Clinical Nutrition 38 (2019) 975–981

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Review

Lean non-alcoholic fatty liver disease

Alice Yuxin Wang [a], Jasbir Dhaliwal [b], Marialena Mouzaki [c,*]

[a] Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada
[b] Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
[c] Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, OH, USA

ARTICLE INFO

Article history:
Received 13 February 2018
Accepted 9 August 2018

Keywords:
NAFLD
Lean
Waist circumference
BMI
Non-obese
Fatty liver disease

SUMMARY

Background & aims: Non-alcoholic fatty liver disease (NAFLD), with its increasing prevalence and association with various co-morbidities, such as diabetes, cardiovascular disease and metabolic syndrome, is a growing concern. Previously thought to predominantly affect obese individuals, NAFLD has been shown to occur in non-obese subjects. This subset of individuals, known to have 'lean NAFLD' or 'non-obese NAFLD', is also growing increasingly prevalent. We summarize the clinical manifestations, pathophysiology and management of lean NAFLD in both adult and pediatric populations.
Methods: Two reviewers performed an independent, formal review and analysis of the literature (PubMed and EMBASE search until April 2018).
Results and conclusions:: Patients with lean NAFLD share metabolic features of insulin resistance and dyslipidemia, similar to obese patients with NAFLD. Genetic predisposition, dietary and environmental factors may play a role in the pathogenesis of lean NAFLD. Genetic and metabolic conditions should be considered as well. Currently, there are no formal recommendations for the treatment of adult or pediatric lean NAFLD; however, lifestyle changes aimed at improving overall fitness are likely to have a favorable impact.

1. Background and aims

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term used to describe a spectrum of conditions, ranging from hepatic steatosis without inflammation (non-alcoholic fatty liver; NAFL) and non-alcoholic steatohepatitis (NASH) to cirrhosis [1]. As the most common liver disease in the world, it affects 20–30% of the Western population [2] and up to 34% of children followed in obesity clinics [3]. Its increasing prevalence is a growing concern, as NAFLD is associated with increased mortality and morbidity, particularly due to its close association with obesity, cardiovascular disease, type 2 diabetes and hepatocellular carcinoma [4,5]. While NAFLD is strongly associated with metabolic syndrome, a proportion of individuals have NAFLD in the context of a normal body mass index (BMI) [6].

The subset of individuals, known to have 'lean NAFLD' or 'non-obese NAFLD', is not insignificant and is growing increasingly prevalent [7]. Subjects with lean NAFLD have been shown to experience similar complications as those with obese NAFLD, but the lean NAFLD population remains poorly characterized, particularly in pediatrics [8,9]. This review summarizes the clinical manifestations, pathophysiology and management of lean NAFLD in both adult and pediatric subjects.

2. Methods

The contents of this review are based on a formal review and analysis of recently published world literature (PubMed and EMBASE search) until April 2018, which was undertaken independently by 2 reviewers.

3. Lean NAFLD

Lean NAFLD can be separated into two categories. The first includes non-obese subjects (BMI<95th percentile for age), who may be overweight (BMI 85th-95th percentile for age) and/or have increased waist circumference and visceral adipose tissue in the context of a normal BMI. For the purposes of this review, we will refer to these patients as having '*metabolically obese, lean NAFLD*'. The second, and less prevalent category includes truly lean patients without increased fat mass, who develop hepatic steatosis

* Corresponding author. 3333 Burnet Ave, Cincinnati, OH 45229, USA.
E-mail address: Marialena.Mouzaki@cchmc.org (M. Mouzaki).

https://doi.org/10.1016/j.clnu.2018.08.008
0261-5614/

secondary to an underlying metabolic or inflammatory disorder, or due to medications. These disorders are summarized in Table 1 but are beyond the scope of this review and will not be discussed further.

The most significant limitation of the published literature to date that addresses the prevalence, histology, metabolic burden and outcomes of patients with metabolically obese lean NAFLD is the lack of data on body composition and the use of BMI thresholds for the determination of leanness. BMI is not a marker of body composition and it fails to identify body fatness in more than half of adults and more than a quarter of children [10,11]. In addition, subjects with similar BMI can have variable degrees of visceral adiposity [12,13]. This is crucial as the latter is what predisposes to the development of fatty liver disease [14]. Compared to BMI, waist circumference is a superior, clinically available tool to determine abdominal obesity; however, it is not often measured or included in studies reporting on lean NAFLD. In cases where waist circumference has been measured the results have underscored the limitations of BMI cutoffs for the determination of obesity, as those individuals that have been labeled as 'non-obese' have increased waist circumference [15,16]. Another limitation of using BMI for the determination of leanness or obesity is the need to apply different cutoffs for different ethnicities. Caucasian adults are thought to be overweight at a BMI of 25–30 kg/m^2 and obese at a BMI >30 kg/m^2[17]. In Asians, overweight is defined as a BMI of 23–25 kg/m^2 and obesity is defined as a BMI >25 kg/m^2. Studies of multiethnic populations that have reported on non-obese NAFLD have not always used these different cutoffs, increasing the likelihood that obese patients are included in the studied cohorts. The aforementioned limitations should be taken into consideration when interpreting the literature on lean or 'non-obese' NAFLD.

