAFLD around the world fluctuates from 10% in USA, to 20% in Hong Kong, to 27% in Korea [8]. There is thus a specific problem with lean NAFLD in South Asia, which is a very densely populated area, with more than 2 billion inhabitants, although we used to believe that the people there consume a very healthy diet and have an intensive physical activity, so that the prevalence of MetS, T2DM, and NAFLD would be low.

Pathophysiology

The underlying pathophysiologic basis of NAFLD in lean subjects remains uncertain, with conflicting

data. It appears that there is no single pathway to this multifactorial phenotype. Genetic predisposition acting together with environmental influences, such as dietary composition and gut microbiome may have an important role [23]. Polymorphisms in genes affecting lipid metabolism, oxidative stress, IR and immune regulation have been identified as predisposing factors for the development of NAFLD. The peripheral IR might contribute to steatosis by increasing lipolysis and delivery of free fatty acids to the liver. It is likely that multiple hits, acting together on genetically predisposed lean subjects, induce NAFLD [23].

There are conflicting and uncertain results from different studies that have included liver biopsy of lean NAFLD cases [8]. Overall, patients with lean NAFLD tend to have less severe disease compared with obese patients; it has been reported that the mean NAFLD activity score in non obese NAFLD patients was significantly lower than that in obese NAFLD patients ($p < 0.001$) [23]. On the other hand, 28% of the lean NAFLD patients met the criteria for NASH, which was statistically not different than the prevalence of NASH in the obese NAFLD (38%) patients [23]. Despite that, the percentage of patients with liver fibrosis was significantly lower in the lean NAFLD patients compared with the obese NASH patients (50% *vs.* 84%, $p < 0.01$) [23].

Although the pathogenesis of NAFLD is not fully understood,24 a growing body of evidence supports the idea that the disease is strongly associated with MetS and its phenotypes, including obesity, T2DM and CVD [25-28]. It has been reported that there is an expression of mRNA of 84 genes encoding proteins related to atherosclerosis in patients with biopsy proven NAFLD [28]. Several strategies were proposed for the application of genetic variants in the risk prediction, particularly the rs738409 in PNPLA3, for improving the diagnostic accuracy of NASH [24]. A 10-20% of all NAFLD cases in Americans and Asians are ascribed to lean NAFLD, and some of them are attributed to genetic causes [28]. The most impressive finding of this study is the lack of difference in the magnitude of the association between the PNPLA3 rs738409 variant and the disease severity in lean NAFLD patients in comparison to obese NAFLD patients [28]. However, in a USA study, this has not been confirmed, perhaps due to the small sample studied [29]. A study conducted in Hong Kong that included a large population (n= 911) reported that the prevalence of NAFLD was 19.3% in lean subjects and 60.5% in obese subjects ($p < 0.001$). The G allele at the patatin-like phospholipase domain-containing protein 3 gene (PNPLA3 rs738409) was more common in non-obese than obese NAFLD patients (78.4 *vs.* 59.8%; p= 0.001) [30]. Increased waist circumference, high HbA1c, IR, high ferritin, and the PNPLA3 G allele were independent factors associated with NAFLD in lean subjects [30]. Recently, it has been shown that NASH is associated with a state of betaine insufficiency and a missense variant (rs1805074-p. Ser646Pro) in DMGDH (dimethylglycine dehydrogenase mitochondrial), that modulates the levels of betaine and related metabolites, is associated with disease severity [31]. The rs1805074 was significantly associated with NASH severity and was related to lean NAFLD (p= 0.011) [31]. In another study from Italy (669 consecutive patients with biopsy-proven NAFLD;20% of patients with lean, however with increased waist circumference, NAFLD had NASH, liver fibrosis scores of ≥2 and carotid atherosclerosis) a significantly greater proportion of patients with lean NAFLD carried rs58542926 C>T in TM6SF2 than obese or overweight individuals with NAFLD (p = 0.001). [32]. Thus, some studies characterize lean NAFLD as a unique phenotype with specific genetic associations asking for further investigation in the effort to elucidate the pathophysiology of NAFLD (**Figure 1**) [33].

