Reviews in Endocrine and Metabolic Disorders (2021) 22:351–366
https://doi.org/10.1007/s11154-020-09621-1

Lean NAFLD: an underrecognized and challenging disorder in medicine

Sheila Maier[1] · Amanda Wieland[2] · Melanie Cree-Green[3] · Kristen Nadeau[3] · Shelby Sullivan[4] · Miguel A. Lanaspa[5] · Richard J. Johnson[5] · Thomas Jensen[1,6]

Accepted: 15 December 2020 / Published online: 3 January 2021

Abstract

Classically, Non-Alcoholic Fatty Liver Disease (NAFLD) has been thought to be driven by excessive weight gain and obesity. The overall greater awareness of this disorder has led to its recognition in patients with normal body mass index (BMI). Ongoing research has helped to better understand potential causes of Lean NAFLD, the risks for more advanced disease, and potential therapies. Here we review the recent literature on prevalence, risk factors, severity of disease, and potential therapeutic interventions.

Keywords Lean · Non-alcoholic fatty liver disease · Nonalcoholic Steatohepatitis · Nonobese · Nonoverweight · Metabolic syndrome

Abbreviations

NAFLD	Non-Alcoholic Fatty Liver Disease
BMI	body mass index
BMI	body mass index
MetS	metabolic syndrome
MAFLD	Metabolic Associated Fatty Liver Disease
T2DM	type 2 diabetes
NASH	Non-alcoholic steatohepatitis
WHO	World Health Organization
AACE	Association of Clinical Endocrinologists
FFA	free fatty acids
PNPLA3	patatin-like phospholipasedomain-containing 3
TM6SF2	transmembrane 6-superfamily member 2
DAG	diacylglyceral
di-PPA	di-palmitoyl phosphatidic acid
AASLD	American Association for the Study of Liver Disease
EASL	European Association for the Study of Liver
EASD	European Association for the Study of Diabetes
EASO	European Association for the Study of Obesity
ADA	American Diabetes Association
APASL	Asian Pacific Association for the Study of the Liver
ALT	Alanine transaminase
FLI	fatty liver index
HCV	hepatitis C
ACG	American College of Gastroenterology
HFCS	high fructose corn syrup
NHANES	National Health and Nutrition Examination Survey
FIB-4	fibrosis-4 index
NFS	NAFLD fibrosis score
ATP	adenosine triphosphate

✉ Thomas Jensen
Thomas.Jensen@ucdenver.edu

[1] Division of Endocrinology, University of Colorado School of Medicine, Aurora, CO, USA

[2] Division of Hepatology, University of Colorado School of Medicine, Aurora, CO, USA

[3] Division of Pediatric Endocrinology, University of Colorado School of Medicine, Aurora, CO, USA

[4] Division of Gastroenterology, University of Colorado School of Medicine, Aurora, CO, USA

[5] Division of Renal Diseases and Hypertension, University of Colorado School of Medicine, Aurora, CO, USA

[6] Division of Endocrinology, University of Colorado, Denver, Denver, CO, USA

LPS	Lipopolysaccharide
TASH	toxicant-associated steatohepatitis
HCC	hepatocellular carcinoma
HSD17B13	hydroxysteroid 17-beta dehydrogenase 13
CETP	Cholesteryl Ester Transfer Protein
SREBF	Sterol regulatory element-binding factor
GCKR	Glucokinase Regulatory Protein
LFT	liver function test
US	ultrasound
DEXA	Dual-energy X-ray absorptiometry
CAP	Controlled Attenuation Parameter
TZD	thiazolidinediones
(GLP-1) agonists	glucagon like-peptide-1
DPP-4	Dipeptidyl peptidase 4
DNL	De novo Lipogenesis

1 Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is a major global health issue. It affects an estimated 24% of the global population, with rates increasing in parallel with the epidemic of obesity, metabolic syndrome (MetS), and type 2 diabetes (T2DM) [1]. Non-alcoholic steatohepatitis (NASH), a more progressive form of NAFLD, is one of the leading causes of liver transplantation [2, 3].

NAFLD and NASH were traditionally considered disorders that affected individuals who were overweight or obese. But the increasing recognition of the "metabolically unhealthy lean" phenotype has led to the identification of NAFLD and NASH in individuals whose BMI is non-obese by WHO categorization. This "lean" or "non-obese" NAFLD was first recognized in Asian populations, but occurs in other ethnic groups as well, and may reflect visceral obesity in the absence of systemic obesity, as well as different definitions of obesity in different ethnic groups. Because of NAFLD's association with Western obesity definitions and the metabolic syndrome, it may go under-recognized or completely undetected in lean populations [4].

Recently, it has been proposed to change the name of NAFLD to Metabolic Associated Fatty Liver Disease (MAFLD) to better reflect the pathophysiology of the disease [5]. The current terminology of "non-alcoholic" may suggest to patients the disorder is less serious, and creates a false dichotomy [6]. Additionally, there is possible stigma for patients with a disorder referencing "alcohol" [6]. MAFLD may better reflect the pathophysiology of the disorder, and provides a broad definition for this heterogeneous disorder. For the purpose of this paper, we will use NAFLD as it is currently more recognizable term in the literature.