4. Prevalence

The literature on the prevalence of metabolically obese, lean NAFLD in general populations is characterized by the use of variable modalities for the diagnosis of NAFLD and different cutoffs for the definition of leanness (Table 2). As a result, the reported prevalence across the globe ranges from 5 to 26%.

In the United States, using NHANES III (1988–1994) data (n = 4457), the prevalence of ultrasound-determined hepatic steatosis in otherwise healthy subjects with a BMI<25 kg/m^2 was 10% [18]. Data from the Dallas Heart Study suggest that non-obese (BMI<30 kg/m^2) hepatic steatosis (determined with magnetic resonance spectroscopy) ranged from 11 to 26% in subjects of different ethnic backgrounds [19]. In South Korea, of 460 subjects with a BMI<25 kg/m^2 and no known liver disease presenting for medical check-up, 74 (16%) had ultrasonographic evidence of hepatic steatosis [16], whereas in Japan, lean NAFLD in a similar context was found in 11% of those with a BMI<23 kg/m^2[20]. In Hong Kong, MR spectroscopy based data suggest that the prevalence of hepatic steatosis in adults with a BMI<25 kg/m^2 was 19%. Lastly, the prevalence of lean NAFLD (BMI<25 kg/m^2) in an urban population from West Bengal, India, was 5% [21]. In this cohort hepatic steatosis was determined with the use of ultrasonography and subsequent confirmation with CT scans.

In children, lean NAFLD is typically defined as hepatic steatosis in the context of a BMI<2SD below the mean. There is a paucity of data on the prevalence of lean NAFLD in the general pediatric population, though a recent systematic meta-analysis of nine studies including children with NAFLD (age 1–19) found the prevalence of NAFLD in those who were of healthy weight to be 2.3% (95% CI 1.5 to 3.6) (n = 9, I2 = 68.9, Tau2 = 0.27) [2]. There is emerging data suggesting that NAFLD is being diagnosed at an increasingly younger age [2], more literature is needed to determine the true prevalence of lean NAFLD across different ages. Though obesity has been recognized as the main driver for decades, genetic predisposition along with prenatal and postnatal factors, are likely to have a complex interplay in the developmental programming of NAFLD [23].

5. Clinical characteristics of patients with lean NAFLD

Patients with lean NAFLD are generally asymptomatic and their liver disease remains undiagnosed or incidentally detected with imaging. Compared to obese patients with NAFLD, patients with lean NAFLD have a lower body weight and waist circumference. Studies have reported that patients with lean NAFLD tend to be younger, male, have higher hemoglobin levels, lower blood pressure, fasting glucose and glycated hemoglobin (HbA1c) levels [18,24–26]. In contrast to healthy controls, patients with lean NAFLD generally have higher homeostasis model assessment-insulin resistance index (HOMA-IRI), malondialdehyde (MDA) levels, blood pressure, BMI, fasting blood sugar and levels of dyslipidemia [27,28]. Various studies have reported different findings with regards to age and gender associations. However, the majority of studies have noted male gender to be associated with lean NAFLD. Finally, compared to obese patients without NAFLD, patients with lean NAFLD were found to have similar HOMA-IRI, HbA1c (in the normal range) and level of dyslipidemia and hypertriglyceridemia [29]. In one German study comparing 5 patients with lean NAFLD to 27 obese patients without NAFLD, serum ferritin, hemoglobin and hematocrit were found to be significantly higher in the lean NAFLD group [29]. Elevated serum ferritin, hemoglobin and triglyceride levels have previously found to be associated with NAFLD and may be additional markers to predict liver dysfunction in a lean population [25,30]. Despite the

Table 1
Secondary causes of steatosis.

General/nutritional	Metabolic	Drug toxicity
Acute systemic disease	Cystic fibrosis	Amiodarone
Acute starvation	Wilson's disease	Methotrexate
Protein calorie malnutrition	α1 antitrypsin deficiency	Prednisolone
Total parenteral nutrition	Galactosemia	L-asparaginase, methorexate
Inflammatory bowel disease	Fructosemia	Vitamin A
Celiac disease	Cholesterol ester storage (Wolman) disease	Valproate
Mauriac syndrome	Glycogen storage disease	Tamoxifen
Hepatitis C	Mitochondrial and peroxisomal defects of fatty acid oxidation	Zidovudine and anti-HIV treatments
	Lipodystrophies	Ethanol
	Abetalipoproteinaemia	Ecstasy
	Weber-Christian disease	

Table 2
Prevalence of lean non-alcoholic fatty liver disease in adult populations.

