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EDITORIAL

Nonalcoholic fatty liver disease in lean subjects: Prognosis, outcomes and management

Lampros Chrysavgis, Eleftheria Ztriva, Adonis Protopapas, Konstantinos Tziomalos, Evangelos Cholongitas

ORCID number: Lampros Chrysavgis 0000-0003-2632-0742; Eleftheria Ztriva 0000-0002-4013-2767; Adonis Protopapas 0000-0002-7117-0547; Konstantinos Tziomalos 0000-0002-3172-1594; Evangelos Cholongitas 0000-0002-3645-582X.

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Lampros Chrysavgis, Evangelos Cholongitas, First Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens 11527, Greece

Eleftheria Ztriva, Adonis Protopapas, Konstantinos Tziomalos, First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki 54636, Greece

Corresponding author: Evangelos Cholongitas, MD, Associate Professor, First Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Agiou Thoma 17, Athens 11527, Greece. cholongitas@yahoo.gr

Abstract

Nonalcoholic fatty liver disease (NAFLD) accounts for most cases of chronic liver disease worldwide, with an estimated global prevalence of approximately 25% and ranges from simple steatosis to nonalcoholic steatohepatitis and cirrhosis. NAFLD is strongly connected to metabolic syndrome, and for many years, fatty liver was considered to be an exclusive feature of obese patients. However, recent studies have highlighted the presence of NAFLD in non-obese subjects, with or without increased visceral fat or even in lean subjects without increased waist circumference. "Lean NAFLD" is a relatively new concept and there is significant scientific interest in understanding the differences in pathophysiology, prognosis and management compared with NAFLD in overweight/obese patients. In the present editorial, we discuss the clinical and metabolic profiles and outcomes of lean NAFLD compared with both obese NAFLD and lean healthy individuals from Asian and Western countries. Moreover, we shed light to the challenging topic of management of NAFLD in lean subjects since there are no specific guidelines for this population. Finally, we discuss open questions and issues to be addressed in the future in order to categorize NAFLD patients into lean and non-lean cohorts.

Key Words: Lean nonalcoholic fatty liver disease; Non-obese nonalcoholic fatty liver disease; Clinical outcomes; Metabolic outcomes; Disease management; Lifestyle interventions

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Core Tip: Affecting approximately one fourth of the global population, non-alcoholic fatty liver disease (NAFLD) is the predominant cause of chronic liver disease and for many years it was considered as a disease affecting only obese people. However, a significant proportion of non-obese or even lean individuals develop NAFLD. Therefore, it is of great interest to discuss the differences in prognosis, metabolic profiles and outcomes as well as the current management of lean NAFLD patients as compared with both obese NAFLD patients and lean healthy controls.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has been recognized as the predominant cause of chronic liver disease in the industrialized world[1]. It encompasses a wide spectrum of clinical and histological entities, ranging from simple steatosis, defined as triglyceride (TG) accumulation > 5% within the hepatic parenchyma, to nonalcoholic steatohepatitis (NASH), which is characterized by inflammation and fibrosis and can lead to cirrhosis and even hepatocellular carcinoma (HCC)[2,3]. The prevalence of NAFLD is increased in patients with type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS) and obesity[4]. Although the latter is not only a risk factor for NAFLD but is also associated with more severe forms of the disease, a significant proportion of subjects develop NAFLD despite having a relatively normal body mass index (BMI), a condition referred to as non-obese or lean NAFLD[5]. Non-obese/lean NAFLD is divided into 2 major categories[5]: The first and more prevalent includes non-obese patients who may be overweight (BMI between the 85th-95th percentile for age) with or without increased waist circumference and adipose tissue, while the second category includes lean subjects with no excess visceral fat mass[5]. In the latter category, several secondary causes have been implicated, such as high fructose intake, protein malnutrition (Kwashiorkor) as well as administration of steatogenic drugs (amiodarone, tamoxifen, methotrexate, prednisolone, *etc*.) and genetic predisposition[5,6]. Regarding the latter, Romeo *et al*[7] have emphasized the involvement of the rs738409 single nucleotide polymorphism in patatin-like phospholipase domain-containing protein 3 (*PNPLA 3*) gene in NAFLD onset and progression. Yet, a plethora of other gene variants have been also associated with increased susceptibility to NAFLD/NASH and progression to liver fibrosis and even HCC, such as the transmembrane 6 superfamily member 2 (*TM6SF2*)[8-10], glucokinase regulatory gene (*GCKR*)[11,12] and membrane bound O-acyltransferase domain containing 7 (*MBOAT7*) genes[13]. In addition, a variant of interferon-λ3 (*IFN-λ3*) gene has been related with increased liver inflammation and fibrosis among NAFLD patients[14], while the rs72613567 polymorphism in hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) gene was recently shown to reduce the risk of liver fibrosis, NASH and HCC[15,16]. Of note, both dietary composition and socioeconomic factors have been correlated with NAFLD development. Adherence to Mediterranean diet has been demonstrated to ameliorate hepatic insulin sensitivity and reduce hepatic fat accumulation while the Western dietary pattern, which mainly consists of high fructose and saturated fats intake, has been involved in NAFLD development[17,18]. Moreover, prolonged sitting time, usually related with high calorie intake and unhealthy dietary composition, and decreased physical activity are independent risk factors for NAFLD, even in lean subjects[19].