2 Defining obesity

BMI is a useful surrogate marker for adiposity and risk of related complications. But the standard definitions of BMI do not consider ethnic differences. It was thought that Lean NAFLD could partly be explained by the need for lower BMI cut-offs in certain populations. That is, patients with "lean" NAFLD were in fact overweight or obese. But even with lower BMI cut-offs, lean NAFLD still represents a significant proportion of cases of NAFLD [7].

Most studies of NAFLD use the WHO criteria for obesity. These criteria were first proposed in 1993, and define a BMI of 25–29.9 kg/m^2 as overweight, 30–34.9 kg/m^2 as grade 1 obesity, 35–39.9 kg/m^2 as grade 2 obesity, and ≥ 40 kg/m^2 as grade 3 obesity [8]. The WHO recognized that different populations experience metabolic risk at lower BMIs, but they do not recommend ethnicity-specific cut-offs. However, other professional organizations do recommend ethnicity-specific BMI ranges (summarized in Table 1) [9, 10].

Ethnic-specific cut-offs for NAFLD risk may help identify patients otherwise categorized as low risk. A study of lean individuals with NAFLD in Iran identified a BMI > 23.14 kg/m^2 (male) or > 23.19 kg/m^2 (female) and waist circumference > 82.5 cm (m), or > 73 cm (f) as identifying those at increased risk for NAFLD [11]. Ultimately, BMI represents a continuum of risk, and any cut-off is somewhat arbitrary. Regardless, ethnic variations in appropriate weight play an important role in understanding what is considered Lean NAFLD.

3 Pathophysiology

A brief overview of risk factors contributing to the development of NAFLD is essential to appreciate the unique issues found in Lean NAFLD. Complex factors, including altered energy balance, excess weight, hormonal changes, insulin resistance, and genetics play a role in the development of NAFLD [12]. High energy intake, especially in the forms of excess fats and sugars has been linked to dysregulation of appetite, increase in free fatty acids (FFA), gut dysbiosis, de novo lipogenesis, and insulin resistance [13]. Excess weight and adipose tissue lead to insulin resistance, with a concomitant decrease in protective factors such as adiponectin and increase in inflammatory markers such as tumor necrosis factor alpha (TNF-α), and increases in circulating FFA [14]. Genetic variants, such as patatin-like phospholipasedomain-containing 3 (PNPLA3) and transmembrane 6-superfamily member 2 (TM6SF2) also lead to increased accumulation of fats in the liver [14]. Ectopic lipid species in the liver in the forms of ceramides, diacylglyceral (DAG), and di-palmitoyl phosphatidic acid (di-PPA) interfere with insulin signaling and increase inflammation, with subsequent hyperinsulinemia

Table 1 Selected definitions of obesity

	Normal weight	Overweight	Obese	Abnormal waist circumference
WHO [8]	18.5–24.9 kg/m^2	25–29.9 kg/m^2	>30 kg/m^2	
AACE [9]	18.5–24.9 kg/m^2 (Asian: 18.5–22.9 kg/m^2)	25–29.9 kg/m^2 (Asian: 23–24.9 kg/m^2)	>30 kg/m^2 (Asian: >25 kg/m^2)	≥102 cm (male) ≥88 cm (female) (Asian: ≥85 cm (male) ≥74 to 80 cm (female))
Clinical Practice Guidelines (Korea) [10]	18.5–22.9 kg/m^2	23 to 24.9 kg/m^2	≥25 kg/m^2	≥90 cm (male) ≥85 cm (female)
IDF [9]				≥94 cm (male) ≥80 cm (female) (Asian: ≥90 cm (male) ≥ 80 cm (female))

WHO, World Health Organization; *AACE*, American Association of Clinical Endocrinologists; *IDF*, International Diabetes Federation

and de novo lipogenesis [12]. These factors then drive recruitment of inflammatory cells such as macrophages and Kupffer cells, leading to progressive fibrosis, including cirrhosis [12].

4 Epidemiology

Lean NAFLD, classically described in Asian populations, has also been described in other populations in both the Americas and Europe with an incidence of 8–20% [15]. Most studies use WHO definitions of obesity, but even studies using an ethnicity-specific BMI range report a significant incidence of NAFLD (Table 3) [7].

5 Screening and diagnosis

NAFLD is prevalent in those with a "normal" BMI, but there is a lack of consensus on who should be screened. The American Association for the Study of Liver Disease (AASLD) recommends against routine screening for NAFLD in any population, regardless of BMI, because of lack of knowledge regarding long-term risks and benefits of screening, cost-effectiveness, and under-utilization of treatment [23]. However, the AASLD does endorse 'vigilance' in patients with T2DM. The European Association for the Study of Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) issued guidelines recommending screening patients with obesity or MetS [24]. The American Diabetes Association (ADA) recommends work up for NASH and fibrosis in patients with T2DM or prediabetes and elevated ALT or fatty liver on ultrasound [25]. The American Academy of Pediatrics recommends screening obese youth at regular intervals [26–28]. Asian Pacific Association for the Study of the Liver (APASL) recommends screening for MAFLD in those with T2DM, metabolic syndrome, or who are overweight/obesity according to ethnic specific cut-offs [29]. Our group recently published recommendations to screen obese patients with another feature of MetS, or patients with MetS, though the rate of MetS in Lean NAFLD patients is much lower compared to overweight and obese [30].