Study	Country	*n*	NAFLD Determination Method	Leanness BMI Cut-Off (*kg/m²*)	Lean NAFLD Prevalence (% of population)	NAFLD Prevalence
Nisholji et al. [39]	Japan	3271	U/S	<25.0	12.6%	24.6%
Sinn et al. [31]	Korea	5878[a]	U/S	≥18.5; <25.0	27.4%	–
Wei et al. [5]	Hong Kong	911	MRS	<25.0	14.8%	28.8%
Xu et al. [69]	China	6905[a]	U/S	<25.0	7.2%	–
Das et al. [21]	India	1911	U/S, then CT	<25.0	6.4%	8.7%
Younossi et al. [18]	USA	11,613	U/S	<25.0	3.7%	18.8%
Kim & Kim [70]	USA	11,277	U/S	<25.0	21.2%	34.0%
Bellentani et al. [2]	Italy	257	U/S	<25.0	16.4%	–
Eguchi et al. [20]	Japan	5075	U/S	<25.0	5.5%	29.7%
Omagari et al. [71]	Japan	3432[a]	U/S	<25.0	12.5%	21.8%
Amarapurkar et al. [72]	India	1168	U/S	<25.0	12.6%	16.6%
Kwon et al. [73]	Korea	29,994	U/S	<25.0	12.6%	20.1%

U/S ultrasound; CT computed tomography; BMI body mass index; MRS magnetic resonance spectroscopy.
[a] Only in non-obese populations.

prevalence of insulin resistance in both obese and lean groups, there might be additional factors that predispose lean patients to NAFLD.

6. Pathophysiology

6.1. Genetic predisposition

Genome wide association studies (GWAS) have implicated single nucleotide polymorphisms (SNPs) in patatin-like phospholipase domain-containing 3 (*PNPLA3*), apolipoprotein 3 (*APOC3*), cholesteryl ester transfer protein (*CETP*), transmembrane 6 superfamily member 2 (*TM6SF2*) and sterol regulatory element-binding factor (*SREBF*) in obese NAFLD and lean NAFLD in adults and children [32,37–41].

The risk of NAFLD is increased in normal weight individuals of varying ethnic backgrounds carrying specific *PNPLA3* polymorphisms [5,32,40]; however, the prevalence of these polymorphisms is not different among lean and obese subjects with NAFLD [35,42]. In a prospective cohort study of biopsy proven NAFLD in non-obese individuals (n = 175), the SREBF-2 rs133291 polymorphism was found to predict incident NAFLD and was associated with worse histological steatosis, inflammation, NAS score and a higher prevalence of NASH [42]. Recently, in an Italian cohort of adults with NAFLD, TM6SF2 polymorphisms were found to be more prevalent in those with a BMI<25 kg/m^2[42]. Finally, APOC3 rs2854116 and rs2854117 polymorphisms have been linked to NAFLD in lean Asian men (n = 258) [43].

A genome wide association study in adolescent NAFLD patients found genetic polymorphisms associated with two genes, rs222054 in group-specific component gene (GC) on chromosome 1 and rs7324845 in lymphocyte cytosolic protein-1 (LCP1) on chromosome 13, and confirmed increased hepatic PNPLA3 gene expression in NAFLD [44]. In pediatric patients, the presence of the PNPLA3 rs738409 G allele has been associated with an earlier presentation of NAFLD [45]. A multiethnic US cohort study (n = 957) of obese children and adolescents found the minor allele of the rs58542926 SNP in TM6SF2 gene, to be associated with elevated hepatic fat content in African Americans and Caucasians, whereas in the Hispanic cohort raised alanine aminotransferase levels was a significant finding [46]. An Australian study of adolescent females found two SNPs in CETP, rs12447924 and rs12597002 to increase the probability of lean NAFLD in homozygotes compared to heterozygotes and wild types (30% compared to 10–15% and 3–5%, respectively) [47]. Genetic polymorphisms, independent of obesity are likely to play a key role in the pathogenesis and prevalence of pediatric lean NAFLD that requires further investigation.

6.2. Metabolic dysregulation

Similar to NAFLD seen in the context of obesity, insulin resistance appears to be a key factor in the pathogenesis of metabolically obese, lean NAFLD. This is supported by studies that show that non-obese subjects with NAFLD are more likely to have insulin resistance compared to their non-NAFLD counterparts [16,18]. Lean NAFLD has been associated with insulin resistance, independently of other components of metabolic syndrome in non-obese, non-diabetic individuals [31]. In a recent prospective cohort study, where healthy lean subjects were compared to subjects with lean NAFLD or obese NAFLD without diabetes, lean NAFLD was associated with impaired glucose tolerance and decreased adiponectin levels, which was almost identical to that seen in obese NAFLD [32].

While it remains to be determined whether insulin resistance is the cause or the result of hepatic steatosis, there is evidence to support a causative role. Insulin resistance can lead to hepatic steatosis through enhanced lipolysis in the peripheral adipose tissue and decreased oxidation of free fatty acids (FFAs) in skeletal muscle and the liver [33,34]. In obese NAFLD, adipose tissue derived FFA are the largest contributor to hepatic steatosis [34]. One could hypothesize that a similar mechanism leads to hepatic steatosis in lean NAFLD in some patients. Hypertriglyceridemia can be a surrogate for insulin resistance, and in lean adults has been shown to correlate with NAFLD development and severity after controlling for confounders, such as BMI and other components of the metabolic syndrome [35,36].

6.3. Cytokines and adipokines

Cytokines and adipokines play an important role in the pathogenesis of NAFLD, but their involvement in the development of lean NAFLD is yet to be determined. In obese NAFLD, several studies have found reduced adiponectin levels, increased leptin levels and elevated levels of pro-inflammatory markers (i.e. tumor necrosis factor alpha (TNF-α) interleukin (IL)-6, IL-1 and IL-8) in adult patients compared to healthy controls [48,49]. Altered cytokine and adipokine levels are thought to up-regulate *de novo* lipogenesis and contribute to a pro-inflammatory state. Lower levels of adiponectin were found in patients with lean NAFLD compared to healthy controls, but were not different from obese patients with NAFLD [32]. However, levels of IL-6, TNF-α and leptin were not considerably different between lean NAFLD and healthy controls. Moreover, in one study comparing patients with lean NAFLD to patients with obese NAFLD, the leptin and adiponectin levels were similar between both groups and within the normal range [48,50]. The role that cytokines and adipokines may play in lean NAFLD has yet to be illustrated.