Current data on the prevalence of non-obese/lean NAFLD worldwide is characterized by wide variability. In a recent systematic review including 84 studies with 10530308 individuals, Ye *et al*[20] demonstrated that among the general population, the prevalence of lean and non-obese NAFLD was 5.1% and 12.1%, respectively. In addition, the overall prevalence of NAFLD among the lean general population was 10.6%, while the prevalence of NAFLD in the non-obese population was 18.3%. Interestingly, the prevalence of non-obese NAFLD among the total NAFLD population

was highest in Europe (51.3%) and lowest in eastern Asia (37.8%)[20]. Of note, NAFLD patients were categorized according to the World Health Organization (WHO) and Asian Pacific recommendations as overweight and lean when their BMI was 25 to 30 kg/m^2 and < 25 kg/m^2, respectively, in non-Asian populations and 23 kg/m^2 to 27.5 kg/m^2 and < 23 kg/m^2, respectively, in Asian populations[21-23]. However, it is well-established that individuals with similar BMI may have different degrees of visceral obesity, which is closely associated with the development of NAFLD[24-26]. Waist circumference is considered a more accurate marker of visceral obesity than BMI, but is not available in the majority of the relevant studies[27]. The present editorial will discuss the metabolic profile, prognosis and related clinical outcomes, as well as the management of non-obese or lean patients suffering from NAFLD.

CLINICAL IMPACT OF NON-OBESE/LEAN NAFLD

Literature search

PubMed database was systematically searched from the date of inception of this editorial until April 2020, to identify studies focusing on non-obese/lean NAFLD. The terms used were "Lean non-alcoholic fatty liver disease" OR "Lean nonalcoholic fatty liver disease" OR "Lean NAFLD" OR "Non-obese non-alcoholic fatty liver disease" OR "Non-obese nonalcoholic fatty liver disease" OR "Non-obese NAFLD" OR "Non-overweight fatty liver disease" OR "Non-overweight NAFLD". Since we aimed to emphasize the metabolic, hepatic and cardiovascular outcomes in obese *vs* non-obese/lean NAFLD patients as well as non-obese/lean individuals with or without NAFLD, studies evaluating the histological aspects of NAFLD were excluded.

Non obese/lean NAFLD vs controls: Metabolic and clinical outcomes (Table 1)

Younossi *et al*[28] in a study performed in the United States reported that lean (BMI < 25 kg/m^2) NAFLD patients compared to lean healthy subjects had higher prevalence of insulin resistance (IR), T2DM, hypercholesterolemia and hypertension, *i.e.*, the components of MetS. In the cross-sectional NHANES III study, Golabi *et al*[29] reported that lean (BMI < 25 kg/m^2) NAFLD patients, had higher risk of all-cause [Hazard Ratio (HR): 1.54] and cardiovascular-related mortality (HR: 2.38) than lean non-NAFLD subjects after adjustment for potential confounding variables[29]. Interestingly, in another study from the United States, Zou *et al*[30] showed that in a non-obese population (BMI < 30 kg/m^2 for non-Asians and < 27 kg/m^2 for Asians), patients with NAFLD had higher blood pressure, fasting plasma glucose (FPG), insulin, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and TG levels and higher Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), a marker of IR, than subjects without NAFLD. In addition, the former group had increased overall, cardiovascular and cancer-related mortality during a 15-year follow-up, but these findings were not confirmed in multivariate analysis[30].

In a post hoc analysis in Japanese subjects, Yoshitaka *et al*[31] reported that lean (BMI < 23 kg/m^2) NAFLD patients had higher blood pressure, increased FPG and TG serum levels, as well as greater risk (HR: 10.4) for cardiovascular events than to lean non-NAFLD individuals, independently of potential confounders. In a retrospective cohort study of 4629 lean Japanese participants (BMI < 23 kg/m^2) who were enrolled in a regular health checkup program, Fukuda *et al*[32] showed that patients with NAFLD had more than 3 times higher incidence of T2DM than subjects without NAFLD. Regarding non-obese subjects, Nishioji *et al*[33] found that non-obese (BMI < 25 kg/m^2) Japanese NAFLD patients had a higher prevalence of MetS components compared with healthy individuals. Both retrospective and prospective studies from South Korea also showed that non-obese NAFLD patients have an increased risk for T2DM than non-NAFLD, non-obese individuals, independently of other risk factors[34,35]. Moreover, Sung *et al*[36] in a large cohort of non-obese (BMI < 27 kg/m^2) South Korean individuals, reported that non-obese NAFLD patients have higher estimated cardiovascular risk based on the Framingham risk score than healthy controls, whereas in another South Korean cross-sectional study, non-obese (BMI < 25 kg/m^2) subjects without NAFLD had better metabolic profile than non-obese patients with NAFLD[37]. Accordingly, Kwon *et al*[38], in another retrospective study from South Korea, showed that non-obese (BMI < 25 kg/m^2) NAFLD patients had higher prevalence of MetS components than non-obese controls and had.

