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MINI REVIEW

Non-alcoholic fatty liver disease in non-obese individuals: Prevalence, pathogenesis and treatment

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Summary Non-alcoholic fatty liver disease (NAFLD) parallels comorbidities such as metabolic syndrome, dyslipidaemia or diabetes. Although NAFLD is very prevalent in overweight-obese individuals (i.e. body mass index $\geq 25\,kg/m^2$), recent studies point to the presence of NAFLD in non-obese individuals, for both the Asian ($< 25\,kg/m^2$) and Caucasian ($< 30\,kg/m^2$) populations. This paper discusses the pathogenic pathways and current treatment options of NAFLD in non-obese populations. In this respect, non-obese subjects also need to undergo the medical screening for NAFLD. Across the scientific community, we aim to promote the advancement of knowledge in this emerging field.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a frequent disease among overweight and obese individuals [1]. NAFLD occurs in patients who present excessive amount of hepatic lipids, consume no or little alcohol and do not have signs of acute or chronic liver disease other than fatty liver [2]. The more aggressive form of NAFLD, non-alcoholic steatohepatitis (NASH), requires an invasive method, namely liver

Abbreviations: BMI, body mass index; HCC, hepatocellular carcinoma; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

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biopsy, to be diagnosed. Interestingly, in the recent years non-invasive tools for measuring liver fibrosis and liver steatosis, such as transient elastography, controlled attenuation parameter or magnetic resonance based-methods have been developed, and their utility in the setting of NAFLD is being extensively investigated [3,4]. NAFLD often accompanies other dysmetabolic conditions such as diabetes, hyperlipidaemia, and metabolic syndrome (MetS) [5]. NAFLD affects approximately 25% of the adult population worldwide and increases to 76% in type 2 diabetics [6]. Furthermore, the mortality risk increases in subjects suffering from both MS and NAFLD [7]. Asia displays the most worrisome trends with regards to body mass index (BMI) when stratified by ages [8], and BMI strongly correlates with both NAFLD and the necro-inflammatory form of NAFLD, i.e., non-alcoholic steatohepatitis (NASH) [9,10]. Recent studies have determined the regional anthropometric measurements for the Asian population as BMI 22.5—24.9 kg/m^2 for overweight and $\geq 25\,kg/m^2$ for obese, and fatty liver is mostly found amongst obese individuals [11]. Notably, a remarkable number of lean individuals in the United States suffer from NAFLD, likely due to distinct components of MetS, such as diabetes and/or hypertension [12]. Indeed, as noticed in the Kangbuk Samsung Health Study, 16,279 non-obese (BMI $< 25\,kg/m^2$) patients with different grades of liver steatosis and fibrosis were at increased risk of subclinical atherosclerosis [13]. They are also at higher risk of mortality [14]. Multiple genetic factors may play a role in the classification of liver steatosis [15]. The amino acid substitution *p.I148M* of the *PNPLA3* gene (also known as adiponutrin) worsens NAFLD and its sequelae [16]. Accumulation of *PNPLA3* was found on hepatic lipid droplets from mice with the *PNPLA3* p.I148M mutation challenged with a high-sucrose diet, which indicates a role of both genetic and non-genetic factors in the development of fatty liver [17]. The *rs738409 c.444G* minor allele (which encodes methionine at position 148) significantly increases the risk of liver disease and NASH as compared to healthy subjects [18]. Carriers of the *PNPLA3* p.I148M risk allele are also at-risk of developing liver cirrhosis and hepatocellular carcinoma (HCC) [11,19]. Several other polymorphisms, such as the *MBOAT7* and *TM6SF2* variants, are predominantly associated with hepatic steatosis and liver fibrosis, respectively [20]. Notably, the frequency of *PNPLA3 p.I148M* allele was higher in non-obese NAFLD patients (74.6%) than in NAFLD obese and control subjects [21]. This finding intensifies the need for understanding the mechanisms seen in the accumulation of triglycerides in the steatotic liver. However, the pathogenesis of NAFLD comprises the interaction between genetic and environmental factors, between genes (epistasis) as well as non-genetic exposures (exposome) [15].

