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

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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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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]. The prevalence of NAFLD is increased in patients with type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS) and obesity[3]. 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[4]. Non-obese/lean NAFLD is divided into 2 major categories[5]: The first and more prevalent involves 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[6]. 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[7]. Regarding the latter, Romeo et al[8] have emphasized the involvement of the rs738409 single nucleotide polymorphism in patatin-like phospholipase domain-containing protein 3 (PNPLA3) 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)[9,10], 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 caloric 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%)\(^5\). 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\(^6\)-\(^9\). 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\(^{10\text{-}13}\). Waist circumference is considered a more accurate marker of visceral obesity than BMI, but is not available in the majority of the relevant studies\(^15\). 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 NAFLD” OR “Non-obese/lean NAFLD”. In addition, the terms used were “Lean non-alcoholic fatty liver disease” OR “Lean nonalcoholic fatty liver disease” OR “Lean NAFLD” OR “Non-obese/lean 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\(^29\) 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\(^33\) 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\(^33\).

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\(^34\)-\(^37\). Moreover, Sung et al\(^38\) 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\(^39\). Accordingly, Kwon et al\(^40\), 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\(^40\). 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 | ↑ Hazard for all-cause and cardiovascular-related mortality |
| Golabi et al[29]/2019/United States | 5375 lean subjects (581) | ↑ Prevalence of metabolic comorbidities | NA | NA | ↑ 15-yr overall, cardiovascular, cancer and other causes-related mortality (not confirmed in Cox model) |
| Zou et al[30]/2020/United States | 9634 controls (1528) | ↑ BP, HOMA-IR, glucose, insulin, TC, LDL-C, TG, ↓ HDL-C | ↑ ALT, AST, γ-GT | NA | ↑ HR of CVD incident |
| Yoshitaka et al[31]/2019/Japan | 1647 individuals; 984 non-overweight subjects (69) | ↑ BP, glucose, TG, UA, ↓ HDL-C | ↑ AST, ALT, γ-GT | NA | NA |
| Nishioji et al[32]/2015/Japan | 3271 enrolled individuals; 2606 non-obese (511) | ↑ BP, TC, HbA1c, glucose | ↑ ALT, AST, γ-GT | NA | NA |
| Kim et al[33]/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[34]/2019/South Korea | 51436 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[35]/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[36]/2013/South Korea | 799 individuals (98 in NAFLD group) | ↑ Glucose, TG, UA, HOMA-IR, ↓ HDL-C | ↑ ALT, AST, γ-GT | NA | NA |
| Kwon et al[37]/2012/South Korea | 2994 study population; 24008 non-obese (3014) | ↑ BP, glucose, insulin, HOMA-IR, ↓ HDL-C | ↑ AST, ALT, γ-GT | NA | NA |
| Feng et al[38]/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[39]/2018/China | 2008 enrolled subjects; 953 non-obese (208) | ↑ TC, TG, glucose | ↑ ALT | NA | NA |
| Zeng et al[40]/2020/China | 2715 enrolled participants (1100 NAFLD patients) | ↑ Prevalence of hypertension and MetS, TG, LDL-C, ↓ HDL-C | NA | NA | NA |
| Yu et al[41]/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  ↑ TG, TC, LDL-C, glucose  ↑ AST, ALT  NA  NA

Wang et al[4] /2015/China  9360 women population (1194 were NAFLD patients)  ↑ Prevalence of MetS, dyslipidemia  NA  NA

Kumar et al[4] /2013/India  205 NAFLD patients (27 lean) plus 131 lean healthy subjects  ↑ Prevalence of MetS, dyslipidemia  NA  NA

Oral et al[4] /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[4] /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[4] /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[4] /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/m²) patients with NAFLD suffered more frequently from hypertension and MetS than healthy non-obese subjects[4,41], whereas a cross-sectional study in China reported that non-obese (BMI < 27.5 kg/m²), 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/m²) 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/m²) 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/m²) 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/m²) 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/m²) NAFLD patients had lower prevalence of hypertension, T2DM and MetS than overweight (25 kg/m² ≤ BMI < 30 kg/m²) and obese (BMI ≥ 30 kg/m²) NAFLD patients\(^2\). Notably, the former group had significantly thinner carotid intima-media, indicating less atherosclerotic burden\(^6\). Although this result was not confirmed in a study by Shao et al\(^4\) in obese (BMI > 25 kg/m²) 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\(^3\) demonstrated that the proportion of Chinese patients with elevated FPG and serum TG levels was higher among obese (BMI > 25 kg/m²) compared with non-obese NAFLD patients, while another cross-sectional study from China confirmed that obese NAFLD women (BMI > 28 kg/m²) had higher FPG than non-obese women\(^4\). In addition, 2 studies from China showed a higher prevalence of MetS and hypertension in obese (BMI > 25 kg/m²) compared to non-obese patients with NAFLD\(^3,5\). In the Indian population, Kumar et al\(^1\) reported that among NAFLD patients, lean (BMI < 23 kg/m²) patients had had lower serum insulin levels and HOMA-IR, as well as lower prevalence of T2DM and MetS than obese (BMI > 25 kg/m²) patients. In a case control study from Sri Lanka, Nirriella et al\(^4\) reported a higher prevalence of hypertension in non-lean (BMI > 23 kg/m²) patients with NAFLD compared with lean NAFLD patients. In studies performed in Japan, Yoshitaka et al\(^4\) reported lower blood pressure and FPG and higher serum high density cholesterol (HDL-C) levels in lean (BMI < 23 kg/m²) than in overweight NAFLD patients\(^4\), while Honda et al\(^4\) reported that FPG, insulin, TG and HOMA-IR were increased among Japanese obese (BMI > 25 kg/m²) NAFLD patients compared with non-obese NAFLD patients. In a study form Hong-Kong, Wei et al\(^3\) reported that non-obese (BMI < 25 kg/m²) 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/m²) NAFLD patients had lower TC, FPG, HOMA-IR and higher HDL-C levels than obese NAFLD patients\(^4\).