In lean (BMI < 23 kg/m^2) Chinese individuals, the presence of NAFLD was associated with increased odds for T2DM and MetS, independently of demographic and lifestyle parameters[39]. Regarding non-obese populations, 2 independent studies in

Table 1 Main findings and outcomes of lean (or non-obese) non-alcoholic fatty liver disease patients' *vs* lean (or non-obese) healthy individuals

Ref./Year/Country	Population (lean/non-obese NAFLD population)	Metabolic profile lean/non-obese NAFLD *vs* healthy controls	Liver function tests findings, lean/non-obese NAFLD *vs* healthy controls	Histological outcomes, lean/non-obese NAFLD *vs* healthy controls	Survival-related outcomes, lean/non-obese NAFLD *vs* healthy controls
Younossi *et al*[28] /2012/United States	11613 study population; 4457 lean subjects (431)	↑ Prevalence of insulin resistance, T2DM, hypercholesterolemia and hypertension		NA	NA
Golabi *et al*[29] /2019/United States	5375 lean subjects (581)	↑ Prevalence of metabolic comorbidities	NA	NA	↑ Hazard for all-cause and cardiovascular-related mortality
Zou *et al*[30]/2020/United States	9654 controls (1528)	↑ BP, HOMA-IR, glucose, insulin, TC, LDL-C, TG, ↓ HDL-C	↑ ALT, AST, γ-GT	NA	↑ 15-yr overall, cardiovascular, cancer and other causes-related mortality (not confirmed in Cox model)
Yoshitaka *et al*[31] /2017/Japan	1647 individuals; 984 non-overweight subjects (69)	↑ BP, glucose, TG, UA, ↓ HDL-C	↑ AST, ALT, γ-GT	NA	↑ HR of CVD incident
Fukuda *et al*[32] /2016/Japan	4629 participants (2989) in the non-overweight group (139)	↑ Adjusted HR for T2DM, ↑ BP, TC, TG, ↓ HDL-C	↑ ALT, AST, γ-GT	NA	NA
Nishioji *et al*[33] /2015/Japan	3271 enrolled individuals; 2606 non-obese (511)	↑ BP, TC, TG, HbA1c, glucose	↑ ALT, AST, γ-GT	NA	NA
Kim *et al*[34]/2018/South Korea	2920 participants; 2119 in non-obese group (420)	↑ HR for T2DM, ↑ TG, TC, LDL-C, ↓ HDL-C	↑ ALT, AST, γ-GT	NA	NA
Sinn *et al*[35]/2019/South Korea	51463 total population; 21984 lean subjects (2262)	↑ HR for T2DM onset, ↑ glucose, HbA1c, TG, TC and LDL-C, ↓ HDL-C	↑ ALT and AST	NA	NA
Sung *et al*[36]/2009/South Korea	30172 all non-obese; (7101)	↑ Prevalence of hypertension, T2DM, MetS in elevated ALT, steatosis and NASH groups	NA	NA	In men: ↑ Cardiovascular risk for group with elevated ALT serum levels and for steatosis and NASH groups. In women: ↑ Cardiovascular risk for steatosis and NASH groups
Kim *et al*[37]/2013/South Korea	759 individuals (98 in NAFLD group)	↑ Glucose, TG, UA, HOMA-IR, ↓ HDL-C	↑ ALT, AST, γ-GT	NA	NA
Kwon *et al*[38]/2012/South Korea	29994 study population; 24008 non-obese (3014)	↑ BP, glucose, insulin, HOMA-IR, ↓ HDL-C	↑ AST, ALT, γ-GT	NA	NA
Feng *et al*[39]/2014/China	1779; 731 in the lean group (134)	↑ OR for hypertension, T2DM, central obesity and MetS, UA, TC, LDL-C, TG, glucose, insulin, HOMA-IR ↓ HDL-C	↑ ALT, AST, γ-GT	NA	NA
Lee *et al*[40]/2018/China	2008 enrolled subjects; 953 non-obese (208)	↑ TC, TG, glucose	↑ ALT	NA	NA
Zeng *et al*[41]/2020/China	2715 enrolled participants (1100 NAFLD patients)	↑ Prevalence of hypertension and MetS, TG, LDL-C, ↓ HDL-C	NA	NA	NA
Yu *et al*[42]/2014/China	1296 non-obese subjects of whom 246 were NAFLD	↑ Arterial stiffness, assessed by the higher brachial-ankle pulse wave velocity, TC, LDL-C,	↑ ALT, AST	NA	NA