Here, we discuss the different genetic variants predisposing non-obese individuals to NAFLD diagnosis, its prevalence as well as the pathogenesis and current treatment strategies.

Prevalence

Recent epidemiological studies have reported that 10 to 30% of non-obese individuals have NAFLD, i.e. 7 to 21% and 3 to 27% in the Western and the Eastern literature, respectively [22]. In Asia, the recommended BMI cut-off value for being overweight and obese is 23—25 kg/m^2 and $> 25\,kg/m^2$, in contrast to 25—30 kg/m^2 and $> 30\,kg/m^2$ for subjects of other ethnicities, respectively [23]. The prevalence of non-obese NAFLD in the Asian population is 8—19% [24]. Other studies report a prevalence of 11—21% in non-obese Asians [11]. In Korean subjects, NAFLD was about 13% of the non-obese population, in comparison to 50% in obese individuals, and was strongly associated with components of MetS [25]. In a recent epidemiological study in India, however, 75% of NAFLD individuals were non-obese, and 54% were neither overweight nor had central obesity [26].

In the United States, about 7% of lean individuals might have NAFLD [12]. The Multi-Ethnic Study of Atherosclerosis (MESA) has identified the prevalence in non-obese NAFLD patients to be 11% for the North-American cohort, with 9% being Caucasians, 6% Afro-Americans and 18% Latino Americans.

For the European population, the NAFLD Clinical Study Group (CSG), a multicentre biopsy-based cohort formed by 515 German patients, reported 63 (12%) of these NAFLD patients to be non-diabetic and non-obese [20]. Other studies in Iceland and Greece have determined a part of their lean population to suffer from NAFLD [27,28]. In Italy, 21% of NAFLD patients were also lean (BMI $< 25\,kg/m^2$), as reported by Fracanzani et al. [29]. Table 1 depicts an analytical review of the major results between non-obese and obese NAFLD subjects according to BMI, epidemiology, genetics, biohumoral markers, liver steatosis and liver fibrosis. Results vary because of reported cut-off or means of Asian or Caucasian populations. In general, however, the prevalence of genetic polymorphisms is higher in non-obese NAFLD subjects.

Pathogenesis

The main pathogenetic mechanisms predisposing for non-obese NAFLD have been summarized in Fig. 1.

NAFLD and MetS patients share common cardiovascular risk factors [30]. Especially in women but also in overall non-obese subjects, NAFLD is associated with a greater risk for the components of MetS [25]. Gender, the genetic polymorphism *PNPLA3* rs738409, hypertension, dyslipidaemia and weight gain $\geq 10\,kg$ after the age of 20 years were also found to be independent predictors for NAFLD in non-obese patients [31]. Epigenetic factors have been cited as part of the complex pathophysiology of lean NAFLD, as reported in the review by Kumar et al. [32]. In this study, diet composition such as high-fructose or high-fat intake predisposed to fatty liver disease, as well as to altered gut microbiome in lean individuals.

On lipidic markers, visceral fat is considered to be more critical than total body fat or waist circumference for NAFLD progression in non-obese subjects [33]. When dealing with body fat, BMI, lean fat, pro-inflammatory metabolic markers and related metabolic abnormalities, however, one should consider the possibility of different obesity subtypes, i.e., metabolically healthy obese, metabolically obese normal weight, normal weight obese, and sarcopenic obese. One of these subtypes is the so-called metabolically obese normal weight, when subjects display a normal BMI, high visceral adiposity, normal lean mass, low cardiorespiratory fitness

Table 1 Main differences between non-obese and obese NAFLD subjects, according to recent literature.