Similar findings were observed in the cross-sectional NHANES III study, in which lean (BMI < 25 kg/m²) NAFLD patients had less frequently hypertension, T2DM and hypercholesteremia as well as lower levels of FPG and HOMA-IR than overweight /obese NAFLD patients\(^3\). In a prospective study from Turkey, Akyuz et al\(^1\) reported that lean (BMI < 25 kg/m²) NAFLD patients had a less prevalence of MetS and hypertension than overweight NAFLD patients, while in a study from Spain, Gonzalez-Cantero et al\(^7\) also confirmed that overweight (BMI: 25-29 kg/m²) 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\(^8\) also reported that lean (BMI < 25 kg/m²) 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/m²) NAFLD patients compared with obese NAFLD patients, even after adjusting for confounders\(^9\). It is possible that unrecorded differences in dietary patterns, physical activity and smoking status between the 2 groups might explain this paradoxical might\(^1\). Lee et al\(^1\) also reported that non-obese (BMI < 25 kg/m²) 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\(^1\).

Studies with both metabolic and clinical outcomes: In a prospective cohort study in 307 NAFLD patients from Hong-Kong, Leung et al\(^3\) 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\(^1\).

In contrast, a United States study in 483 biopsy-confirmed NAFLD patients showed that lean (BMI < 25 kg/m²) 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\(^9\). In the NHANES study, Zou et al\(^1\)
| 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.[29]/2020/United States | 4711 patients with NAFLD (3528 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.[30]/2017/Japan | 1647 individuals; 312 NAFLD patients (69 non-overweight) | ↓ BP, glucose, ↑ HDL-C | ↓ AST, ALT, and γ-GT | NA | NA |
| Kwon et al.[31]/2012/South Korea | 2994 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.[32]/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.[33]/2018/China | 2008 enrolled subjects; 493 NAFLD patients (208 non-obese) | ↑ Prevalence of MetS and hypertension, ↑ HDL-C | NA | NA | NA |
| Zeng et al.[34]/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.[35]/2015/China | 9360 women population; 1194 were NAFLD patients (514 non-obese) | ↑ U.A, glucose | ↓ ALT, AST but ↑ AST/ALT ratio | NA | NA |
| Kumar et al.[36]/2013/India | 205 NAFLD patients (27 lean) | ↓ Hyperinsulinemia, HOMA-IR, ↓ prevalence of T2DM, MetS | ↓ Mean NAS and ↓ proportion of patients with liver fibrosis | NA | NA |
| Feldman et al.[37]/2017/Austria | 187 subjects; 116 NAFLD patients (53 lean) | ↓ Glucose, insulin, HOMA-IR, ↑ HDL-C, adiponectin | ↓ ALT | NA | NA |
| Fracanzani et al.[38]/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.[39]/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.[40]/2019/China | 496 NAFLD patients (101 lean) | ↑ Proportion of patients with ↑ TG, glucose | ↓ Proportion of patients with ↑ ALT | NA | NA |