During the last few years evidence supports a novel perspective for NAFLD, in which the liver is at the center of a complex interplay involving different organs and systems, other than adipose tissue and glucose homeostasis [34]. Bone and the skeletal muscle are fat-free tissues which appeared to be independently associated with NAFLD in several cross-sectional studies [33-34]. The deterioration of bone mineral density and lean body mass, leading to osteoporosis and sarcopenia, respectively, are age-

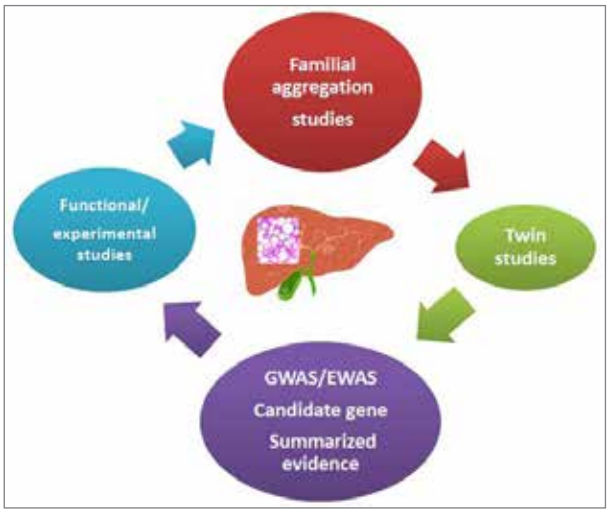

Figure 1. *Description of studies that support the genetic contribution of non-alcoholic fatty liver disease pathogenesis*

related processes [33]. The prevalence of NAFLD also increases with age [34]. Moreover, abnormalities in gut microbiota seem to play a pathogenetic role in lean NAFLD and administration of symbiotic supplements improves the inflammatory indices of the disease [35]. About 1/8 of NAFLD patients coming to a specialized liver center (n= 162) has normal BMI [36]. These patients do not have IR (the basis of metabolic disorders leading to MetS, T2DM, and NAFLD in obese people), but they have higher levels of ALT/aspartate Aminotransferase (AST) than the overweight or obese NAFLD patients [median ALT (92 *vs.* 62 IU/L; p = 0.032) and AST (45 *vs.* 37 IU/L; p= 0.036)] [36].

Finally, we have to report that there are two approaches of the issue: As reported by a meta-analysis, lean and obese patients with NAFLD share a common altered metabolic and CVD profile [37]. The lean patients, while having normal body weight, showed excess of abdominal adipose tissue as well as other MetS features [37]. The second approach, coming from another meta-analysis, one year later, that compared the histological outcomes in lean (n= 493) *versus* overweight/obese (n= 2,209) patients, coming from the same authors of the previous meta-analysis, suggests that lean NAFLD patients have less severe histological features as compared to overweight/obese NAFLD patients [38]. Subsequent assessment of outcome is needed to understand the clinical impact of these findings; however, the significant 25% increase of mean fibrosis score in overweight/obese patients suggests that obesity could predict a worse liver disease or CVD long-term prognosis [38].

Relation of histological NAFLD/NASH severity in lean patients with the prognosis of the metabolic and cardiovascular complications

Regrettably, being lean does not necessarily mean that you are healthy; in fact, being lean is not always related to a lower risk of T2DM, CVD (mainly carotid plaques), or NAFLD, as it has recently been established. [1,39-45].