6.4. Environmental factors

Environmental factors, such as dietary intake, play an important role in the pathogenesis of NAFLD [28]. Consumption of fructose-sweetened beverages and soft drinks have been linked to NAFLD. Several studies have shown that when patients with NAFLD and no risk factors for metabolic syndrome are compared to healthy matched controls, soft drink/sugar sweetened beverage consumption is associated with hepatic steatosis, independent of metabolic risk factors [28,51]. In one study comparing 31 patients with lean NAFLD to 30 healthy controls, soft drink consumption was the only independent variable to predict NAFLD, controlling for age, sex, BMI and total caloric intake [28]. Cholesterol intake may play a role in the pathogenesis of lean NAFLD as well, through increased *de novo* lipogenesis via activation of sterol regulatory element binding protein 1c (SREBP1c). Studies have found increased dietary cholesterol and decreased omega-3 polyunsaturated fatty acids (PUFAs) intake in patients with lean NAFLD compared to their obese NAFLD counterparts, however, these results have not been compared against lean healthy controls [52,53].

7. Histological features

From a histology perspective, lean NAFLD is identical, in terms of possible findings, to NAFLD occurring in the context of obesity [54](Kleiner et al. Hepatology 2005). Steatosis involving more than 5% of hepatocytes is considered abnormal, and in the context of NASH possible findings include the presence of ballooning degeneration, lobular or portal inflammation and fibrosis. To date, the histological studies on the severity of lean NAFLD have yielded somewhat conflicting results, which are summarized in Table 3. The prevalence of NASH in non-obese patients with NAFLD is high and ranges from 43 to 53% [15,35,58]. The limited data in terms of histological disease progression suggest that non-obese patients with NAFLD are less likely to progress to advanced fibrosis within a mean interval of approximately 2.5 years [35].

Currently, there are no dedicated pediatric studies available on the histological features of pediatric lean NAFLD. One study, whose main purpose was to study hepatic siderosis in the context of NAFLD, did not find a difference in liver histology between normal weight (defined as BMI <85th percentile for gender and age), overweight and obese patients using the non-alcoholic steatohepatitis Clinical Research Network (NASH CRN) criteria [22].

8. Approach to screening

Patients with NAFLD are typically asymptomatic or may have vague, non-specific symptoms, such as abdominal pain. In the context of obesity, NAFLD is either an incidental finding (e.g. evidence of steatosis on an abdominal ultrasound obtained to investigate the cause of abdominal pain), or is determined through screening of at risk patients (e.g. obesity and type 2 diabetes mellitus who are screened for liver disease through serum aminotransferase levels) [55,60]. Practitioners need to have a high level of suspicion to identify patients at risk of lean NAFLD. Measuring waist circumference in patients undergoing routine physical examinations is a cheap and practical approach to identifying patients with abdominal obesity, and hence, screen for risk of lean NAFLD. In children and young adults, waist circumference and waist to height ratios not only provide better estimates of adiposity, but they correlate with serum aminotransferase levels as well [56]. The presence of metabolic dysregulation (insulin resistance, dyslipidemia) and obstructive sleep apnea should also raise suspicion for the presence of lean NAFLD [57].

When patients are deemed to be at risk of lean NAFLD, serum alanine aminotransferase (ALT) levels can be measured as a first step, similarly to the screening approach recommended for obese patients with suspected NAFLD [55,60]. While evidence of abnormal ALT levels in those at risk of lean NAFLD would be highly suggestive of this condition given its aforementioned prevalence, work up to exclude other liver diseases (e.g. alcoholic liver disease, infectious hepatitis, autoimmune hepatitis, etc.) will have to be undertaken as well. The limited data on the diagnostic accuracy of imaging modalities such as ultrasonography for the determination of hepatic steatosis in lean patients preclude the formulation of formal recommendations regarding its use. Other imaging tools, such as MRI, are too costly to consider using in this context. It should be noted that there are currently no studies on the cost-effectiveness of screening patients for lean NAFLD and for performing subsequent testing in those who screen positive.

9. Prognosis

There have been limited studies on the outcome of patients with metabolically obese, lean NAFLD. When compared to lean subjects without hepatic steatosis, non-obese patients with fatty liver are at increased risk of developing type 2 diabetes mellitus in the following decade [58]. In addition, their metabolic risk may be similar to that of obese subjects with NAFLD, as shown in a recent study from Italy that revealed a similar prevalence of carotid plaque formation in those with lean versus obese NAFLD. That was despite that fact that those with lean NAFLD had decreased prevalence of all the components of metabolic syndrome [41]. This is a concerning finding as cardiovascular disease is the leading cause of mortality in patients with NAFLD that occurs in the context of obesity, and suggests that those with metabolically obese, lean NAFLD may be at increased risk of cardiovascular mortality as well.