The indications for screening are even less clear for Lean NAFLD. Lean NAFLD may be easily missed since patients do not fit the classic phenotype of obesity [14]. Potential screening tools include NAFLD liver fat score [31], the Hepatic Steatosis Index, and the Lipid Accumulation Product, all of which have been validated to identify the presence of NAFLD, but not severity of disease [32]. The fibrosis-4 index (FIB-4) and NAFLD fibrosis score (NFS) have also been well-validated, but are more useful in excluding fibrosis rather than identifying it [14, 33, 34]. It should be noted a recent paper by Eren, et al. revealed that NFS and FIB4 is less accurate in discriminating severity of disease in Lean NAFLD patients [35].

but to our knowledge only fatty liver index (FLI) has any validations studies in Lean NAFLD. Additionally, these tools identify Yu, et al. found that a FLI ≥ 15 was useful as a cut-off for screening for Lean NAFLD, and a FLI ≤ 5 had a negative predictive value of 95% [36].. Their study population was relatively homogenous, in Taiwan, who had laboratory, clinical, and ultrasonographic evidence of NAFLD. The FLI is cost-effective, non-invasive, and does not require specialized lab testing. The FLI score was initially developed in the general NAFLD population, based on an Italian cohort, and is commonly used in epidemiological studies. Those authors recommended ruling out NAFLD if FLI <30, and if ≥60 to consider it a positive screen [37]. This discrepancy is probably partially due to the emphasis on BMI and waist circumference, and different ethnicity of the two cohorts.

Differentiating simple steatosis from NASH is important because the negative sequelae of NAFLD are most evident

in those with fibrosis. Patients with NASH have a 25% risk of developing cirrhosis after nine years, while 0–4% of patients with simple steatosis go on to develop cirrhosis [38]. In a cohort of Lean NAFLD patients, risk of NASH was found to be higher in patients on thyroid hormone replacement, higher fasting blood sugars, and higher INR [39].

Liver biopsy remains the gold standard for diagnosis of NAFLD and NASH, but is cumbersome, invasive, and carries small, but significant risks, including major bleeding and death, so it is not a feasible option in all patients or settings. Ultrasound can detect steatosis involving as little as 10% of the liver but is more reliable when steatosis is >30%. Transient elastography (Fibroscan®) is commonly used to estimate fibrosis and can be used for serial monitoring [40]. Liver MRI can assess liver fat content, as well as fibrosis, but expense and limited availability means this is less often used [14]. In most cases, NAFLD is diagnosed incidentally on abdominal imaging or after work up of elevated liver enzymes [14].

6 Secondary causes of fatty liver disease

NAFLD is ultimately a diagnosis of exclusion. It may be difficult to identify in patients who have MetS in addition to other potential causes. The differential diagnosis of steatosis includes excessive alcohol consumption, HCV, Wilson's disease, abetalipoproteinemia, and medications [23], and the work up has been covered elsewhere [5, 6]. In addition, increased hemoglobin has been found to associate with NAFLD, NASH, and fibrosis independent of MetS. This may be due to increased blood viscosity reducing oxygen delivery to liver, and increasing oxidative stress along with being a proxy for iron overload [41]. This may suggest that NAFLD pathology may not be simply a hepatic manifestation of MetS.

Excluding alcohol as a cause can be difficult. Different studies have used different thresholds as "excessive" or "significant" alcohol intake, with some studies excluding patients with any alcohol intake. Guidance from the American College of Gastroenterology (ACG) recommends a threshold of "significant" alcohol intake as >21 standard drinks/week for men and 14 standard drinks/week for women, where 1 standard drink contains 14 g of ethanol [23].

Patients should also be evaluated for co-morbid liver conditions like alpha-1 antitrypsin deficiency, hemochromatosis, autoimmune hepatitis, viral hepatitis, and drug-induced liver disease [24].

7 Risk factors

Risk factors for the development of Lean NAFLD are similar to those for nonlean NAFLD, and have significant overlap with other conditions associated with the metabolic syndrome, including age, gender, visceral adiposity, diet, genetics, lipodystrophy and alterations in the microbiome [42].

7.1 Diet

7.1.1 Total calories

Excess total calories and carbohydrates affect NAFLD status in those with obesity, but there is limited data in non-obese individuals. A study in a single center in China compared lean and obese individuals with NAFLD with weight matched controls, and found that all patients with NAFLD had a higher caloric intake, and more calories from grain, potatoes, and fruit than those without NAFLD [43]. Lean NAFLD patients consumed more grain, potatoes, and fruit than non-NAFLD controls, but less than obese NAFLD.

7.1.2 Fructose and sugar

Added sweeteners such as high fructose corn syrup (HFCS) and sucrose appear to be major causes of NAFLD [44]. Fructose is metabolized differently than glucose. It is initially metabolized by fructokinase before joining the glycolysis pathway. In the liver, this phosphorylation pathway leads to a transient ATP depletion, leading to oxidative stress and mitochondrial dysfunction [44]. Fructose is also a stronger driver of de novo lipogenesis than glucose [45]. Intake of fructose, primarily in soft drinks containing HFCS, is strongly associated with both the development of NAFLD and with its progression to NASH [46, 47]. Mice lacking fructokinase are significantly protected from developing NAFLD, suggesting that the development of NAFLD from a high-fat, high-sugar diet is due to the fructose [48]. There is also evidence that the fatty liver induced by high glycemic diets or high salt diets is due to the endogenous generation of fructose [49, 50].