Finding(s)	Ethnicity	Non-obese NAFLD	Obese NAFLD	Comment	Reference
Body mass index	Asian	$< 25\ kg/m^2$	$\geq 25\ kg/m^2$	Different cut-offs and means of results according to ethnic origin and gender	[23]
	Caucasian	$<30\ kg/m^2$	$\geq 30\ kg/m^2$		
	Asian	$23\ kg/m^2$ (M) $22.6\ kg/m^2$ (F)	$27.7\ kg/m^2$ (M) $28.6\ kg/m^2$ (F)		[35]
	Asian	$23.4\ kg/m^2$	$29.2\ kg/m^2$		[22]
	Asian	$23.5\ kg/m^2$	$29.7\ kg/m^2$		[60]
Subcutaneous adipose tissue (computed tomography), mean	Asian	$152\ cm^2$	$245.7\ cm^2$	Thicker fat in Asian obese NAFLD subjects	[22]
	Asian	$169.1\ cm^2$	$287.4\ cm^2$		[60]
Visceral adipose tissue (computed tomography), mean	Asian	$113.8\ cm^2$	$147.3\ cm^2$	Thicker fat in Asian obese NAFLD subjects	[22]
	Asian	$124.6\ cm^2$	$168.8\ cm^2$		[60]
Prevalence of NAFLD	Asian	3—27%	NA	Different range for different studies	[23]
	Caucasian	7—21%	NA		
	Asian	23.5%	76.5%		[38]
	Asian	68.5%	15.2%		[35]
	All	4.2—27.5%	6.3-30%	Wide range, close overlapping	[33]
Prevalence of PNPLA3 rs738409	Asian	78.4%	59.8%	Trend to higher prevalence in Asian non-obese NAFLD subjects	[42]
Prevalence of TM6SF2 p.E167 K	Caucasian	28.6%	19.4%	Higher prevalence in Caucasian non-obese NAFLD subjects	[21]
Prevalence of MBOAT7 rs641738	Caucasian	22.2%	22.1%	Comparable between groups in Caucasian subjects	[21]
Total serum cholesterol (mean)	Asian	5.1 mmol/l	5.3 mmol/l	Comparable between groups and genders in Asian subjects	[42]
	Asian	202.6 mg/dl (M) 210.9 mg/dl (F)	199.3 mg/dl (M) 210.7 mg/dl (F)		[35]
	Asian	182.1 mg/dl	183.2 mg/dl		[22]
Fasting glucose (mean)	Asian	5.0 mmol/l	5.5 mmol/l	Comparable between groups and genders in Asian subjects	[42]
	Asian	102.7 mg/dl (M) 101.6 mg/dl (F)	106.3 mg/dl (M) 106.4 mg/dl (F)		[35]
	Asian	108.5 mg/dl	105 mg/dl		[22]
	Asian	95.3 mg/dl	104 mg/dl	Higher in Asian obese NAFLD subjects	[60]
Triglycerides (mean)	Asian	1.0 mmol/l	1.4 mmol/l	Comparable between groups	[42]
	Asian	136.5 mg/dl (M) 121.1 mg/dl (F)	154.7 mg/dl (M) 123.3 mg/dl (F)	Slightly higher in Asian male and comparable in Asian female obese NAFLD subjects	[35]
	Asian	123.5 mg/dl	142 mg/dl	Higher in Asian non-obese NAFLD subjects	[22]
	Asian	146.7 mg/dl	196.9 mg/dl		[60]

Table 1 (*Continued*)

Finding(s)	Ethnicity	Non-obese NAFLD	Obese NAFLD	Comment	Reference
ALT/AST levels (mean)	Asian	27.9/23.8 IU/l (M) 24.2/24.8 IU/l (F)	38.3/28.1 IU/l (M) 27.3/25.5 IU/l (F)	Lower in non-obese Asian male and female subjects	[35]
	Asian	34.5/32 IU/l	49.5/42 IU/l		[22]
	Asian	67.8/37 IU/l	87.4/54 IU/l		[60]
LDL serum cholesterol (mean)	Asian	3 mmol/l	3.2 mmol/l (A)	Comparable between groups and genders in Asian subjects	[42]
	Asian	129.3 mg/dl (M) 130.4 mg/dl (F)	127.9 mg/dl (M) 131.8 mg/dl (F)		[35]
	Asian	105.1 mg/dl	105.5 mg/dl		[22]
Prevalence of IHTG content (NMR spectroscopy), mean	Asian	1.5%	6.5%	Less prevalent in Asian non-obese NAFLD subjects	[42]
Liver stiffness (transient elastography), mean	Asian	6.3 kPa	8.6 kPa	Less in Asian non-obese NAFLD subjects	[38]
	Asian	4.5 kPa	5.6 kPa		[42]
Liver fibrosis degree (liver biopsy), mean	Asian	1.3	1.7	Comparable between Asian NAFLD subjects	[38]