The available data on liver disease progression and overall liver-related morbidity and mortality are limited and contradictory. Liver disease progression, particularly development of advanced fibrosis, was found to be less rapid in a non-obese, multiethnic NAFLD cohort from the United States compared to their obese counterparts [35]. In addition, severe outcomes such as liver failure, hepatocellular carcinoma and overall mortality were lower in those with non-obese versus obese NAFLD [35]. A recent retrospective cohort study of patients with lean NAFLD with a mean follow-up of 19.9 years found no increased mortality, but an increased risk of more

Table 3
Comparisons of histological injury between lean and non-lean subjects with fatty liver disease.

Study	Leanness definition	n; mean age	Steatosis[a]	NASH prevalence[a]	Fibrosis[a]
Leung et al. [35] USA	BMI< 25 kg/m^2	397 (23% lean); 51 (±11) years	↓severity	No difference	Less prevalent, ↓severity
Dela Cruz et al. [74] USA	BMI< 25 kg/m^2	1090 (11.5% lean); 46 (±13) years	↓severity	No difference	↓severity
Alam et al. [57] Bangladesh	BMI< 25 kg/m^2	465 (26% lean); 41 (±10) years	No difference	No difference	No difference
Margariti et al. [15] Greece	BMI <25 kg/m^2	56 (14% lean); 47 (±14) years	No difference	No difference	No difference

[a] The results refer to findings in lean subjects.

severe liver disease [59]. In contrast, another recent report suggested that subjects with lean NAFLD had lower cumulative survival rates than their lean counterparts over an 11-year follow up [55]. There are currently no available studies on prognosis and natural history of pediatric lean NAFLD. Additional studies are warranted to assess the prognosis and natural history of lean NAFLD in adults and children.

10. Treatment

No guidelines currently exist for the treatment of lean NAFLD. The American Association for the Study of Liver Diseases currently recommends weight loss, in the form of hypocaloric diet alone or along with increased physical activity for the improvement of NAFLD that occurs in the context of obesity [60,61]. In randomized controlled trials on lifestyle interventions for NAFLD, the histological improvement in NAFLD has been proportional to the weight lost [36,62]. In lean NAFLD patients, weight loss does not represent a feasible strategy to control insulin resistance and metabolic derangement, but physical activity and dietary lifestyle interventions aimed at improving insulin resistance (e.g. decreased consumption of sugar-sweetened beverages, increased consumption of ω-3 fatty acids, etc.) may be appropriate. While there is inconclusive evidence for whether exercise improves NAFLD independently of weight loss, the available data suggests that aerobic exercise may improve hepatic and visceral adipose tissue independently of weight loss [63–67].

Dietary considerations, including decreased fructose consumption, caffeine and a Mediterranean diet have been shown to be beneficial in NAFLD patients. However, these interventions have not been investigated in patients in lean NAFLD. While the protective effects of caffeine have not been specifically studied in lean NAFLD, one study has shown caffeine to be protective against hepatic fibrosis in patients with NAFLD. Dietary interventions have not been studied in children and will warrant further investigation.

While many different pharmacologic interventions have been investigated for the treatment of NAFLD, there are fewer pharmacologic options for lean NAFLD. Liraglutide, a glucagon-like peptide-1 (GLP-1) analog indicated for Type 2 diabetes, has been shown to improve biopsy-proven non-alcoholic steatohepatitis in non-obese patients [68]. The preliminary data suggests that liraglutide may be beneficial in the treatment of lean NAFLD, but requires further evaluation in larger trials and in pediatric patients. At present, there is insufficient evidence to recommend a specific regimen for the improvement of lean NAFLD or to support one intervention over another.

11. Strengths and weaknesses

Our review is the first to summarize the available literature on adult and pediatric lean NAFLD. This review may have benefited from a more systematic search strategy, independent review and extraction by two reviewers independently and quality assessment of individual studies. However, given the limited literature on lean NAFLD in adult and pediatric populations, the authors decided a narrative review approach was more appropriate.

12. Conclusion

The literature on patients with metabolically obese, lean NAFLD is limited. NAFLD is present in obese and non-obese individuals of all ethnicities and ages and it is important to consider NAFLD in lean individuals. There is data to suggest that individuals with lean NAFLD may have an increased risk of developing type 2 diabetes compared to their lean counterparts and may experience similar metabolic risks as subjects with obese NAFLD. The lack body composition data and use of BMI in lean NAFLD presents a significant limitation as the use of BMI may fail to identify visceral adiposity and requires different cutoffs for different ethnicities. Waist circumference is a superior clinical measure to BMI to detect visceral adiposity, but is less frequently reported. While there is no treatment guideline for lean NAFLD, NAFLD interventions include lifestyle modifications, such as weight loss, physical activity and dietary intervention.

Conflict of interest

The authors have no competing interests to declare.

Author contributions

MM conceived the idea for the study. All authors contributed to drafting, revising and approving the final article.

References

[1] Sattar N, Forrest E, Preiss D. Non-alcoholic fatty liver disease. BMJ 2014 Jul 29. https://doi.org/10.1136/bmj.g4596. 349g4596.

[2] Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. Dig Dis 2010;28(1):155–61. https://doi.org/10.1159/000282080.

[3] Anderson EL, Howe LD, Jones HE, Higgins JPT, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. PLoS One 2015;10(10):1–14.