Chrysavgis L et al. Nonalcoholic fatty liver disease in lean subjects
| Study Reference | Country | Number of Patients | Metabolic Characteristics | Liver Characteristics | Clinical Outcomes |
|-----------------|---------|-------------------|------------------------|----------------------|-------------------|
| Leung et al.\(^{(52)}\) | Hong Kong | 307 NAFLD patients (72 non-obese) | ↓ Prevalence of MetS, hypertension | NA | ↓ NAS, ↓ fibrosis stage, serum cytokeratine-18 fragments and liver stiffness measurement |
| Niriella et al.\(^{(53)}\) | 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 | ↓ Prevalence of MetS, hypertension |
| Honda et al.\(^{(54)}\) | 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 |
| Wei et al.\(^{(55)}\) | Hong Kong | 262 patients with NAFLD (135 non-obese) | ↓ Insulin resistance, BP and cytokeratin-18 fragments and ↓ prevalence of MetS, ↓ genotype (PNPLA3 GG) prevalence | NA | ↓ Prevalence of MetS, hypertension |
| Alam et al.\(^{(56)}\) | 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 |
| Akyuz et al.\(^{(57)}\) | Turkey | 483 NAFLD patients (37 lean) | ↓ BP, ↓ prevalence of MetS, less severe hepatic steatosis, ↑ hemoglobin levels | NA | ↓ Prevalence of MetS, hypertension |
| Cruz et al.\(^{(58)}\) | United States | 1090 NAFLD patients (125 lean) | ↓ Insulin resistance, ↓ prevalence of low HDL-C, hypertriglyceridemia and hypertension | ↓ ALT | ↓ Cumulative survival |
| Hagström et al.\(^{(59)}\) | Sweden | 646 NAFLD patients (123 lean, 335 overweight, 188 obese) | ↓ TG, glucose | ↓ ALT, AST compared to both overweight and obese counterparts | ↓ 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 NAFLD. 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\(^{(30,56,59)}\), although not all\(^{(52)}\), reported a worse prognosis in non-obese/lean patients with NAFLD compared with obese...
NAFLD patients. Zou et al\textsuperscript{[6]} 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\textsuperscript{[6]} 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\textsuperscript{[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\textsuperscript{[60]}. 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\textsuperscript{[62,64]}. 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\textsuperscript{[84,85]}.  

**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\textsuperscript{[66]}. Moreover, 2 studies showed that 5\% of body weight reduction led to significant decrease in steatosis in lean patients with NAFLD\textsuperscript{[65,66]}. 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\textsuperscript{[66]}, 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\textsuperscript{[60]}.  

**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\textsuperscript{[69,70]}. However, the former have higher intake of cholesterol and lower intake of polyunsaturated fatty acids (PUFAs)\textsuperscript{[63]}. 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\textsuperscript{[66]}. 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 |
| Comorbidities                 | 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[28,53].

Management of comorbidities: As already mentioned, lean patients with NAFLD appear to have higher incidence of T2DM compared with overweight patients without NAFLD[30]. 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[83]. 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 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.

REFERENCES

1 Yousnossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, Qiu Y, Burns L, Afendy A, Nader F. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol 2019; 71: 793-801 [PMID: 31279902 DOI: 10.1016/j.jhep.2019.06.021]

2 Papatheodoridi AM, Chrysavgis L, Koutsilieris M, Chatzigeorgiou A. The Role of Senescence in the Development of Nonalcoholic Fatty Liver Disease and Progression to Nonalcoholic Steatohepatitis. Hepatology 2020; 71: 363-374 [PMID: 31230380 DOI: 10.1002/hep.30831]

3 Yousnossi Z, Ansee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018; 15: 11-20 [PMID: 28930295 DOI: 10.1038/nrgastro.2017.109]

4 Chalasani N, Yousnossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018; 67: 328-357 [PMID: 28714183 DOI: 10.1002/hep.29367]

5 Wang Y, Dhalwal J, Mouri Z. Lean non-alcoholic fatty liver disease. Clin Nutr 2019; 38: 975-981 [PMID: 30466950 DOI: 10.1016/j.clnu.2018.08.008]

6 Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. JHEP Rep 2019; 1: 329-341 [PMID: 32039383 DOI: 10.1016/j.jhep.2019.08.002]

7 Romeo S, Kozlitina J, Xing C, Persimilidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008; 40: 1461-1465 [PMID: 18820647 DOI: 10.1038/ng.257]

8 Dongiovanni P, Petta S, Maglio C, Fracanzani AL, Pipitone R, Mozz M, Motta BM, Kaminska D, Rametta R, Giraudou S, Pelusi S, Montalbini T, Alisi A, Maggioni M. A genetic predisposition to non-alcoholic fatty liver disease. J Hepatol 2015; 63: 399-404 [PMID: 25513399 DOI: 10.1016/j.jhep.2014.07.043]

9 Liu YL, Reeves H, Burt AD, Tinakos D, McPherson S, Leathart JB, Allison ME, Alexander GJ, Piguet AC, Anty R, Donaldson P, Aithal GP, Francque S, Van Gaal L, Clement K, Ratzou V, Dufour JF, Day CP, Daly AK, Ansee QM. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. Nat Commun 2014; 5: 4309 [PMID: 24978903 DOI: 10.1038/ncomms5309]

10 Donati B, Dongiovanni P, Romeo S, Moroni M, McCain M, Miele L, Petta S, Maier S, Rosso C, De Luca L, Vanni R, Giraudou S, Romagnoli R, Colli F, Ferri F, Mancina RM, Iruzubieta P, Craxi A, Fracanzani AL, Greco A, Corradini SG, Aghemo A, Colombo M, Soardo G, Bugianesi E, Reeves H, Ansee QM, Fargion S, Valenti L. MBOAT7 variant rs641738 alters hepatic phosphatidylinositols and increases severity of non-alcoholic fatty liver disease in non-cirrhotic individuals. Sci Rep 2017; 7: 4492 [PMID: 28674415 DOI: 10.1038/s41598-017-04991-0]