However, the risk factors and the natural history of NAFLD/NASH in lean patients have not been elucidated, and the existing data are controversial [38]. Also, the evolution of histological features, the most reliable data on liver disease evolution [38], of "lean NAFLD" defining the histological progression to disease severity has not been entirely revealed [38]. The purpose of the recently published meta-analysis was to provide a quantitative estimation of the magnitude of fibrosis, the most important aspect of NASH in terms of liver and CVD risk, as well as histological features associated with the disease severity, in lean-NAFLD *vs.* overweight/obese-NAFLD patients [38]. The analysis of liver fibrosis, which was performed based on pooled data extracted from eight studies [39,46-51], showed that overweight/obese patients (N=2,209) with NAFLD have significantly greater fibrosis scores than lean patients (N=493) (p= 0.032) [38]. The observed difference between the two groups was an increase by 25% in the mean fibrosis score in overweight/obese-NAFLD patients vs. lean-NAFLD, while, there was a reduction by 17% as well as 14% in the mean NAFLD activity and steatosis score, respectively, in lean-NAFLD patients when compared with overweight/obese-NAFLD, but higher than lean normal controls (**Figure 2**) [38]. The magnitude of fibrosis and the rest of the other negative effects of all the histological

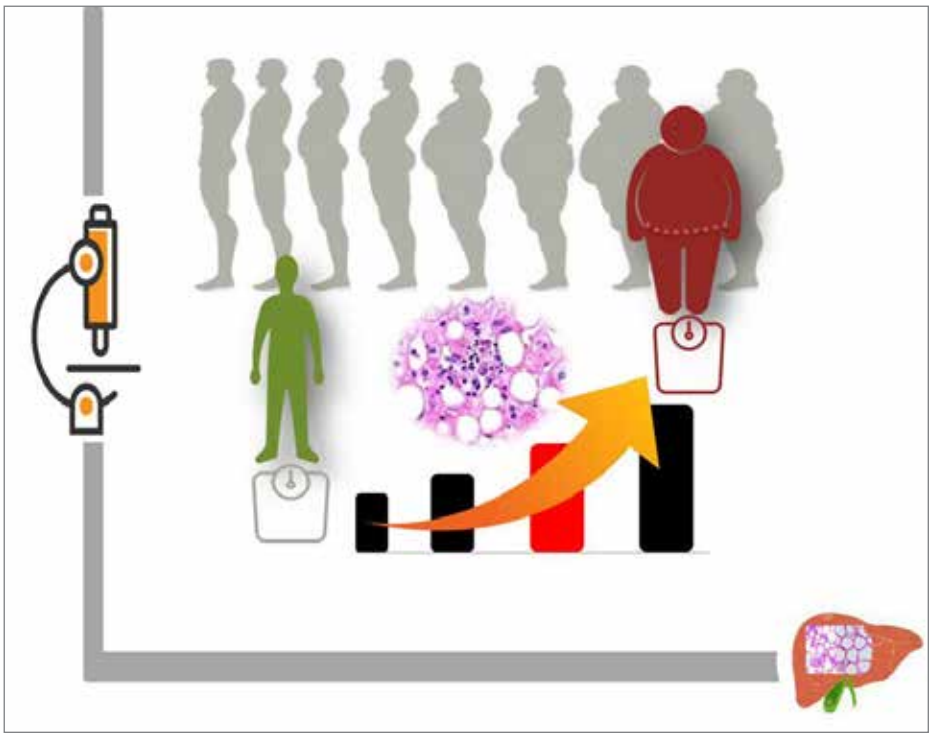

Figure 2.Body Mass Index and risk of liver fibrosis from lean to obese patients

outcomes were consistently found in both South-Asians and Caucasians [38]. In lean NAFLD patients, the possibility of histological advance to NASH was 40% less than in obese NAFLD patients (p= 0.04) [38]. Thus, in lean subjects with NAFLD the risk of NASH, fibrosis, cirrhosis and CVD is higher than that of the lean people without NAFLD but less than overweight/obese-NAFLD patients, which seem to have a poorer long-term prognosis [38].