Fructose plays a role in the development of Lean NAFLD also. Rats placed on caloric restriction will develop pronounced fatty liver and diabetes if placed on a high sugar diet, even in the absence of weight gain [51]. NAFLD and insulin resistance can also occur with protein malnutrition on high glycemic diets, as seen in Kwashiorkor [52, 53]. A study in Israel of 31 non-obese patients with NAFLD showed a strong correlation between soft drink consumption and extent of fatty liver infiltration on US [54]. Interestingly, 39% of patients who stopped sweetened beverages had a normal liver US after 6 months, suggesting that decreasing added sugar could be a high impact intervention [54]. A 2007 Israeli nutritional survey found a statistically significant increase in fructose intake, specifically soft drinks [55]. However, US National Health and Nutrition Examination Survey (NHANES) data from 2012 did not show a statistically significant difference in fructose consumption between individuals with Lean NAFLD and

lean controls, although there was a significant difference in saccharin intake, possibly reflecting increased diet soda intake [17].

Fructose appears to induce fatty liver by its unique ability to lower intracellular ATP levels associated with purine degradation and uric acid generation. The uric acid produced induces mitochondrial oxidative stress that triggers both lipogenesis and impaired fatty acid oxidation [44]. Hyperuricemia itself is associated with NAFLD, even without obesity. We reported that the presence of ultrasound-documented NAFLD in non-obese (BMI < 20) dialysis patients correlated with the presence of hyperuricemia compared to other lean dialysis patients without NAFLD [56].

Additionally, fructose can alter the gut microbiome, leading to increased gut permeability with endotoxemia that accelerates hepatic fat accumulation [57]. Cho YE, et al. published data suggesting that fructose ingestion precipitates inflammation and a "leaky gut" in a mouse model [58]. These mice also had alterations in gut microbiome consistent with previous reports in NASH patients [58].

7.2 Microbiome

There is increasing evidence for the role of the microbiome in mediating NAFLD. Besides the relationship between the microbiome and fructose, there is evidence for multiple mechanisms for the microbiome to influence NAFLD risk. Alterations in the gut microbiome can lead to increased energy harvest, increased intestinal permeability leading to increased lipopolysaccharides (LPS) or microbe products, decreased choline, increased endogenous alcohol, and dysregulation of bile acids, all contributing to liver inflammation and steatosis [14, 59] .

At least two studies have attempted to characterize differences in the microbiome between Non-Lean NAFLD, Lean NAFLD, and healthy controls. Yun et al. showed that patients with NAFLD had less diverse stool microbiome compared to healthy controls in a Korean population [60]. Interestingly, this difference was driven primarily by the Lean NAFLD group. Both NAFLD groups had a decrease in *Firmicutes* and *Ruminococcaceae* species, but a decrease in *Leuconostocaceae* was seen only in obese NAFLD. Lean NAFLD also had decreased diversity in blood microbiota profiles, but obese NAFLD did not. Increased *Bacteroidetes/Firmicutes* ratio in NAFLD patients has been reported previously [14, 59], and has also been observed in mice [61]. Chen, et al. similarly reported a distinct microbiome profile in a Caucasian population with Lean NAFLD. Lean NAFLD patients had increased *Ruminococcaceae* compared to obese NAFLD, and increased *Dorea* and decreased *Marvinbryantia* and the *Christensellenaceae* compared to healthy controls [61].

Alterations in the gut microbiome may predispose individuals to develop NAFLD at a lower BMI, and unlike genetic predispositions, it may be a modifiable risk factor. However, there are very few studies in humans, and even fewer on modulation of the microbiome as a therapy for NAFLD [62]. Since alterations in the microbiome correlate with presence and severity of liver disease, and can be measured noninvasively in the blood, they could potentially be used as a biomarker to identify and follow NAFLD [63].

7.3 Marijuana

Interestingly, marijuana use was associated with a 15% lower risk of NAFLD in a cross-sectional study [64]. Cannabis users were more likely to be overweight, but less likely to be obese, and less likely to have MetS. A separate study using NHANES data, which includes people with ultrasound-confirmed NAFLD, also showed a reduced risk of NAFLD in active marijuana users, in a dose-dependent manner [65].

This is especially intriguing because while marijuana use is associated with alcohol use, lower socioeconomic status, and increased calorie intake (including more soda); there is also reduced risk of obesity, diabetes, and MetS [65]. Additionally, in a metanalysis of biopsy studies, cannabis does not appear to worsen fibrosis in patients who already have NAFLD or chronic liver disease due to other etiologies [66], although there are few studies in this area. Potential mechanisms include an anti-inflammatory effect of cannabanoids [65] and modulation of lipid metabolism via hepatic endocannabinoids [67].