11 Zain SM, Mohamed Z, Mohamed R. Common variant in the glucokinase regulatory gene rs7800894 and risk of nonalcoholic fatty liver disease: a meta-analysis. J Gastroenterol Hepatol 2015; 30: 21-27 [PMID: 25167786 DOI: 10.1111/jgh.12714]

12 Petta S, Miele L, Bugianesi E, Cammà C, Rosso C, Boccia S, Cabibi S, Di Marco V, Giraudou S, Greco A, Pipitone RM, Marchesini G, Craxi A. Glucokinase regulatory protein gene polymorphism affects liver fibrosis in non-alcoholic fatty liver disease. PLoS One 2014; 9: e87523 [PMID: 24498332 DOI: 10.1371/journal.pone.0087523]

13 Luukkonen PK, Zhou Y, Hyytöläinen T, Leivonen M, Arola J, Orho-Melander M, Orešič M, Yki-Järvinen H. The MBOAT7 variant rs641738 alters hepatic phosphatidylinositols and increases severity of non-alcoholic fatty liver disease in humans. J Hepatol 2016; 65: 1263-1265 [PMID: 27520876 DOI: 10.1016/j.jhep.2016.07.045]

14 Petta S, Valenti L, Tuttolomondo A, Dongiovanni P, Pipitone RM, Cammà C, Cabibi D, Di Marco V, Fracanzani AL, Badiali S, Nobili V, Fargion S, Giraudou S, Craxi A. Interferon lambda 4 rs368234815
TT→8G variant is associated with liver damage in patients with nonalcoholic fatty liver disease. *Hepatology* 2017; 66: 1885-1893 [PMID: 28741298 DOI: 10.1002/hep.29395]

Abul-Husa NS, Cheng X, Li AH, Xin Y, Schurmann C, Stevis P, Liu Y, Kozlitina J, Stender S, Wood GC, Stepanchick AN, Still MD, McCarthy S, O'Dushlaine C, Packer JS, Balasubramaniam S, Gosalian N, Espi D, Kim SY, Mukherjee S, Lopez AE, Fuller ED, Penn J, Chu X, Luo JZ, Mirshahi UL, Carey DJ, Still CD, Feldman MD, Small A, Danzauer SM, Rader DJ, Zambrowicz B, Olson W, Murphy AJ, Borecki IB, Shuldiner AR, Reid JG, Overton JD, Yancopoulos GD, Hobbs HH, Cohen JC, Gottesman O, Teslovich TM, Baras A, Mirshahi T, Gromada J, Dewey FE. A Protein-Truncating HSD17B13 Variant and Protection from Chronic Liver Disease. *N Engl J Med* 2018; 378: 1096-1106 [PMID: 29562163 DOI: 10.1056/NEJMoa1712191]

Luukkonen PK, Tukiainen T, Jouti A, Sammal Korpi H, Haridas PAN, Niemelä O, Arola J, Ohro-Melaneder M, Hakkaranen A, Kovanen PT, Dwivedi O, Groop L, Hovden L, Gualdi A, Hyltudden T, Orezić M, Yki-Järvinen H. Hydroxysteroid 17-β dehydrogenase 17 increases phospholipids and protects against fibrosis in nonalcoholic fatty liver disease. *JCI Insight* 2020; 5 [PMID: 32161197 DOI: 10.1172/jci.insight.122158]

Zelber-Sagi S, Salomone F, Mlynarsky L. The Mediterranean dietary pattern as the diet of choice for non-alcoholic fatty liver disease: Evidence and plausible mechanisms. *Liver Int* 2017; 37: 936-949 [PMID: 28371239 DOI: 10.1111/liv.13455]

Trovato FM, Martines GF, Brischetto D, Trovato G, Catalano D. Neglected features of lifestyle: Their relevance in non-alcoholic fatty liver disease. *World J Hepatol* 2016; 8: 1459-1465 [PMID: 27957244 DOI: 10.4254/wjh.v8.i3.1459]

Ryu S, Chang Y, Jung HS, Yun KE, Kwon MJ, Choi Y, Kim CW, Cho J, Suh BS, Cho YK, Chung EC, Shin H, Kim YS. Relationship of sitting time and physical activity with non-alcoholic fatty liver disease. *J Hepatol* 2015; 63: 1229-1237 [PMID: 26385766 DOI: 10.1016/j.jhep.2015.07.010]

Ye Q, Zou B, Yeo YH, Li J, Huang DQ, Wu Y, Yang H, Liu C, Kam LY, Tan XXE, Chien N, Trinh S, Henry L, Stave CD, Hosaka T, Cheung RC, Nguyen MH. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; 5: 739-752 [PMID: 32413340 DOI: 10.1016/S2468-1253(20)30077-7]

WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157-163 [PMID: 14726171 DOI: 10.1016/S0140-6736(03)12568-3]

Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. *Lancet* 2005; 366: 1059-1062 [PMID: 16182882 DOI: 10.1016/S0140-6736(05)67402-8]