	patients	TG, glucose, insulin, UA, HOMA-IR			
Wang *et al*[43]/2015/China	9360 women population (1194 were NAFLD patients)	↑ TG, TC, LDL-C, glucose	↑ AST, ALT	NA	NA
Kumar *et al*[44]/2013/India	205 NAFLD patients (27 lean) plus 131 lean healthy subjects	↑ Prevalence of MetS, dyslipidemia		NA	NA
Oral *et al*[45]/2019/Turkey	367 non-obese individuals (225 in NAFLD group and 142 in the control group)	↑ TG, TC, UA, creatinine, HOMA-IR	↑ AST, ALT	NA	NA
Erkan *et al*[46] /2014/Turkey	219 non-obese non diabetic individuals of whom 143 NAFLD patients	↑ Prevalence of hypertension, MetS, hyperglycemia, hypertriglyceridemia and insulin resistance, insulin, HOMA-IR	↑ AST, ALT, γ-GT	NA	NA
Feldman *et al*[47] /2017/Austria	187 subjects (116 suffering from NAFLD of whom 55 were lean)	↑ Prevalence of T2DM, glucose, ↓ adiponectin	↑ ALT, γ-GT	NA	NA
Gonzalez-Cantero *et al*[48] /2018/Spain	113 non-obese enrolled individuals (55 NAFLD patients)	↑ HOMA-IR, TG, insulin, ↓ HDL-C, adiponectin	↑ ALT, AST, γ-GT	NA	NA

NAFLD: Non-alcoholic fatty liver disease; ALT: Alanine aminotransferase; T2DM: Type 2 diabetes mellitus; NASH: Non-alcoholic steatohepatitis; NAS: NAFLD activity score; BP: Arterial blood pressure; TC: Total cholesterol; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; TG: Triglycerides; HR: Hazard ratio; HbA1c: Glycosylated hemoglobin, type A1C; HOMA-IR: Homeostasis Model Assessment Insulin Resistance; CVD: Cardiovascular disease; HCC: Hepatocellular carcinoma; NA: Not applicable; UA: Uric acid; AST: Aspartate aminotransferase; γ-GT: γ-Glutamyl transferase; MetS: Metabolic syndrome.

China confirmed that non-obese (BMI < 25 kg/m^2) patients with NAFLD suffered more frequently from hypertension and MetS than healthy non-obese subjects[40,41], whereas a cross-sectional study in China reported that non-obese (BMI < 27.5 kg/m^2), normotensive and non-diabetic NAFLD patients had increased arterial stiffness, higher serum levels of FPG, TC, LDL-C, TG and greater HOMA-IR than non-obese, healthy subjects[42]. Similar findings were observed in Chinese women[43]. Moreover, a cohort study in India also showed that NAFLD patients are at higher risk for metabolic disorders irrespectively of the presence of obesity[44].

In accordance to the aforementioned studies, Oral *et al*[45] reported that non-obese (BMI < 30 kg/m^2) NAFLD patients from Turkey were more frequently glucose intolerant and had higher TG and TC levels than non-obese controls. Similar findings were also reported in another Turkish study, where lean (BMI < 25 kg/m^2) NAFLD patients had higher prevalence of hypertension and MetS as well as higher HOMA-IR[46]. Finally, in Europe, Feldman *et al*[47] reported that Austrian lean (BMI < 25 kg/m^2) healthy subjects were more frequently glucose tolerant and had lower prevalence of T2DM than lean NAFLD patients and these findings were confirmed by Gonzalez-Cantero *et al*[48] in a non-obese (BMI < 30 kg/m^2) Spanish cohort.

Obese vs non-obese/lean NAFLD (Table 2)

Studies with metabolic outcomes: Regarding metabolic outcomes in NAFLD obese and NAFLD non-obese/lean patients, in a retrospective study of 669 NAFLD patients in Italy, lean (BMI < 25 kg/m^2) NAFLD patients had lower prevalence of hypertension, T2DM and MetS than overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) NAFLD patients[49]. Notably, the former group had significantly thinner carotid intima-media, indicating less atherosclerotic burden[49]. Although this result was not confirmed in a study by Shao *et al*[50] in obese (BMI > 25 kg/m^2) and non-obese Chinese NAFLD patients, the authors showed that the latter group had lower FPG and serum TC and TG levels as well as a lower prevalence of hypertension. Moreover, Li *et al*[51] demonstrated that the proportion of Chinese patients with elevated FPG and serum TG levels was higher among obese (BMI > 25 kg/m^2) compared with non-obese NAFLD patients, while another cross-sectional study from China confirmed that obese NAFLD women (BMI > 28 kg/m^2) had higher FPG than non-obese women[43]. In addition, 2 studies from China showed a higher prevalence of MetS and hypertension in obese (BMI > 25 kg/m^2) compared to non-obese patients with NAFLD[41,52]. In the Indian population, Kumar *et al*[44] reported that among NAFLD patients, lean (BMI < 23 kg/m^2) patients had had lower serum insulin levels and HOMA-IR, as well as lower prevalence of T2DM and MetS than obese (BMI > 25 kg/m^2) patients. In a case control study from Sri Lanka, Niriella *et al*[53] reported a higher prevalence of hypertension in non-lean (BMI > 23 kg/m^2) patients with NAFLD compared with lean NAFLD patients. In studies performed in Japan, Yoshitaka *et al*[31] reported lower blood pressure and FPG and higher serum high density cholesterol (HDL-C) levels in lean (BMI < 23 kg/m^2) than in overweight NAFLD patients[44], while Honda *et al*[54] reported that FPG, insulin, TG and HOMA-IR were increased among Japanese obese (BMI > 25 kg/m^2) NAFLD patients compared with non-obese NAFLD patients. In a study form Hong-Kong, Wei *et al*[55] reported that non-obese (BMI < 25 kg/m^2) NAFLD patients had lower IR than obese NAFLD patients. Moreover, the prevalence of MetS and hypertension was increased in obese patients. A study performed in Bangladesh also showed that non-obese (BMI < 25 kg/m^2) NAFLD patients had lower TC, FPG, HOMA-IR and higher HDL-C levels than obese NAFLD patients[56].