Thus, the overweight/obese NAFLD patients present an increase of all scores of histological outcomes, including liver fibrosis, which could have substantial impact on the natural history of NAFLD, associated with significantly higher all-cause mortality [52], while lean NAFLD patients have this property in comparison with lean people with normal liver but to a lesser degree than the obese ones [38]. This does not mean that we should not be treating lean patients with NAFLD, according to current guidelines or recommendations [53-56].

Treatment

The recent (2016) European Association for the Study of the Liver (EASL)-European Association for the Study of Diabetes (EASD)-European Association for the Study of Obesity (EASO) clinical practice guidelines and recommendations for the management of NAFLD suggest only pioglitazone for the treatment of biopsy proven NASH patients both in those with or without T2DM (with the legal and moral responsibility of the physician). [53-55]. A recent expert panel statement on NAFLD treatment also suggests pioglitazone in all, sodium-glucose co-transporter 2 (SGLT2) inhibitors or glucagon-like peptide (GLP)-1 receptor analogs in those with T2DM, and mainly specific statins (titration of atorvastatin or rosuvastatin) plus ezetimibe (if needed to attain the LDL-C target) in those with dyslipidaemia (the vast majority of NAFLD/NASH patients with or without T2DM) [56]. The most important aspect of this approach is that the use of statins reduced CVD morbidity and mortality in those with dyslipidaemia double as much than those with a normal liver structure and function [56].

Many other clinical attempts have been directed at treating the individual components of MetS [53]. Therefore, lifestyle changes targeted at weight loss, dietary modifications and exercise remain the first-line therapy, however difficult to maintain during long

term intervention. There is no reliable data to suggest effectiveness of lifestyle modifications in lean patients with NAFLD [51]. However, the presence of fibrosis in lean NAFLD/NASH people provides a significant clue for a possible beneficial intervention.

Data from the National Health and Nutrition Examination Survey (NHANES III), conducted in 1988-1994, included 11,613 participants from the general population and followed them up for mortality through to 2006 [6]. This survey showed that 34% of the participants had NAFLD, which projected to a minimum of a total of 43.2 million American adults [6]. NAFLD patients had a 25.1% probability of fibrosis; these findings project a total of 11 million American adults with advanced fibrosis [6]. Subjects with simple steatosis did not have a significantly higher mortality after a 14.5 year follow-up (5% increase), suggesting that steatosis alone is of benign prognosis during a long term follow up [6]. However, those with fibrosis had a major increase in total mortality compared with the general population ranging from 66 to 85%, according to the fibrosis index used, all significant ($p \leq 0.0001$) [6]. This increase was mainly shaped by CVD mortality, ranging from 253 to 346%, all significant ($p \leq 0.0001$), according to the fibrosis index used [6]. The same results applied to Chinese people [57].

One study from Italy [58] (n= 107) and one study from Italy and Finland [59] (n= 346) showed that potent statin treatment protected from the development of NASH (and fibrosis) in biopsy proven NAFLD patients, while one study from Greece (n = 20) showed that 10 mg/d of rosuvastatin monotherapy reversed established liver fibrosis (as well as inflammation and ballooning) and reduced liver enzymes, without substantial loss of body weight, within one year [60,61].

Most importantly, the use of atorvastatin in the GReek Atorvastatin Coronary-artery-disease Evaluation trial (GREACE; n = 1,600 CVD patients) [62] with a mean dose of 24 mg/d for three years and in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study (n = 8,863 CVD patients) [63] with a mean dose of 80 mg/d for five years, was shown to significantly decrease CVD risk to a greater extent in those patients with elevated liver enzymes at baseline compared with those with normal enzymes. These results included both lean and obese NAFLD/NASH patients and were verified by all studies with these two (atorvastatin or rosuvastatin) statins [64-66].