Kim D, Kim WR. Nonobese Fatty Liver Disease. *Clin Gastroenterol Hepatol* 2017; 15: 474-485 [PMID: 27581063 DOI: 10.1016/j.cgh.2016.08.028]

Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr* 2007; 86: 353-359 [PMID: 17684205 DOI: 10.1093/jcn/acn.86.2.353]

Barreira TV, Broyles ST, Gupta AK, Katmarzyk PT. Relationship of anthropometric indices to abdominal and total body fat in youth: sex and race differences. *Obesity (Silver Spring)* 2014; 22: 1340-1350 [PMID: 24493150 DOI: 10.1002/oby.20714]

Ha Y, Sae N, Shim JH, Kim SY, Park JA, Han S, Kim KW, Yu E, Kim KM, Lim YS, Lee HC, Chung YH, Lee YS. Intimate association of visceral obesity with non-alcoholic fatty liver disease in healthy Asians: A case-control study. *J Gastroenterol Hepatol* 2015; 30: 1666-1672 [PMID: 25974139 DOI: 10.1111/j.1440-9744.12313]

Margariti A, Deutsch M, Manolakopoulos S, Tiniakos D, Papatheodoridis GV. The severity of histologic liver lesions is independent of body mass index in patients with nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2013; 47: 280-286 [PMID: 23391869 DOI: 10.1097/MCG.0b013e1825b23c82]

Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, Srisrich M. Nonalcoholic fatty liver disease in lean individuals in the United States. *Medicine (Baltimore)* 2012; 91: 319-327 [PMID: 23178851 DOI: 10.1097/MD.0b013e1152797049]

Golabli P, Paik J, Fukui N, Locklear CT, de Avilla L, Younossi ZM. Patients With Lean Nonalcoholic Fatty Liver Disease Are Metabolically Abnormal and Have a Higher Risk for Mortality. *Clin Diabetes* 2019; 37: 65-72 [PMID: 30705499 DOI: 10.2337/cd18-0026]

Zou B, Yeo YH, Nguyen VH, Cheung R, Ingelsson E, Nguyen MH. Prevalence, characteristics and mortality outcomes of obese, nonobese and lean NAFLD in the United States, 1999-2016. *J Intern Med* 2020; 288: 139-151 [PMID: 32319718 DOI: 10.1111/jim.13069]

Yoshitake H, Hamaguchi M, Kojima T, Fukuda T, Obhora A, Fukui M. Nonoverweight nonalcoholic fatty liver disease and incident cardiovascular disease: A post hoc analysis of a cohort study. *Medicine (Baltimore)* 2017; 96: e6712 [PMID: 28471965 DOI: 10.1097/MD.0000000000006712]

Fukuda T, Hamaguchi M, Kojima T, Hashimoto Y, Obhora A, Kato T, Nakamura N, Fukui M. The impact of non-alcoholic fatty liver disease on incident type 2 diabetes mellitus in non-overweight individuals. *Liver Int* 2016; 36: 275-283 [PMID: 26176710 DOI: 10.1111/liv.12912]

Nishioji K, Sumida Y, Kamaguchi M, Mochizuki N, Kobayashi M, Nishimura T, Yamaguchi T, Itoh Y. Prevalence of and risk factors for non-alcoholic fatty liver disease in a non-obese Japanese population, 2011-2012. *J Gastroenterol* 2015; 50: 95-108 [PMID: 24619537 DOI: 10.1007/s00535-014-0948-9]

Kim SS, Cho HJ, Kim HJ, Kang DR, Berry JR, Kim JH, Yang MJ, Lim SG, Kim S, Cheong YJ, Cho SW. Nonalcoholic fatty liver disease as a sentinel marker for the development of diabetes mellitus in non-obese subjects. *Dig Liver Dis* 2018; 50: 370-377 [PMID: 29398414 DOI: 10.1016/j.dld.2017.12.018]

Sinn DH, Kang D, Cho SJ, Paik SW, Guellar E, Cho J, Gwak GY. Lean non-alcoholic fatty liver disease and development of diabetes: a cohort study. *Eur J Endocrinol* 2019; 181: 185-192 [PMID: 31176297 DOI: 10.1530/EJE-19-0143]
Chrysavgis L et al. Nonalcoholic fatty liver disease in lean subjects.