Similar findings were observed in the cross-sectional NHANES III study, in which lean (BMI < 25 kg/m^2) NAFLD patients had less frequently hypertension, T2DM and hypercholesteremia as well as lower levels of FPG and HOMA-IR than overweight /obese NAFLD patients[28]. In a prospective study from Turkey, Akyuz *et al*[57] reported that lean (BMI < 25 kg/m^2) NAFLD patients had a less prevalence of MetS and hypertension than overweight NAFLD patients, while in a study from Spain, Gonzalez-Cantero *et al*[48] also confirmed that overweight (BMI: 25-29 kg/m^2) patients with NAFLD had higher HOMA-IR and TG and lower HDL-C serum levels than lean NAFLD patients. In a study from Austria, Feldman *et al*[47] also reported that lean (BMI < 25 kg/m^2) NAFLD patients had lower FPG, insulin and HOMA-IR and higher HDL-C levels than obese NAFLD patients.

In contrast to these findings, a retrospective study from South Korea reported a higher prevalence of MetS components in non-obese (BMI < 25 kg/m^2) NAFLD patients compared with obese NALFD patients, even after adjusting for confounders[38]. It is possible that unrecorded differences in dietary patterns, physical activity and smoking status between the 2 groups might explain this paradoxical might[38]. Lee *et al*[40] also reported that non-obese (BMI < 25 kg/m^2) NAFLD patients had higher prevalence of MetS and hypertension as well as lower serum HDL-C levels than obese NAFLD patients. However, this study was hospital- and not community-based suggesting the presence of selection bias as an explanation for these unexpected findings[40].

Studies with both metabolic and clinical outcomes: In a prospective cohort study in 307 NAFLD patients from Hong-Kong, Leung *et al*[52] reported that non-obese patients (23.5% patients of the total cohort) had lower prevalence of MetS and hypertension as well as lower NAFLD activity score, serum cytokeratin-18 fragments and decreased liver stiffness based on transient elastography than obese patients. Of note, deaths, HCC and liver failure occurred only in obese patients during a follow-up period of 49 mo[52].

In contrast, a United States study in 483 biopsy-confirmed NAFLD patients showed that lean (BMI < 25 kg/m^2) patients had higher all-cause mortality than non-lean patients during a follow-up of 133 mo, although they had lower prevalence of T2DM, MetS, hypertriglyceridemia and hypertension, and less advanced fibrosis. Notably, even after adjustment for potential confounders, lean NAFLD was an independent risk factor (HR: 11.8) for higher all-cause mortality[58]. In the NHANES study, Zou *et al*[30]

Table 2 Main findings and outcomes of lean (or non-obese) non-alcoholic fatty liver disease patients' *vs* obese ones