7.4 Environmental

Toxic exposures have been associated with liver injury and NASH, and may be the main etiology in some cases of Lean NASH. Investigators in Taiwan found that heavy metal exposure was significantly associated with fatty liver disease in men (OR (95% CI) 1.834 (1.161 to 2.899), but not women [68]. When stratified by BMI, high levels of heavy metals increased the severity of NAFLD, with lean men (BMI <24 kg/m^2) most affected. In a study of non-obese workers exposed to high levels of vinyl chloride, every patient in the exposed group had abnormalities on liver biopsy, 84% had NAFLD, and 80% had NASH [69]. These patients also had insulin resistance. Vinyl chloride is metabolized similarly to alcohol, possibly accounting for this pattern of liver injury. Cave, et al. proposed classifying these patients as "toxicant-associated steatohepatitis" (TASH) [69]. Evidence of NAFLD in lean individuals has also been seen in studies of petrochemical workers [70].

7.5 Polycystic ovarian syndrome

Recent evidence indicates that lean girls and women with polycystic ovarian syndrome (PCOS) have higher rates of NAFLD than women without PCOS [71]. PCOS is often associated with hyperandrogenism and insulin resistance [72] . There is some evidence that the degree of hyperandrogenism is associated with risk of NAFLD in lean women with PCOS [71, 73, 74].

8 Genetics

Several genes have been implicated in the development of NAFLD and may also predispose to Lean NASH [75]. Further, ethnic associations with certain genes may be a source for the variation in prevalence and severity of disease across populations. Some of these variants play a role in NAFLD in general, and some appear to be either drivers or protective against Lean NAFLD specifically (Table 2).

8.1 Patatin-like phospholipase domain-containing protein 3 (PNPLA3)

PNPLA3 is an enzyme with lipase activity towards triglycerides and retinyl esters, and acyltransferase activity on phospholipids. The rs738409 I148M variant C- > G allele has been associated with worsening severity of steatosis, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) in a variety of liver diseases, including NAFLD [81, 82]. Despite this, carriers of PNPLA3 may actually have a greater therapeutic response to exercise [83].

In an Asian NAFLD population, the I148M variant occurs more frequently in nonobese than obese, suggesting that this gene plays an important role in the development of NAFLD in nonobese patients. A study in Japanese adults with NAFLD found a significantly higher prevalence of the G allele in normal weight (18.5 kg/m^2 – 22.9 kg/m^2) (OR 3.52; 95%-CI: 1.42–8.71; $P = 0.0063$) and overweight patients (23 kg/m^2–24.9 kg/m^2) (OR 2.60; 95%-CI: 1.14–5.91; $P = 0.0225$), but not in obese patients (BMI ≥ 25 kg/m^2) [84]. Another study out of Japan also found a higher incidence of the GG allele (47.8% vs 36.5% P = 0.02) in non-obese NAFLD (BMI < 25 kg/m^2) vs obese (BMI ≥ 25 kg/m^2). In controls without NAFLD, there was no significant difference in gene expression and overall lower expression (nonobese 19.9% and obese 18.7%, $P = 0.67$) [85]. An Italian study did not find a difference in presence of PNPLA3 variant between lean (BMI 18.5 kg/m^2–24.9 kg/m^2), overweight (BMI 25.0 kg/m^2–29.9 kg/m^2), and obese NAFLD (≥30 kg/m^2 BMI), but the variant was the only factor in lean patients associated with NASH or Fibrosis Score 2 or greater [79]. Overall, these studies lend support to PNPLA3 I148M being a potential driver of NAFLD in lean/nonobese patients.

Ethnic differences in PNPLA3 expression may also explain higher rates of NAFLD in some populations. In a NHANES Study, rates of NAFLD in lean patients (BMI <25 kg/m^2) was 7.39%, though Hispanic Ethnicity was a risk factor for lean NAFLD compared to lean controls (OR 1.74 (1.20–2.51) $p = 0.0037$) [17]. In the Dallas Heart Study, a multi-ethnic cohort study, the allele frequency of PNPLA3-148 M was 0.49 in Hispanic populations, 0.23 in European Americans, and 0.17 in African Americans [77]. Interestingly, the prevalence of the GG phenotype has been reported as 13–19% in Asian studies, compared to 4% in Non-Hispanic Whites, 2% in African Americans, and 25% in Hispanics [86].

PNPLA3 I148M variant appears to be strongly associated with presence and severity of NAFLD, appears to disproportionately occur in certain ethnic groups, and may explain higher rates of NALFD in Asian and Hispanic populations, especially in lean patients.

8.2 Transmembrane 6 superfamily member 2 (TM6SF2)

TM6SF2 is a gene involved in regulating hepatic VLDL secretion. Variants with diminished expression are associated with excess hepatic fat accumulation [87]. A missense variant rs58542926[T], encoding E167K, has been linked to liver fat accumulation and increased risk of NASH [18]. An Australian study comparing NAFLD patients with BMI <25 kg/m^2 compared to BMI ≥25 kg/m^2 had a higher rate of the T allele expression in lean patients [61]. An Italian cohort also showed a higher expression of the variant in Lean NAFLD (4%) compared to overweight/obese NAFLD (0.3%) patients ($p = 0.001$) [79]. In contrast, a retrospective Austrian study comparing lean, overweight, and obese patients did not find a higher expression of T allele, though there was a tendency for higher percentage of T allele homozygotes in lean (21.9%) compared to obese (16.5%) [39].