[4] Schwimmer JB, Pardee PE, Lavine JE, Blumkin AK, Cook S. Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. Circulation 2008 Jul 15;119(3):277–83. https://doi.org/10.1161/CIRCULATIONAHA.107.739920.

[5] Mellinger JL, Pencina KM, Massar HM, Hoffman U, Seshadri S, Fox CS, et al. Hepatic steatosis and cardiovascular disease outcomes: an analysis of the Framingham Heart Study. J Hepatol 2015 Aug;63(2):470–6. https://doi.org/10.1016/j.jhep.2015.02.045.

[6] Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. J Gastroenterol 2003;38(10):954–61.

[7] Kojima S, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty liver in Japan over the past 12 years: analysis of clinical background. J Gastroenterol 2003;38(10):954–61.

[8] Liu CJ. Prevalence and risk factors for non-alcoholic fatty liver disease in Asian people who are not obese. J Gastroenterol Hepatol 2012 Oct;27(10):1555–60. https://doi.org/10.1111/j.1440-1746.2012.07222.x.

[9] Wei JL, Leung JC, Loong TC, Wong GL, Yeung DK, Chan RS, et al. Prevalence and severity of nonalcoholic fatty liver disease in non-obese patients: a population study using proton-magnetic resonance spectroscopy. Am J Gastroenterol 2015 Sep;110(9):1306–14. quiz 1315.

[10] Javed A, Jumean M, Murad MH, Okorodudu D, Kumar S, Somers VK, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity in children and adolescents: a systematic review and meta-analysis. Pediatric Obes Jun 2015;10(3):234–44.

[11] Okorodudu DO, Jumean MF, Montori VM, Romero-Corral A, Somers VK, Erwin PJ, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. Int J Obes (Lond) May 2010;34(5):791–9. https://doi.org/10.1038/ijo.2010.5.

[12] 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 Aug 2007;86(2):353–9.

[13] Barreira TV, Broyles ST, Gupta AK, Katzmarzyk PT. Relationship of anthropometric indices to abdominal and total body fat in youth: sex and race differences. Obesity May 2014;22(5):1345–50.

[14] Ha Y, Seo N, Shim JH, Kim SY, Park JA, Han S, et al. Intimate association of visceral obesity with non-alcoholic fatty liver disease in healthy Asians: a case-control study. J Gastroenterol Hepatol 2015 Nov;30(11):1666–72. https://doi.org/10.1111/jgh.12996.

[15] 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 Mar 2013;47(3):280–6.

[16] Kim HJ, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, et al. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med 2004 Oct 25;164(19):2169–75.