36 Sung KC, Ryan MC, Wilson AM. The severity of nonalcoholic fatty liver disease is associated with increased cardiovascular risk in a large cohort of non-obese Asian subjects. *Atherosclerosis* 2009; 203: 581-586 [PMID: 18774137 DOI: 10.1016/j.atherosclerosis.2008.07.024]

37 Kim S, Choi J, Kim M. Insulin resistance, inflammation, and nonalcoholic fatty liver disease in non-obese adults without metabolic syndrome components. *Hepatol Int* 2013; 7: 586-591 [PMID: 26201791 DOI: 10.1007/s12072-012-9412-1]

38 Kwon YM, Oh SW, Hwang SS, Lee C, Kwon H, Chung GE. Association of nonalcoholic fatty liver disease with components of metabolic syndrome according to body mass index in Korean adults. *Am J Gastroenterol* 2012; 107: 1852-1858 [PMID: 23032989 DOI: 10.1038/ajg.2012.314]

39 Feng RN, Du SS, Wang C, Li YC, Liu LY, Guo FC, Sun CH. Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population. *World J Gastroenterol* 2014; 20(18): 5793-5799 [PMID: 24833974 DOI: 10.3748/wjg.v20.i18.5793]

40 Lee SW, Lee TY, Yang SS, Tung CF, Yeh HZ, Chang CS. Risk factors and metabolic abnormality of patients with non-alcoholic fatty liver disease: Either non-obese or obese Chinese population. *Hepatobiliary Pancreat Dis Int* 2018; 17: 45-48 [PMID: 29428103 DOI: 10.1016/j.jpbd.2018.01.007]

41 Zeng J, Yang RX, Sun C, Pan Q, Zhang RN, Chen GY, Hu Y, Fan JG. Prevalence, clinical characteristics, risk factors, and indicators for lean Chinese adults with nonalcoholic fatty liver disease. *World J Gastroenterol* 2020; 26: 1792-1804 [PMID: 32351294 DOI: 10.3748/wjg.v26.i15.1792]

42 Yu XY, Zhao Y, Song XX, Song ZY. Association between non-alcoholic fatty liver disease and arterial stiffness in the non-obese, non-hypertensive, and non-diabetic young and middle-aged Chinese population. *J Zhejiang Univ Sci B* 2014; 15: 879-887 [PMID: 25294377 DOI: 10.1631/jzus.B1400028]

43 Wang Z, Xu M, Hu Z, Shrestha UK. Prevalence of nonalcoholic fatty liver disease and its metabolic risk factors in women of different ages and body mass index. *Menopause* 2015; 22: 667-673 [PMID: 25513983 DOI: 10.1097/GME.0000000000000352]

44 Kumar R, Rastogi A, Sharma MK, Bhatia V, Garg H, Bihari C, Sarin SK. Clinicopathological characteristics and metabolic profiles of non-alcoholic fatty liver disease in Indian patients with normal body mass index: Do they differ from obese or overweight non-alcoholic fatty liver disease? *Indian J Endocrinol Metab* 2013; 17: 665-671 [PMID: 23961483 DOI: 10.4103/2220-8210.113758]

45 Oral A, Sahin T, Turker F, Kocak E. Relationship Between Serum Uric Acid Levels and Nonalcoholic Fatty Liver Disease in Non-Obese Patients. *Medicina (Kaunas)* 2019; 55 [PMID: 31533345 DOI: 10.3390/medicina55090600]

46 Erkan G, Sayın I, Polat FB, Çorakçı A, Atac GK, Değertekin H. The relationship between insulin resistance, metabolic syndrome and nonalcoholic fatty liver disease in non-obese diabetic Turkish individuals: A pilot study. *Turk J Gastroenterol* 2014; 25 Suppl 1: 63-68 [PMID: 25910371 DOI: 10.5152/tjg.2014.6223]

47 Feldman A, Eder SK, Felder TK, Kedenko L, Paulweber B, Stadlmayr A, Huber-Schönauer U, Niederseer D, Stickel F, Auer S, Haschke-Becher E, Patsch W, Datz C, Aigner E. Clinical and Metabolic Characterization of Lean Caucasian Subjects With Non-Alcoholic Fatty Liver. *Am J Gastroenterol* 2017; 112: 102-110 [PMID: 27527746 DOI: 10.1038/ajg.2016.318]

48 González-Cantero J, Martín-Rodriguez JL, González-Cantero A, Arrebola JP, González-Calvín JL. Insulin resistance in lean and overweight non-diabetic Caucasian adults: Study of its relationship with liver triglyceride content, waist circumference and BMI. *PLoS One* 2018; 13: e0192663 [PMID: 29425212 DOI: 10.1371/journal.pone.0192663]

49 Fracanzani AL, Petta S, Lombardi R, Pisano G, Russello M, Consomni D, Di Marco V, Cammar C, Menši L, Dongiovanni P, Valenti L, Craxì A, Fargion S. Liver and Cardiovascular Damage in Patients With Lean Nonalcoholic Fatty Liver Disease, and Association With Visceral Obesity. *Clin Gastroenterol Hepatol* 2017; 15: 1664-1661.e1 [PMID: 28554682 DOI: 10.1016/j.cgh.2017.04.043]

50 Shao C, Ye J, Li F, Lin Y, Wu T, Wang W, Feng S, Zhong B. Early Predictors of Cardiovascular Disease Risk in Nonalcoholic Fatty Liver Disease: Non-obese Versus Obese Patients. *Dig Dis Sci* 2020; 65: 1850-1860 [PMID: 31724099 DOI: 10.1007/s10620-019-05926-7]