An exome-wide association study based on the Dallas Heart Study found a higher frequency of Glu167Lys TM6SF2 variant in Non-Hispanic White individuals compared to Hispanic and African American (7.2% vs 4.7% and 3.4%) [87]. The prevalence is much lower compared to the PNPLA3 variant in this same study, but may help to account for higher rates of NAFLD in Caucasians compared to African Americans. In addition, a Chinese study of 992 patients showed the variant was occurred in only 0.4% of patients and was not significantly associated with liver disease, suggesting little to no role for this gene in this population [88].

Table 2 Genetic variants associated with NAFLD

	Country	Population	Gene analyzed	Prevalence	Effect
Petersen, 2010 [76]	New Haven, Conn, USA	Asian Indian men ($n = 95$) Multiethnic ($n = 163$)	APOC3 variant alleles (C-482 T, T-455C)	Indian – 20% wild type, 80% with one or both variants Multiethnic cohort 34% wild type, 76& with one or both variants.	Prevalence of NAFLD was 38% in those with variant alleles compared to 0% in homozygote wild type. Variant allele associated with 30% increase in fasting glucose, 60% increase in triglycerides compared to homozygote wild type.
Romeo, 2008 [77]	Dallas, TX, USA	Multiethnic	PNPLA3-I148M PNPLA3-S453I	PNPLA3-I148M 49% - Hispanics 23% -European Americans 17%African Americans PNPLA3-S453I, 10.4% - African Americans .03 - European-Americans .08- Hispanics	PNPLA3 (rs738409; I148M) - associated with higher hepatic fat, independent of IR and other lipid levels PNPLA3-S453I – associated with low hepatic fat 2 variants account for 72% of observed ethnic differences in hepatic TG, independent of BMI and IR
Abul-Husn, 2018 [78]	United States	European and Hispanic Americans	HSD17B13	26% allele frequency	rs72613567:TA- loss of function, associated with lower odds of liver disease. Homozygous had less NASH and fibrosis, appears to protect against liver disease in dose dependent manner
Wei JL, 2015 [20]	Hong Kong	Asian	PNPLA3 (rs738409)	Non obese NAFLD (BMI < 25) incidence - 78.4% Obese NAFLD (BMI ≥25) incidence - 59.8% ($P = 0.001$)	Polymorphism independent risk factor for NAFLD in lean patients. 19.3% of lean population had NAFLD, higher likelihood of PNPLA3 variant than obese NAFLD patients.
Chen F, 2020 [61]	Australia	Caucasian Cohort Lean BMI < 25 ($N = 99$) Non-Lean BMI ≥ 25 ($n = 439$)	TM6SF2 E167K T allele	Lean NAFLD Patients had higher likelihood of T allele vs Non-Lean NAFLD Patients; CC/CT/TT (Number/%) Lean 59 (70.2)/22 (26.2)/3 (3.6) vs Non-Lean 321 (85.1)/50 (13.3)/6 (1.6).	Higher prevalence of T allele of TM6SF2 in Lean NAFLD than Non-Lean NAFLD Patients, though PNPLA3 G allele (hetero or homozygote) prevalence was similar between the two groups.
Fracanzani, 2017 [79]	Italy	Italian Cohort Lean BMI < 25 ($N = 143$) Overweight/ obese BMI ≥ 25 ($N = 526$)	TM6SF2 E167K T allele PNPLA3 (rs738409)	Higher TM6SF2 variant expression in Lean (4%) vs overweight/obese (0.3%) ($p = 0.001$) No significant difference in PNPLA3 expression in Lean vs overweight/obese	In Lean NAFLD, only independent variable associated with NASH or Fibrosis Stage 2 or higher was GG PNPLA3(rs738409) polymorphism
Feldman, 2017 [80]	Austria	Caucasian Cohort Lean NAFLD BMI ≤ 25($N = 55$) Lean control BMI ≤ 25 ($N = 71$) Obese NAFLD BMI ≥ 30 ($N = 61$).	TM6SF2 E167K TT allele compared to heterozygote CT and CC allele PNPLA3 (rs738409) GG allele compared to heterozygote CG and homozygote CC allele	PNPLA3 GG allele was associated with presence of NAFLD (OR 2.676 $p = 0.007$) though not TM6SF2 TT allele (OR 1.935, p = 0.098)	Lean NAFLD had worse metabolic parameters, but not as severe as obese NAFLD. PNPLA3 GG allele expression was similar in lean and obese NAFLD.

8.3 -HSD17B13

HSD17B13 encodes hydroxysteroid 17-beta dehydrogenase 13, which is expressed in human liver and has enzymatic activity against several lipid species [78]. It was identified in a GWAS study linking genetic data to EHR data. The splice variant rs72613567:TA appears to be protective against all categories of liver disease in a dose-dependent manner. In a replication cohort of patients undergoing bariatric surgery, homozygotes for the splice variant had significantly reduced risk of biopsy-proven NASH and fibrosis [78]. This variant also appeared to mitigate the risk of liver protein injury in individuals who were also carriers of the PNPLA3 I148M variant [89].