[17] Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome–a new worldwide definition. Lancet 2005 Sep 24-30;366(9491):1059–62.
[18] Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine Nov 2012;91(6):319–27.
[19] Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology Dec 2004;40(6):1387–95.
[20] Eguchi Y, Hyogo H, Ono M, Mizuta T, Ono N, Fujimoto K, et al. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. J Gastroenterol May 2012;47(5):586–95.
[21] Das K, Das K, Mukherjee PS, Ghosh S, Mridha Ar, Dhibar T, et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology May 2010;51(5):1593–602.
[22] Manco M, Alisi A, Real JF, Equitani F, DeVito R, Valenti L, et al. Early interplay of intra-hepatic iron and insulin resistance in children with non-alcoholic fatty liver disease. J Hepatol 2011 Sep;55(3):647–53. https://doi.org/10.1016/j.jhep.2010.12.007. Epub 2010 Dec 17.
[23] Wesolowski SR, Kasmi KC, Jonscher KR, Friedman JE. Developmental origins of NAFLD: a womb with a clue. Nat Rev Gastroenterol Hepatol 2017;14(2):81–96.
[24] Petersen KF, Dufour S, Fen J, Befroy D, Dziura J, Dalla Man C, et al. Increased prevalence of insulin resistance and non-alcoholic fatty liver disease in Asian-Indian men. Proc Natl Acad Sci USA 2006 Nov 28;103(48):18273–7.
[25] Akyuz U, Yesil A, Yilmaz Y. Characterization of lean patients with fatty liver disease: potential role of high hemoglobin levels. Scand J Gastroenterol 2015 Mar;50(3):341–6. https://doi.org/10.3109/00365521.2014.983160.
[26] Vos B, Moreno C, Nagy N, Fery F, Cnon M, Vereerstraeten P, et al. Lean non-alcoholic fatty liver disease (Lean-NAFLD): a major cause of cryptogenic liver disease. Acta Gastrenterol Belg 2011 Sep;74(3):389–94.
[27] Kumar R, Rastogi A, Sharma MK, Bhatia V, Gard H, Bihari C, et al. Clinico-pathological 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 Jul;17(4):665–71.
[28] Assy N, Nasser G, Kamayse I, Nseir W, Beniashvili Z, Djibre A, et al. Soft drink consumption linked with fatty liver in absence of traditional risk factors. Can J Gastroenterol 2008 Oct;22(1):811–6.
[29] Bernhardt P, Kratzer W, Schmidberger J, Graeter T, Cruener B, EMIL Study Group. Laboratory parameters in lean NAFLD: comparison of subjects with lean NAFLD with obese subjects without hepatic steatosis. BMC Res Notes 2018;11:101. Published online 2018 Feb 6.
[30] Jiang Y, Zeng J, Chen B. Hemoglobin combined with triglyceride and ferritin in predicting non-alcoholic fatty liver. J Gastroenterol Hepatol 2014;29(7):1508–14.
[31] Sinn DH, Gwak GY, Park HN, Kim JE, Min YW, Kim KM, et al. Ultrasonographically detected non-alcoholic fatty liver disease is an independent predictor for identifying patients with insulin resistance in non-obese, non-diabetic middle-aged Asian adults. Am J Gastroenterol Apr 2012;107(4):561–7.
[32] Feldman A, Eder SK, Felder TK, Kedenko L, Paulweber B, Stadlmayr A, et al. Clinical and metabolic characterization of lean caucasian subjects with non-alcoholic fatty liver. Am J Gastroenterol 2017 Jan;112(1):102–10. https://doi.org/10.1038/ajg.2016.318.
[33] Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in non-alcoholic fatty liver disease. Curr Pharm Des 2010 Jun;16(17):1941–51.
[34] Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 2005 May;115(5):1343–51.
[35] Leung JC, Loong TC, Wei JL, Wong GL, Chan AW, Choi PC, et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology Jan 2017;65(1):54–64.
[36] Wong V, Wong G, Yeung DK, Lau TK, Chan CK, Chim AM, et al. Incidence of non-alcoholic fatty liver disease in Hong Kong: a population study with paired proton-magnetic resonance spectroscopy. J Hepatol 2015;62(1):182–9.
[37] Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008 Dec;40(12):1461–5. https://doi.org/10.1038/ng.257.
[38] Day CP. Genes or environment to determine alcoholic liver disease and non-alcoholic fatty liver disease. Liver Int 2006 Nov;26(9):1021–8.
[39] Nishioji K, Mochizuki N, Kobayashi M, Kamaguchi M, Sumida Y, Nishimura T, et al. The impact of PNPLA3 rs738409 genetic polymorphism and weight gain >/=10 kg after age 20 on non-alcoholic fatty liver disease in non-obese Japanese individuals. PLoS One 2015;10(10). e0140427.
[40] Wattacheril J, Lavine JE, Chalasani NP, Guo X, Kwon S, Schwimmer J, et al. Genome-wide associations related to hepatic histology in nonalcoholic fatty liver disease in hispanic boys. J Pediatr 2017 Nov;190:100–107.e2. https://doi.org/10.1016/j.jpeds.2017.08.004.
[41] Fracanzani A. Lean-non alcoholic fatty liver disease (NAFLD): liver and cardiovascular damage and its relation with visceral obesity. Washington, DC: AASLD; 2016.
[42] Musso G, Bo S, Cassader M, De Michieli F, Gambino R. Impact of sterol regulatory element-binding factor-1c polymorphism on incidence of nonalcoholic fatty liver disease and on the severity of liver disease and of glucose and lipid dysmetabolism. Am J Clin Nutr 2013 Oct;98(4):895–906. https://doi.org/10.3945/ajcn.113.063792.
[43] Petersen KF, Dufour S, Hariri A, Nelson-Williams C, Foo JN, Zhang XM, et al. Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease. N Engl J Med 2010 Mar 25;362(12):1082–9. https://doi.org/10.1056/NEJMoa0907295.
[44] Adams LA, White SW, Marsh JA, Lye SJ, Connor KL, Maganga R, et al. Association between liver-specific gene polymorphisms and their expression levels with nonalcoholic fatty liver disease. Hepatology 2013;57:590–600.
[45] Lin YC, Chang PF, Hu FC, Yang WS, Chang MH, Ni YH. A common variant in the PNPLA3 gene is a risk factor for non-alcoholic fatty liver disease in obese taiwanese children. J Pediatr 2011;158(5):740–4.
[46] Goffredo M, Caprio S, Feldstein AE, D'Adamo E, Shaw MM, Pierpont B, et al. Role of TM6SF2 rs58542926 in the pathogenesis of nonalcoholic pediatric fatty liver disease: a multiethnic study. Hepatology 2016;63(1):117–25.
[47] Adams LA, Marsh JA, Ayonrinde OT, Olynyk JK, Ang WQ, Beilin LJ, et al. Cholesteryl ester transfer protein gene polymorphisms increase the risk of fatty liver in females independent of adiposity. J Gastroenterol Hepatol 2012;27:1520–7. https://doi.org/10.1111/j.1440-1746.2012.07120.x.
[48] Kumar R, Prakash S, Chhabra S, Singla V, Madan K, Gupta SD, et al. Association of pro-inflammatory cytokines, adipokines & oxidative stress with insulin resistance & non-alcoholic fatty liver disease. Indian J Med Res 2012 Aug;136(2):229–36.
[49] Stojsavljevic S, Gomercic Palcic M, Virovic Jukic L, Smircic Duvnjak L, Duvnjak M. Adipokines and proinflammatory cytokines, the key mediatros in the pathogenesis of nonalcoholic fatty liver disease. World J Gastroenterol 2014 Dec 28;20(48):18070–91. https://doi.org/10.3748/wjg.v20.i48.18070.
[50] Yasutake K, Nakamuta M, Shima Y, Ohyama A, Masuda K, Haruta N, et al. Nutritional investigation of non-obese patients with non-alcoholic fatty liver disease: the significance of dietary cholesterol. Scand J Gastroenterol 2009;44(4):471–7.
[51] Abid A, Taha O, Nseir W, Farah R, Grosovski M, Assy N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. J Hepatol 2009 Nov;515:918–24.
[52] Toshimitsu K, Matsuura B, Ohkubo I, Niiya T, Furukawa S, Hiasa Y, et al. Dietary habits and nutrient intake in non-alcoholic steatohepatitis. Nutiriton 2007;23:46–52.
[53] Musso G, Gabino R, De Michieli F, Cassader M, Rizzetto M, Durazzo M, et al. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology 2003;37:909–16.
[54] Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al., Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41(6):1313–21.
[55] Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the north american society of pediatric gastroenterology, hepatology and nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr 2017 Feb;64(2):319–34. https://doi.org/10.1097/MPG.0000000000001482.
[56] Nobili V, Cutrera R, Liccardo D, Pavone M, Devito R, Giorgio V, et al. Obstructive sleep apnea syndrome affects liver histology and inflammatory cell activation in pediatric nonalcoholic fatty liver disease, regardless of obesity/insulin resistance. Am J Respir Crit Care Med 2014 Jan 1;189(1):66–76. https://doi.org/10.1164/rccm.201307-1339OC.
[57] 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 Sep 2014;33(5):452–7.
[58] Fukuda T, Hamaguchi M, Kojima T, Hashimoto Y, Ohbora A, Kato T, et al. The impact of non-alcoholic fatty liver disease on incident type 2 diabetes mellitus in non-overweight individuals. Liver Int Feb 2016;36(2):275–83.
[59] Hagstrom H, Nasr P, Ekstedt M, Hammar U, Stal P, Hultcrantz R, et al. Risk for development of severe liver disease in lean patients with non-alcoholic fatty liver disease: a long-term follow-up study. Hepatol Commun 2018 Jan;2(1):48–57. https://doi.org/10.1002/hep4.1124.
[60] Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al., American Gastroenterological Association. American association for the study of liver diseases; american college of gastroenterology. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the american gastroenterological association, american association for the study of liver diseases, and american college of gastroenterology. Gastroenterology 2012 Jun;142(7):1592–609. https://doi.org/10.1053/j.gastro.2012.04.001.
[61] Chalasani N, Younossi Z, Lavine JR, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018 Jan;67(1):328–57. https://doi.org/10.1002/hep.29367.
[62] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015 Aug;149(2):367–78. https://doi.org/10.1053/j.gastro.2015.04.005. e5; quiz e14-5.
[63] Slentz CA, Bateman LA, Willis LH, Shields AT, Tanner CJ, Piner LW, et al. Effects of aerobic vs. resistance training on visceral and liver fat stores, liver enzymes,