Ref./Year/Country	Population (lean/non-obese NAFLD patients)	Metabolic profile, lean/non-obese NAFLD *vs* non-lean/obese NAFLD	Liver function tests findings, lean/non-obese NAFLD *vs* non-lean/obese NAFLD	Histological outcomes, lean/non-obese NAFLD *vs* non-lean/obese NAFLD	Survival-related outcomes, lean/non-obese NAFLD *vs* non-lean/obese NAFLD
Younossi *et al*[28] /2012/United States	11613 study population; 2491 NAFLD patients (431 lean)	↓ Prevalence of insulin resistance, T2DM, hypocholesteremia, hypertension, HOMA score	↓ AST, ALT	NA	NA
Zou *et al*[30]/2020/ United States	4711 patients with NAFLD (1528 non-obese)	Similar prevalence of T2DM and MetS, Metabolic comorbidities: More common	NA	↑ Prevalence of advanced liver fibrosis	↑ 15-yr overall, cardiovascular, cancer and other causes related mortality (not significant in a Cox model)
Yoshitaka *et al*[31] /2017/Japan	1647 individuals; 312 NAFLD patients (69 non-overweight)	↓ BP, glucose, ↑ HDL-C	↓ AST, ALT, and γ-GT	NA	NA
Kwon *et al*[38]/2012/South Korea	29994 study population; 6039 NAFLD patients (3014 non-obese)	↑ Prevalence ratios for high BP, glucose intolerance, and ↑ TG, ↓ HDL-C especially among women population	NA	NA	NA
Feng *et al*[39]/2014/China	1779 study population; 898 NAFLD patients (134 lean)	↓ Insulin, TC, UA, HOMA-IR, ↑ HDL-C	↓ ALT and γ-GT	NA	NA
Lee *et al*[40]/2018/China	2008 enrolled subjects; 493 NAFLD patients (208 non-obese)	↑ Prevalence of MetS and hypertension, ↓HDL-C	NA	NA	NA
Zeng *et al*[41]/2020/China	2715 enrolled participants; 1100 NAFLD patients (142 lean)	↑ Prevalence of MetS	NA	Less severe hepatic steatosis, evaluated by ameliorated values of CAP and FLI	NA
Wang *et al*[43]/2015/China	9360 women population; 1194 were NAFLD patients (514 non-obese)	↑ UA, glucose	↓ ALT, AST but ↑ AST/ALT ratio	NA	NA
Kumar *et al*[44] /2013/India	205 NAFLD patients (27 lean)	↓ Hyperinsulinemia, HOMA-IR, ↓ prevalence of T2DM, MetS		↓ Mean NAS and ↓ proportion of patients with liver fibrosis	NA
Feldman *et al*[47] /2017/Austria	187 subjects; 116 NAFLD patients (55 lean)	↓ Glucose, insulin, HOMA-IR, ↑ HDL-C, adiponectin	↓ ALT	NA	NA
Fracanzani *et al*[49] /2017/Italy	669 NAFLD patients (143 lean)	↓ Prevalence of hypertension, T2DM, MetS, NASH, carotid plaques and significant thinner carotid intima-media	NA	↓ Prevalence of NAFLD and ↓ median NAS	NA
Shao *et al*[50]/2020/China	534 NAFLD patients (240 non-obese)	No ↑ risk of cardiovascular damage and ↑ TC, FFA, TG, BP, insulin resistance	↓ ALT and AST	NA	NA
Li *et al*[51]/2019/China	496 NAFLD patients (101 lean)	↑ Proportion of patients with ↑ TG, glucose	↓ Proportion of patients with ↑ ALT	NA	NA

Leung *et al*[52] /2017/Hong-Kong	307 NAFLD patients (72 non-obese)	↓ Prevalence of MetS, hypertension	NA	↓ NAS, ↓ fibrosis stage, serum cytokeratine-18 fragments and liver stiffness measurement	Severe clinical outcomes (6 deaths, 2 HCC,1 liver failure) were observed only in the obese group
Niriella *et al*[53]/2018/Sri Lanka	2985 initial cohort; 936 NAFLD patients (120 lean)	↓ Prevalence of hypertension and central obesity, no significant difference in prevalence of other metabolic comorbidities at baseline. No remarkable alterations of new onset of metabolic comorbidities at the completion of follow-up	NA	NA	NA
Honda *et al*[54] /2016/Japan	1562 enrolled subjects; 540 NAFLD patients (134 non-obese)	↑ HOMA-IR, glucose, insulin, TG, ↓ genotype prevalence of (*PNPLA3*) GG	↓ ALT and AST	↓ Lobular inflammation, steatosis grade, hepatocyte ballooning and NAS	NA
Wei *et al*[55]/2015/Hong-Kong	262 patients with NAFLD (135 non-obese)	↓ Insulin resistance, BP and cytokeratin-18 fragments and ↓ prevalence of MS, ↑ genotype (*PNPLA3*) GG prevalence	NA	Less non-obese NAFLD patients with ↑ NAFLD fibrosis score	NA
Alam *et al*[56] /2014/Bangladesh	465 NAFLD patients (119 non-obese)	Similar prevalence of T2DM and hypertension and ↓ TC, glucose, HOMA-IR, ↑ HDL-C	↓ ALT, AST, γ-GT	No significant difference in histological findings	NA
Akyuz *et al*[57] /2015/Turkey	483 NAFLD patients (37 lean)	↓ BP, ↓ prevalence of MetS, less severe hepatic steatosis, ↑ hemoglobin levels	NA	Less severe hepatic fibrosis	NA
Cruz *et al*[58]/2014/United States	1090 NAFLD patients (125 lean)	↓ Insulin resistance, ↓ prevalence of low HDL-C, hypertriglyceridemia and hypertension	↓ ALT	↓ Steatosis degree and less advanced fibrosis	↓ Cumulative survival
Hagström *et al*[59] /2018/Sweden	646 NAFLD patients (123 lean, 335 overweight, 188 obese)	↓ TG, glucose	↓ ALT, AST compared to both overweight and obese counterparts	↓ Prevalence of NASH and ↓ mean fibrosis stage compared to both overweight/obese patients	↓ Risk for overall mortality, ↑ risk for severe hepatic disease development as compared to overweight patients