ALT: alanine transaminase; AST: aspartate transaminase; F: females; IHTG: intrahepatic triglyceride; LDL: low-density lipoproteins; M: males; NA: not available; NAFLD: non-alcoholic fatty liver disease; NMR: nuclear magnetic resonance.

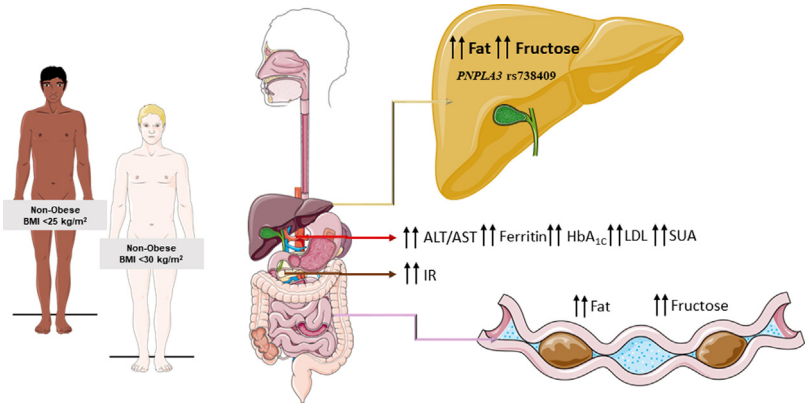

Figure 1 Pathogenetic mechanisms predisposing for non-obese NAFLD. ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; HbA_{1C}: glycosylated haemoglobin; IR: insulin resistance; LDL: low-density lipoproteins; SUA: serum uric acids. Adapted from http://smart.servier.com, 2019.

and occurrence of metabolic abnormalities [34]. In this respect, the onset and natural history of ectopic fat deposition in the liver might follow different pathways.

According to Nishioji et al., however, waist circumference was more significant in the non-obese group ($n = 872$) than in the obese one ($n = 575$), and was independently associated with NAFLD, regardless of gender [35]. Increased waist circumference and high HbA_{1C}, insulin resistance, hyperferritinemia and the *PNPLA3* risk allele were all independently associated with NAFLD in non-obese subjects [36]. In a study by Hagström et al. [37], including biopsy-proven NAFLD patients ($n = 646$), the mortality risk was 38% (hazard ratio 1.04) for lean subjects ($n = 123$). Regarding the histopathological patterns of NAFLD, Leung et al. [38] found no differences between obese and non-obese patients ($n = 72$ and $n = 235$, respectively). Similar results were obtained by Kim et al. [22], with the exception of a higher degree of liver steatosis in non-obese NAFLD patients, and in the study of Caucasian patients by Fracanzani et al. [29]. A meta-analysis by Sookoian et al. [30], however, revealed that lean subjects with NAFLD still display higher serum activities of hepatic aminotransferases (ALT/AST) as compared to their overweight and obese counterparts [30]. Serum uric acid concentrations were also increased in a non-obese Chinese population with NAFLD [39]. Central obesity has been a recurrent risk factor in the pathogenesis linking NAFLD and non-obese patients, as reported by Wong et al. [40] in 40% of the lean participants (< 25 kg/m^2). Increased low-density