and insulin resistance by HOMA in overweight adults from STRRIDE AT/RT. Am J Physiol Endocrinol Metab 2011 Nov;301(5):E1033–9. https://doi.org/10.1152/ajpendo.00291.2011.

[64] Johnson NA, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. Hepatology 2009 Oct;50(4):1105–12. https://doi.org/10.1002/hep.23129.

[65] Bae JC, Suh S, Park SE, Rhee EJ, Park CY, Oh KW, et al. Regular exercise is associated with a reduction in the risk of NAFLD and decreased liver enzymes in individuals with NAFLD independent of obesity in Korean adults. PLoS One 2012;7(10):e46819. https://doi.org/10.1371/journal.pone.0046819.

[66] Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, et al. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. J Hepatol 2013 Sep;59(3):536–42. https://doi.org/10.1016/j.jhep.2013.04.013.

[67] Kistler KD, Brunt EM, Clark JM, Diehl AM, Sallis JF, Schwimmer JB, NASH CRN Research Group. Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. Am J Gastroenterol 2011 Mar;106(3):460–8. https://doi.org/10.1038/ajg.2010.488. quiz 469.

[68] Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurt JM, Guo K, , LEAN trial team, Abouda G, Aldersley MA, Stocken D, Gough SC, Tomlinson JW, Brown RM, Hubscher SG, Newsome PN. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016 Feb 13;387(10019):679–90. https://doi.org/10.1016/S0140-6736(15)00803-X.

[69] Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 2013 Aug;108(8):1299–304. https://doi.org/10.1038/ajg.2013.104.

[70] Kim D, Kim W. Non-overweight fatty liver disease (NOFLD): a distinct entity? Hepatology 2012;56:A886–7.

[71] Omagari K, Kadokawa Y, Masuda J, Egawa I, Sawa T, Hazama H, et al. Fatty liver in non-alcoholic non-overweight Japanese adults: incidence and clinical characteristics. J Gastroenterol Hepatol 2002 Oct;17(10):1098–105.

[72] Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, et al. Prevalence of non-alcoholic fatty liver disease: population based study. Ann Hepatol 2007 Jul-Sep;6(3):161–3.

[73] 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 Dec;107(12):1852–8. https://doi.org/10.1038/ajg.2012.314.

[74] Dela Cruz AC. Characteristics and long-term progrnosis of lean patients with nonalcoholic fatty liver disease. Paper presented at: AASLD2014; Boston, MA.