NAFLD: Non-alcoholic fatty liver disease; ALT: Alanine aminotransferase; T2DM: Type 2 diabetes mellitus; BP: Blood pressure; MetS: Metabolic syndrome; TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; TG: Triglycerides; UA: Uric acid; NASH: Non-alcoholic steatohepatitis; NAS: NAFLD activity score; HOMA-IR: Homeostasis Model Assessment Insulin Resistance; HCC: Hepatocellular carcinoma; CAP: Controlled attenuation parameter; FLI: Fatty liver index; HR: Hazard ratio; PNPLA 3: Patatin-like phospholipase domain-containing protein 3; NA: Not applicable; AST: Aspartate aminotransferase; γ-GT: γ-Glutamyl transferase; MetS: Metabolic syndrome.

also reported that non-obese NAFLD (BMI < 30 kg/m^2 for non-Asians and < 27 kg/m^2 for Asians) patients had a higher prevalence of metabolic comorbidities, more advanced fibrosis and higher mortality due to cardiovascular disease and cancer and higher all-cause mortality than obese NALFD. However, these findings were not confirmed in a multivariate analysis, where only T2DM and fibrosis stage were independent risk factors for mortality[30]. Finally, in a retrospective cohort study in 646 NAFLD patients in Sweden, Hagström *et al*[59] reported that lean (BMI < 25 kg/m^2) NAFLD patients had higher risk for cirrhosis, decompensated cirrhosis and HCC than overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2) patients, independently of confounders; all-cause mortality did not differ between the 2 groups. Of note, lean patients had lower serum TG and FPG levels as well as lower prevalence of NASH and lower fibrosis stage[59].

It may seem paradoxical that most studies[30,58,59], although not all[52], reported a worse prognosis in non-obese/lean patients with NAFLD compared with obese

NAFLD patients. Zou *et al*[30] attributed the worse outcome of non-obese NAFLD patients to the advanced fibrosis stage and the higher frequency of metabolic comorbidities in this group. Hagström *et al*[59] speculated that genetic predisposition and unhealthy lifestyle were associated with the worse liver-related outcomes of lean NAFLD patients. Another explanation could be that in all studies, BMI was used as a surrogate marker to define the thresholds for leanness or obesity. However, BMI is not a specific marker of abdominal obesity; waist circumference reflects more accurately the visceral adiposity fat fraction[60]. Nonetheless, even waist circumference cannot distinguish visceral from subcutaneous fat and cannot allow quantification of adipose tissue parts. Accordingly, more accurate markers of abdominal obesity, such as magnetic resonance imaging (MRI), might be useful in distinguishing between obese and lean patients with NAFLD. Indeed, MRI is considered a more accurate and quantitative tool for evaluation of visceral adipose tissue[61]. Thus, both the definition of lean/non-obese NAFLD and the categorization of patients into lean/non-obese or obese should be based in the near future on MRI to overcome the limitation of current, BMI-based definitions.

MANAGEMENT OF NON-OBESE/LEAN NAFLD

Management of NAFLD in lean patients is particularly challenging, since the cornerstone of NAFLD treatment is weight loss, which might not apply in these patients. In addition, there are no specific guidelines for the management of NAFLD in lean subjects. However, accumulating data suggest that several interventions might be useful in this population. A summary of the key elements of management of lean NAFLD is given in Table 3.

Initial workup and assessment of disease severity

To select the most appropriate management, a thorough diagnostic workup should be performed. The initial workup of a lean patient with suspected NAFLD may include a variety of modalities. Usually, ultrasound is the screening imaging method of choice and can provide information regarding the presence and severity of steatosis and the presence of cirrhosis. The Fibrosis-4 (FIB-4) and NAFLD fibrosis score can be useful for assessing the severity of liver fibrosis in patients with NAFLD[62,63]. In patients with inconclusive findings, elastography (transient, shear wave, or magnetic resonance) is the most widely used method to assess the severity of hepatic fibrosis, otherwise liver biopsy is recommended[64,65].

Management of NAFLD in lean subjects

Weight reduction: Similar with obese patients with NAFLD, weight reduction appears effective in lean subjects with NAFLD. In a study in 333 patients with NAFLD, weight change was an independent predictor of disease progression or resolution after a mean follow-up of 28.7 mo. Interestingly, among patients who also experienced NAFLD progression, non-obese subjects had greater weight gain than obese patients whereas among patients who experienced NAFLD resolution, non-obese patients showed smaller weight loss than obese subjects[66]. Moreover, 2 studies showed that 5% of body weight reduction led to significant decrease in steatosis in lean patients with NAFLD[67,68]. In the first study (n = 120 patients with NAFLD), a 10-wk program including diet modification and exercise resulted in improvement in steatosis in the repeated liver biopsy[67], while in the second one (n = 14 Lean NAFLD patients), an 8-wk intervention consisting of intensive dietary and lifestyle measures induced a decrease in both steatosis and stiffness assessed with transient elastography[68].