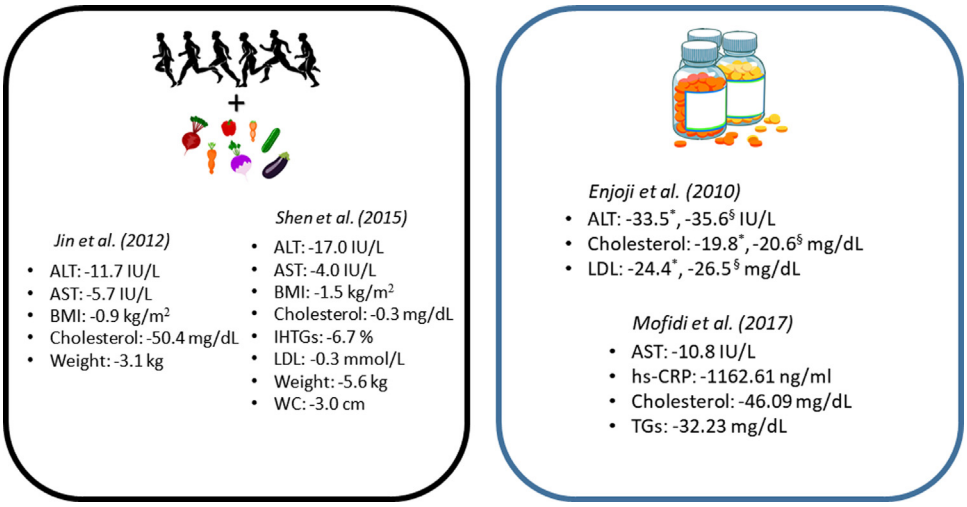

Figure 2 Main results of lifestyles vs. pharmacological interventions for non-obese NAFLD. *: 6 months; §: 12 months; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; hs-CRP: high-sensitivity c-reactive protein; IHTGs: intra-hepatic triglycerides; LDL: low-density lipoproteins; TGs: triglycerides; WC: waist circumference. Adapted from http://smart.servier.com, 2019.

lipoprotein levels (LDL) correlated with an increasing risk for NAFLD in non-obese individuals, as observed in 19,796 non-obese Chinese NAFLD patients [41]. In an Asian cohort, Wei et al. found intrahepatic triglyceride content to be lower in non-obese subjects when compared to obese ones [42]. Regarding fibrosis stage, most of the studies reported an increase of fibrosis stage with body weight [22]. However, the *PNPLA3* variant acts as a predisposing factor to fibrosis independently of age, gender, and BMI [43], and is associated with increased ALT/AST activity in some studies [44,45] but not in others [16,46]. Finally, lean NAFLD patients are less likely to develop non-alcoholic steatohepatitis (NASH) than obese patients [47]. Both increased triglyceridemia and creatininemia, however, are associated with advanced liver disease in this non-obese cohort [38].

Lipid accumulation and free fatty acid (FFA) distribution from adipose tissue to liver plays an important role in the pathogenesis of NAFLD. A recent study found that FFA profiles vary between normal and NAFLD subjects. FFA concentration increases in NAFLD individuals and is positively associated with blood glucose, lipids and liver enzymes [48]. The chromatographic analysis of FFAs in the serum of 67 lean NAFLD patients (BMI $22.58 \pm 0.75\,kg/m^2$) showed that FFA levels differ between overweight and obese subjects [48]. Interestingly, the fatty acid profile of lean patients is like overweight patients, but not like obese NAFLD patients. Other possible causes of NAFLD among lean persons may be sarcopenia and protein malnutrition, especially in early life. According to the criteria of the European Working Group on Sarcopenia (EWGS), sarcopenia is defined as a decline in muscle mass and function, expressed as impaired strength or performance [49]. The study of a large cohort of NAFLD subjects (both non-obese and obese) ($n = 15{,}132$) found a strong inverse relationship between skeletal muscle mass and function with NAFLD presence [50]. The release of several hepatokines and proinflammatory adipokines (leptin, resistin, TNF-α, IL-6, leptin,) which affect muscle mass and quality might explain the link between NAFLD and sarcopenia. As reported by Feldman et al. [51], adiponectin concentrations in serum of lean NAFLD subjects ($n = 55$, BMI $\leq 25\,kg/m^2$) were lower than in healthy controls and similar to obese and underweight NAFLD patients. Serum leptin levels are significantly associated with the severity of NAFLD, but probably in a BMI-dependent way. Rotundo et al. [52] showed that leptin concentrations in lean NAFLD patients ($n = 1{,}523$, BMI: $24.0 \pm 0.1\,kg/m^2$) were normal (< 5.9 ng/mL), and not associated with severe steatosis. Furthermore, protein and caloric malnutrition may be relevant, since severe malnutrition occurred among children with steatosis and hypoalbuminemia [53]. In an Indian study, maternal malnutrition, low birth weight of children and malnutrition in early life have been related to metabolic syndrome and the lean NASH phenotype in adults [54].