NAFLD/NASH, usually of high CVD risk, patients are heavily undertreated with statins [67-69]. Information from tertiary centres report that only 10% of high CVD risk patients with NAFLD/NASH are treated with statins [67]; we believe that we should work to overcome this barrier [67-70]. The evidence discussed above suggests that statins could be a valuable option to be considered in patients with NAFLD/NASH, lean and obese. Obviously, this should be carried out with caution because the evidence is limited to post hoc analyses of clinical studies and on relatively low numbers of patients with biopsy-based diagnosis of NAFLD/NASH. In this regard, the effect of statins on the hard histological end-point, fibrosis, would be of paramount importance [38].

In conclusion, the NAFLD/NASH in lean people is less frequent than in overweight/obese people and is related to environmental and mainly to genetic reasons. Lean NAFLD leads to a significant percentage of patients to NASH with fibrosis, which is a potent risk factor for cirrhosis but mainly for CVD, both with high morbidity and mortality. The use of pioglitazone and specific statins (atorvastatin or rosuvastatin, which are safe even in high doses in NASH people) could protect from the development of liver fibrosis or reverse established liver fibrosis and thus substantially reduce liver and CVD morbidity and mortality.

Conflict of Interest

VGA has given talks and participated in studies sponsored by AMGEN, Sanofi, MSD, and Mylan, NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, Galenica, MSD, Novartis, Novo Nordisk, Sanofi-Aventis and WinMedica. The rest of the authors have no conflict of interest. In regard to the specific review, there is no conflict of interest of any of the authors whatsoever.

Περίληψη

Η μη αλκοολική λιπώδης ηπατική νόσος σε μη υπέρβαρα άτομα ως παράγοντας καρδιαγγειακού κινδύνου

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Η μη αλκοολική λιπώδης νόσος του ήπατος (ΜΑΛΝΗ) διαγιγνώσκεται συνήθως σε παχύσαρκους ή υπέρβαρους ασθενείς. Ωστόσο, τα φυσιολογικού βάρους άτομα με ΜΑΛΝΗ αντιπροσωπεύουν ένα αξιόλογο μέρος των φαινοτυπικών κλινικών περιπτώσεων της ΜΑΛΝΗ. Τα υπάρχοντα στοιχεία υποδεικνύουν ότι οι αδύνατοι ασθενείς με ΜΑΛΝΗ και τα παχύσαρκα άτομα με ΜΑΛΝΗ έχουν διαφορετικά προφίλ κινδύνου μεταβολικών και καρδιαγγειακών νοσημάτων (ΚΑΝ). Η ΜΑΛΝΗ σε ισχνά άτομα και η εξέλιξή της στη σοβαρή μορφή της μη αλκοολικής στεατοηπατίτιδας (ΜΑΣΗ) χρειάζεται περαιτέρω διερεύνηση, συμπεριλαμβανομένης της επιδημιολογίας, της κλινικής εκτίμησης του ηπατικού και ΚΑΝ κινδύνου, των ιστολογικών μεταβολών του ήπατος, των γενετικών και προδιαθεσικών παθοφυσιολογικών μηχανισμών, της φυσικής εξέλιξης, του σχετικού κινδύνου για ΚΑΝ και των στρατηγικών θεραπείας σε αυτό τον υπο-διαγνωσμένο πληθυσμό. Πάντως στο βαθμό που εμφανίζει ηπατική ίνωση στα ισχνά άτομα (50% των ατόμων με ΜΑΣΗ) είναι εξίσου επικίνδυνη με αυτή των παχύσαρκων ατόμων και χρειάζεται θεραπεία με πιογλιταζόνη και συγκεκριμένη ισχυρή στατίνη για την ελάττωση της ηπατικής και ΚΑΝ νοσηρότητας και θνητότητας.

Λέξεις ευρετηρίου: μη αλκοολική λιπώδης νόσος του ήπατος, μη αλκοολική στεατοηπατίτιδα, ηπατική κίρρωση, καρδιαγγειακή νοσηρότητα, καρδιαγγειακή θνητότητα

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