8.4 Cholesteryl Ester transfer protein (CETP)

CETP is a critical factor in reverse cholesterol transport (from the peripheral tissues back to the liver) and HDL metabolism. Two polymorphisms (rs12447924 and rs12597002) have been associated with increased risk of NAFLD in lean individuals [90]. In a general population cohort of Caucasian Australian teenagers, these were associated with increased probability of NAFLD. For lean females, the risk of NAFLD was 30% for homozygotes, 10–15% for heterozygotes, and 3–5% for wild type [91]. Interestingly, this association was lost in obese patients when modified by excess visceral fat. It was also not seen in male participants.

8.5 Sterol regulatory element-binding factor (SREBF)

The SREBF gene codes for SREBP-2, which is a transcription factor that regulates genes involved in cellular cholesterol biosynthesis and homeostasis. Upregulation of SREBP-2 is correlated with worsening severity of NAFLD [90]. The rs133291 polymorphism of SREBP-2 was identified in a cohort of lean individuals with NAFLD and associated with an increased risk of Lean NAFLD as well as increased severity of disease [92].

8.6 Glucokinase regulatory protein (GCKR)

The GCKR variant rs1260326 (TT allele) has been associated with increased risk of NAFLD in Caucasian and Hispanic individuals due to reduced inhibitory effect on glucokinase in the liver, leading to increased de novo lipogenesis [93]. It is also associated with increased severity of fibrosis [94]. However, the association between this polymorphism and NAFLD has not been consistent between studies. In a Chinese population, the polymorphisms rs780094 and rs1260326 were not associated with NAFLD [95]. There was also no association between NAFLD and rs780094 in an Iranian population [96]. In an Austrian study of Caucasian patients, the rs6834314 polymorphism was not associated with NAFLD (OR 1.935 $p = 0.098$) [80]. In contrast, there was a positive correlation between the rs780094 TT allele and NAFLD status in Taiwanese children [97]. Hence, the role of GCKR polymorphisms in the development of NAFLD in lean populations is not clear (Table 3).

9 Metabolic risk in comparison to overweight/obese NASH

Similar to NAFLD in obese populations, Lean NAFLD has been associated with a number of co-morbid conditions including PCOS, T2DM, and MetS [98]. People with Lean NAFLD are also at risk of developing the sequelae of NAFLD: NASH, cirrhosis, and HCC. Compared to overweight or obese patients, Lean patients with NAFLD tend to have less severe features of MetS, [17, 39] though in Asian populations the presence of MetS in lean patients more strongly correlates with NAFLD than in overweight or obese patients [80]. A prospective cohort study of 406 lean adults in Hong Kong (BMI < 23 kg/m^2) found that new onset of NAFLD (7.9%) was associated with increases in waist circumference and triglycerides over a period of 3–5 years [20]. A Chinese cohort of Lean NAFLD compared to overweight/obese NAFLD found a higher visceral adiposity index (a measurement associated with cardiometabolic risk and insulin sensitivity) in lean NAFLD than overweight/obese controls [21]. This suggests that people who develop NAFLD at lower BMI are less able to adapt to the metabolic challenges of modest weight gain, when compared to people who develop NAFLD at higher BMIs (Table 4).

In general, Lean NAFLD patients have less severe features of MetS than patients with Non-Lean NAFLD. There is also a greater prevalence of NAFLD in overweight and obese individuals compared to lean. In an Italian study, although rates of MetS increased with weight (18% normal weight compared to 67% in obese), rates of NASH were similar across weight groups (normal weight, 65%; overweight, 73%; and obese, 84%; $p = 0.184$) [101]. This was despite MetS being an independent risk factor for NASH (OR, 3.2; 95% CI, 1.2–8.9; $P = .026$) and severe fibrosis (OR, 3.5; 95% CI, 1.1–11.2; $P = .032$). Lean patients from Austria also had similar rates of ballooning, lobular inflammation, and fibrosis as obese NAFLD [39]. Interestingly, there was a higher rate of cirrhosis in lean (8.1%) compared to obese patients (2.0% $p = 0.027$). On the contrary, another Italian study found lower rates of NASH (55% vs 72%) and fibrosis in the lean group [102]. Finally, a study from India found lower rates of NAFLD Activity Score, ballooning, and fibrosis in Lean NAFLD compared to obese patients [100]. One limitation with these studies is that they are typically tertiary care centers that might suffer from referral bias.