Further, a study by Feldman et al. [51] showed that lean NAFLD and obese NAFLD differed by serum metabolome of the essential amino acids. They showed higher concentrations of lysine in serum (what can be an indicator of a dysfunctional metabolic phenotype) and lower concentrations of alanine, tyrosine and valine in lean NAFLD compared with obese NAFLD. Simultaneously, lean NAFLD and healthy controls vary by their phosphatidylcholines, sphingolipid and their lyso-PC profile [51].

Treatment

The results of lifestyles vs. pharmacological interventions for non-obese NAFLD appear in Fig. 2.

The literature on NAFLD, including therapeutic benefits, has mainly focused on obese populations. Data on treatment in non-obese NAFLD patients are lacking, although subjects are exposed to cardiovascular events as well [33]. Thus, benefits of treatment might be evident also in non-obese NAFLD. Physical exercise and dietary modifications are the cornerstone therapy for the management of NAFLD

and NASH [55,56], and similar recommendations, including weight loss can also stand for non-obese NAFLD patients [33]. Body weight change (together with fasting serum triglyceride levels), were strong indicators for the development and regression of NAFLD in a non-obese population [57]. Shen et al. [58] reported that the presence of the *PNPLA3* rs738409 risk allele was associated with a better response to lifestyle modifications, which were most effective in homozygous carriers of the variant. This is also in line with the data we obtained in obese individuals undergoing bariatric surgery [59]. Similarly, physical activity at moderate levels (< 2 h/week) and carbohydrate intake were both independently related to NAFLD in non-obese individuals [60]. The timing of meals may also be a predisposing factor for NAFLD, as shown in a non-obese Japanese cohort [35]. In the study by Nishioji et al. [35], eating within 2 h before bedtime (≥ 3 days/week) was negatively associated with NAFLD in non-obese females. Late bedtime was furthermore associated with increased NAFLD prevalence in the study by Wang et al. [61]. Therefore, interventions aiming to reduce weight loss by either increasing physical fitness, and/or modifying dietary and sleeping habits are warranted.

Regarding pharmacological interventions, ezetimibe, the potent inhibitor of cholesterol absorption from the small intestine via the Niemann—Pick C1—like 1 (NPC1L1) pathway [62], has been shown to suppress hepatic injury in non-obese NAFLD patients [63]. Main changes were seen in the alanine aminotransferase activity (ALT). Supplementation by symbiotic was also studied in 25 NAFLD patients (BMI 23.2 kg/m^2). Fasting glucose, triglycerides and steatosis stage decreased significantly, among others, as compared with the placebo group [64]. As a close relationship exists between abdominal circumference and insulin resistance in lean NAFLD subjects, pharmacological interventions should also be considered when appropriate [30].

Conclusion

The occurrence of NAFLD in non-obese subjects remains a challenge and raises several questions regarding the pathophysiological mechanisms governing fat deposition/accumulation in the liver of apparently healthy subjects. A combination of both genetic and non-genetic factors may play a role in this context. The prevalence is rising in both the Asian and Caucasian populations, and is going to affect other populations worldwide, irrespective of age, gender and race. Comparably to the obesity-associated form of NAFLD, several treatments are being considered, to efficiently mitigate NAFLD in lean subjects. Given the genetic exposure, a pharmacological approach may also be required together with change of lifestyle habits.

Disclosure of interest

The authors declare that they have no competing interest.

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