51 Li H, Chen Y, Tian X, Hong Y, Chen C, Sharokh NK, Jiao J. Comparison of clinical characteristics between lean and obese nonalcoholic fatty liver disease in the northeast in Chinese population. *Arch Med Sci Atheroscler Dis* 2019; 4: c19-c195 [PMID: 31538123 DOI: 10.5114/amsad.2019.87122]

52 Leung JC, Loong TC, Wei JL, Wong GL, Chan AW, Choi PC, Shu SS, Chim AM, Chan HL, Wong VW. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. *Hepatology* 2017; 65: 54-64 [PMID: 27339817 DOI: 10.1002/hep.28267]

53 Niirella MA, Kasturiratne A, Pathmeswaran A, De Silva ST, Perera KR, Subasinghe SKCE, Kodisinghe SK, Priyaratna TACL, Vithyo K, Dassanayaka AS, De Silva AP, Wickramasinghe AR, Takeuchi F, Kato N, de Silva HJ. Lean non-alcoholic fatty liver disease (lean NAFLD): characteristics, metabolic outcomes and risk factors from a 7-year prospective, community cohort study from Sri Lanka. *Hepatol Int* 2019; 13: 314-322 [PMID: 30539516 DOI: 10.1007/s12072-018-9916-4]

54 Honda Y, Yoneda M, Kessoku T, Ogawa Y, Tomono W, Imajo K, Mawatari H, Fujita K, Hyogo H, Ueno T, Chayama K, Saito S, Nakajima A, Hotta K. Characteristics of non-obese non-alcoholic fatty liver disease: Effect of genetic and environmental factors. *Hepatol Res* 2016; 46: 1011-1018 [PMID: 26763865 DOI: 10.1111/hepr.12648]

55 Wei JL, Leung JC, Loong TC, Wong GL, Yeung DK, Chan RS, Chan HL, Chim AM, Woo J, Chu WC, Wong VW. Prevalence and Severity of Nonalcoholic Fatty Liver Disease in Non-Obese Patients: A Population Study Using Proton-Magnetic Resonance Spectroscopy. *Am J Gastroenterol* 2015; 110: 1306-1314; quiz 1315 [PMID: 26215532 DOI: 10.1038/ajg.2015.235]

56 Alam S, Gupta UD, Alam M, Kabir J, Chowdhury ZR, Alam AK. Clinical, anthropometric, biochemical, and histological characteristics of nonobese nonalcoholic fatty liver disease patients of Bangladesh. *Indian J Gastroenterol* 2014; 33: 452-457 [PMID: 25023045 DOI: 10.4103/0970-2088.14-0488-7]

57 Akyuz U, Yesil A, Yilmaz Y. Characterization of lean patients with nonalcoholic fatty liver disease: potential role of high hemoglobin levels. *Scand J Gastroenterol* 2015; 50: 341-355 [PMID: 25409773 DOI: 10.3109/03005655.2014.981600]
Lipids Health Dis
inhibitor ezetimibe is a reliable therapeutic agent for non-obese patients with nonalcoholic fatty liver disease. A long-term follow-up study. Hepatol Commun 2018; 2: 48-57 [PMID: 29404512 DOI: 10.1002/hep4.1124]

Ghaemi A, Hosseini N, Oasti S, Naghizadeh MM, Dehghan A, Ehrampoush E, Honarvar B, Homayoonfar R. Waist circumference is a mediator of dietary pattern in Non-alcoholic fatty liver disease. Sci Rep 2018; 8: 4788 [PMID: 29555595 DOI: 10.1038/s41598-018-23192-x]

Klopfenstein BJ, Kim MS, Krisky CM, Szumowski J, Rooney WD, Parnell JQ. Comparison of 3 T MRI and CT for the measurement of visceral and subcutaneous adipose tissue in humans. Br J Radiol 2012; 85: e826- e830 [PMID: 22514099 DOI: 10.1259/bjr.257987644]

Sterling RK, Lissen E, Chumeck N, Sola R, Correa MC, Montaner J, S Sulkowski M, Torriani FJ, Dietrich DT, Thomas DL, Messinger D, Nelson M. APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006; 43: 1317-1325 DOI: 10.1002/hep.21178

Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Sakensa S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007; 45: 846-854 [PMID: 17393509 DOI: 10.1002/hep.21496]

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). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64: 1388-1402 [PMID: 27062661 DOI: 10.1016/j.jhep.2015.11.004]

Papatheodoridi M, Chologitias E. Diagnosis of Non-alcoholic Fatty Liver Disease (NAFLD): Current Concepts. Curr Pharm Des 2018; 24: 4574-4586 [PMID: 30652642 DOI: 10.2174/1381612825666190117102111]

Kim NH, Kim JH, Kim YJ, Yoo HJ, Kim HY, Jeo SA, Kim NH, Choi KM, Bui KH, Choi DS, Kim SG. Clinical and metabolic factors associated with development and regression of nonalcoholic fatty liver disease in nonobese subjects. Liver Int 2014; 34: 604-611 [PMID: 24382209 DOI: 10.1111/liv.12454]