Dietary modifications and physical activity: Diet appears to improve NAFLD in lean patients independently of weight loss. It has been reported that lean patients with NAFLD have comparable total caloric intake with obese patients with NAFLD[69,70]. However, the former have higher intake of cholesterol and lower intake of polyunsaturated fatty acids (PUFAs)[70]. In a study in 120 patients with NAFLD who followed a 10-wk program including diet modification and exercise, most patients achieved a reduction of steatosis without weight reduction; instead, a reduction in fat intake and in overall body fat was observed and might have contributed to the improvement in steatosis[67]. Therefore, low-fat diet appears more appropriate for lean patients with NAFLD.

There are also reports highlighting physical exercise as a contributing factor to NAFLD amelioration irrespectively of its effect on body weight. In a large

Table 3 Key elements of management of lean non-alcoholic fatty liver disease

Evaluation of severity of liver	Liver fibrosis (serological markers, elastography, biopsy)
	Presence of NASH (biopsy or serological evidence of inflammation)
Weight reduction	5% of body weight reduction can be effective in reducing steatosis
Physical activity	Positive effect regardless of weight reduction
Dietary Intervention	↓ Fat intake, ↑ protein intake
Commorbidities	Strict control of:
	Diabetes mellitus (consider pioglitazone)
	Hypertriglyceridemia (baseline triglyceride count was independently correlated with NAFLD resolution)
	Hypercholesterolemia (reduction of total cholesterol was independently correlated with steatosis reduction)
	Hypertension
Sleep patterns	Emphasize the significance of adequate sleep duration and quality
Pharmacological therapy	Pioglitazone and vitamin E as the only accepted therapies, but proposed only on an individual basis
	Possible role of probiotics
	Small number of trials for lean patients
	According to the results of trials focusing on non-lean patients

NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease.

retrospective study (n = 3718), lack of physical activity was independently associated with the presence of NAFLD, after adjusting for visceral adiposity and IR. These results might be particularly relevant for lean patients with NAFLD, who have lower prevalence of IR and visceral adiposity compared with obese patients[28,58].

Management of comorbidities: As already mentioned, lean patients with NAFLD appear to have higher incidence of T2DM compared with overweight patients without NAFLD[32]. Given that T2DM is a major risk factor for NAFLD progression[71-73], these findings highlight the importance of T2DM prevention in this population. Furthermore, it has been reported that elevated TG levels are independently associated with development or resolution of NAFLD, especially in non-obese patients[66]. In another study, a ≥ 10% reduction in TC levels was independently associated with ≥ 20% reduction of steatosis in biopsy after a 10-wk exercise and diet modification program[67]. Given the increased cardiovascular risk of lean NAFLD patients, screening for and management of cardiometabolic comorbidities are essential to reduce cardiovascular morbidity in this population.

Sleep patterns: Short duration and poor quality of sleep have been associated with increased incidence of NAFLD[74-77]. Considering that a substantial proportion of lean patients with NAFLD have disturbed sleep[69], recommendations for more rest and efforts to improve sleep quality should be considered in this population.

Pharmacological interventions

Treatment options for NAFLD include pioglitazone and vitamin E but are limited to non-diabetic patients with biopsy-proven NASH. However, in both European and American guidelines, these agents are recommended to be used with caution and in carefully selected patients[4,64]. In addition, only ezetimibe has been evaluated in lean patients with NAFLD. In a pilot study (n = 8 non-obese patients), treatment with ezetimibe for 12 mo resulted in a decrease in aminotransferase levels but had no effect on hepatic steatosis assessed with ultrasound[78]. Interestingly, BMI did not change during the study. A larger, placebo-controlled, randomized study evaluated a symbiotic supplement consisting of seven bacterial strains in 50 lean NAFLD patients who also received lifestyle recommendations[79]. The supplement resulted in a greater reduction in liver stiffness and steatosis, in serum TG and TC levels and in inflammatory markers including high-sensitivity C-reactive protein and nuclear factor-κB activity than placebo. This study supports the findings of a previous report in obese patients with NAFLD[80] and suggests a role of gut microbiota manipulation in the management of NAFLD.

CONCLUSION

Even though NAFLD is strongly associated with obesity and related comorbidities, a substantial proportion of lean subjects can also develop NAFLD. Visceral obesity as opposed to general obesity, genetic predisposition, unhealthy dietary pattern consisting of high cholesterol and fructose intake may be associated with lean NAFLD. Although lean patients appear to have a worse prognosis but a healthier metabolic profile than obese patients with NAFLD, we should bear in mind that the current categorization into lean or obese cohorts was mostly based on BMI and not on visceral fat mass evaluation. Thus, the use of MRI as a reliable and quantitative diagnostic tool for evaluating the presence and severity of abdominal obesity in NAFLD patients might be useful. Currently, lifestyle interventions including weight loss, physical activity and a healthier dietary pattern seem to have beneficial impact on lean NAFLD. Beyond that, sleep interventions and pharmacotherapy along with strict management of comorbidities should also be incorporated in the management of this disease. Without a doubt, lean NAFLD raises many challenges since the pathophysiology and the natural history of the disease has not been widely studied and physicians should have high clinical suspicion in order to identify individuals at risk of lean NAFLD who lack the common, easily recognizable phenotype of obesity.

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