Jin YJ, Kim KM, Hwang S, Lee SG, Ha TY, Song GW, Jung DH, Kim KH, Yu E, Shim JH, Lim YS, Lee HC, Chung YH, Lee Y, Suh DJ. Exercise and diet modification in non-obese non-alcoholic fatty liver disease: analysis of biopsies of living liver donors. J Gastroenterol Hepatol 2012; 27: 1341-1347 [PMID: 22554085 DOI: 10.1111/j.1440-1746.2012.07165.x]

Hamurcu Varol P, Kaya E, Alphan E, Yilmaz Y. Role of intensive dietary and lifestyle interventions in the treatment of lean nonalcoholic fatty liver disease patients. Eur J Gastroenterol Hepatol 2020; 32: 1352-1357 [PMID: 32092046 DOI: 10.1097/MEG.0000000000001656]

Li C, Guo P, Okekeule AP, Li X, Huang M, Qi J, Jiang Y, Feng R, Li R. Lean non-alcoholic fatty liver disease patients had comparable total caloric, carbohydrate, protein, fat, iron, sleep duration and overtime work as obese non-alcoholic fatty liver disease patients. J Gastroenterol Hepatol 2019; 34: 256-262 [PMID: 29949199 DOI: 10.1111/jgh.14360]

Yasutake K, Nakamura M, Shinya Y, Ohyama A, Masuda K, Haruta N, Fujino T, Aoyagi Y, Fukuzumi K, Yoshimoto T, Takemoto R, Miyanohara T, Harada N, Hayata F, Nakashima M, Enjoji M. Nutritional investigation of non-obese patients with non-alcoholic fatty liver disease: the significance of dietary cholesterol. Scand J Gastroenterol 2009; 44: 471-477 [PMID: 19058085 DOI: 10.1111/j.1120-914X.2009.00513.x]

McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-late fibrohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015; 62: 1148-1155 [PMID: 25477264 DOI: 10.1016/j.jhep.2014.11.034]

Pais R, Charlotte F, Fedchuk L, Bedossa P, Lebray P, Poynard T, Ratziu V, LIDO Study Group. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol 2013; 59: 550-556 [PMID: 23665288 DOI: 10.1016/j.jhep.2013.04.027]

Denkmary L, Feldman A, Stichemesser L, Eder SK, Zandanel S, Schranz M, Strasser M, Huber-Schönauer U, Buch S, Hampe J, Paulweber B, Lackner C, Haube H, Sotlar K, Datz C, Aigner E. Lean Patients with Non-Alcoholic Fatty Liver Disease Have a Severe Histological Phenotype Similar to Obese Patients. J Clin Med 2018; 7 [PMID: 30562976 DOI: 10.3390/jcm7210562]

Chen F, Esmaili S, Rogers GB, Bugarinonis E, Petta S, Marchesini G, Bayoumi A, Metwally A, Azadaryanda MK, Coulter S, Choo JM, Younes R, Rosso C, Ciddle C, Adams LA, Craxi A, George J, Eslam M. Lean NAFLD: A Distinct Entity Shaped by Differential Metabolic Adaptation. Hepatology 2020; 71: 1213-1227 [PMID: 31442319 DOI: 10.1002/hep.30908]

Taheri S, Lin L, Austin D, Young T, Mignon E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 2004; 1: e62 [PMID: 15602591 DOI: 10.1371/journal.pmed.0010062]

Wang H, Gu Y, Zheng L, Liu L, Meng G, Wu H, Xia Y, Bao X, Shi H, Sun S, Wang X, Zhou M, Jia Q, Song K, Zhang Q, Niu K. Association between bedtime and the prevalence of newly diagnosed non-alcoholic fatty liver disease in adults. Liver Int 2018; 38: 2277-2286 [PMID: 29851261 DOI: 10.1111/liv.13896]

Wijanrunpreecha K, Thongprayoon C, Panjawatanan P, Ungerprat S. Short sleep duration and risk of nonalcoholic fatty liver disease: A systematic review and meta-analysis. J Gastroenterol Hepatol 2016; 31: 1802-1807 [PMID: 27029776 DOI: 10.1111/jgh.13391]

Enjoji M, Machida K, Kohjima M, Kato M, Kotoh K, Masunaga K, Nakashima M, Nakamura M. NPC1L1 inhibitor ezetimibe is a reliable therapeutic agent for non-obese patients with nonalcoholic fatty liver disease. Lipids Health Dis 2010; 9: 29 [PMID: 20222991 DOI: 10.1186/1476-511X-9-29]
Mofidi F, Poustchi H, Yuri Z, Nourinayyer B, Merat S, Sharafikhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial. *Br J Nutr* 2017; **117**: 662-668 [PMID: 28345499 DOI: 10.1017/S0007114517000204]

Eslamparast T, Poustchi H, Zamani F, Sharafikhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. *Am J Clin Nutr* 2014; **99**: 535-542 [PMID: 24401715 DOI: 10.3945/ajcn.113.068890]