Table 3 Prevalence of Lean and Non-Lean NAFLD in selected studies

Study	Country	Definition of lean	Prevalence of NAFLD in population
Naderian, 2017 [11]	Tehran, Iran	BMI <25 kg/m^2	17.5%; diagnosed by US
Das,2010 [16]	West Bengal, India	BMI 18.5–24.9 kg/m^2	Lean NAFLD: 3.2% Total NAFLD: 8.7% Diagnosed by US, CT, or biopsy
Younossi, 2012 [17]	United States	Lean BMI <25 kg/m^2 Non-Lean BM ≥ 25 kg/m^2	Rate of NAFLD in lean vs non-lean (7.39% ± 0.65% vs. 27.75% ± 1.00%, respectively; $p < 0.0001$). Hispanic ethnicity ($p = 0.0037$), diabetes ($p < 0.0001$) and hypertension ($p = 0.0033$) were independent risk factors for Lean NAFLD
Selvakumar, 2018 [15]	United States	Weight < 85% by CDC criteria. Excluded patient without evidence of MetS	8% (5–11.5% depending on study year) Study population - adolescents age 12–18 Patients identified by LFTs as high risk of NAFLD
Sinn, 2019 [18]	Seoul, South Korea	Lean BMI <23 kg/m^2 Overweight/obese BMI ≥ 23 kg/m^2	Lean NAFLD - 10.3% Non-Lean NAFLD - 46.1%
Kwon, 2012 [19]	Seoul, South Korea	Lean BMI <25 kg/m^2 Obese BMI ≥ 25 kg/m^2	Lean NAFLD - 12.6% Non-Lean NAFLD - 50.1%
Wei, 2015 [20]	Hong Kong	Lean BMI <25 kg/m^2	Lean NAFLD - 19.3% Non-Lean NAFLD - 60.5%
Feng, 2014 [21]	Harbin, China	Lean BMI < 24 kg/m^2 overweight-obese BMI ≥ 24 kg/m^2	Lean NAFLD - 18.33% Non-Lean NAFLD - 72.90%
Niriella, 2018 [7]	Sri Lanka	Lean BMI < 23 kg/m^2 Non-Lean BMI ≥ 23 kg/m^2	Lean NAFLD - 4% in 2007 and 13.2% in 2014. Non-Lean NAFLD - 27.3% in 2007. Diagnosed by US
Cho HC, 2016 [22]	Seoul, South Korea	Obese BMI of ≥25 kg/m^2	Lean NAFLD - 12.4%
Akyuz, 2014[13]	Turkey	Lean BMI <25 kg/m^2	Lean NAFLD – 7.6%

NAFLD, non-alcoholic fatty liver disease; *BMI*, body mass index

Overall potential mechanisms for development and progression of Lean NAFLD is proposed here (Fig. 1).

10 Treatment for NAFLD and NASH

10.1 Lifestyle

Lifestyle modifications are the cornerstone of treatment of NAFLD. Currently it is the only evidence-based treatment for Lean NAFLD [17]. As little as 3% weight loss can lead to improvement in biomarkers, and 7–10% weight loss can lead to regression of NAFLD [103]. There is even evidence that improvements in liver fat can be seen even if there is no change in overall weight [104, 105].

Weight loss is a strong predictor of regression of NAFLD. Kim et al., followed nonobese and obese patients with NAFLD, and found that nonobese subjects had regression of NAFLD with smaller reduction in body weight [106]. Also, exercise improves insulin resistance even in lean individuals [107]. A study of insulin sensitivity, fatness, and fitness in lean and obese individuals who were healthy showed that physical activity improved liver insulin sensitivity, and had more of an impact on liver insulin sensitivity than adiposity [108].

Devries, et al. did not find any significant effects of endurance exercise on liver steatosis in lean or obese subjects [109]. However, the participants did not have evidence of steatosis, LFT abnormalities, or a diagnosis of NAFLD at the time of the study. In contrast, Keating, et al. found that even low intensity exercise elicited improvement of hepatic steatosis and visceral adipose tissue as measured by MRI in obese subjects. This benefit was unrelated to weight loss, although the study was underpowered to determine an optimal dose or threshold effect of exercise [103]. Aerobic exercise elicited 2.4–2.6% reduction in liver fat in 8 weeks, which could be sufficient to cause remission of NAFLD in mild disease. Zelber-Sagi, et al. showed a beneficial effect of resistance exercise. [110]. Their cohort was sedentary, overweight or obese patients with NAFLD. After 3 months of resistance training program, there was significantly decreased liver fat by US, and decreased adiposity and increased lean mass by DEXA.

Beside adiposity, sarcopenia may contribute to the development of NAFLD. In a subgroup analysis of the Rotterdam study, skeletal muscle mass was consistently associated with NAFLD in normal- weight women [33]. However, fat mass

Table 4 Metabolic abnormalities in lean NAFLD vs others

	Country	Compared to Lean Control	Compared to nonLean with AFLD.
Naderian, 2017 [9]	Tehran, Iran	Higher TG, SBP, BMI >23.2 kg/m^2. MS increased risk of NAFLD	NA
Selvakumar, 2018 [15]	United States	Lean NAFLD had higher Triglycerides, lower HDL, but similar BMI. Insulin resistance and white compared to black ethnicity increased risk of NAFLD	. NA
Cantero, 2018 [99]	Granada, Spain	Compared to lean without NAFLD, more likely male, greater waist circumference, liver enzymes, and IR. Compared with over-weight control, had greater IR, liver enzymes.	Compared with obese without NAFLD, Lean NAFLD had worse IR and lower adiponectin levels.
Kwon, 2012 [19]	Seoul, South Korea	Higher BMI and components of MetS (high BP, high FBG, low HDL-C, and high TG), fat percentage, current smoker and less likely to exercise in NAFLD compared to Lean controls.	Prevalence ratios for non-obese NAFLD patients was higher for components of MetS (high BP, low HDL, high TG, presence of IR) than obese NAFLD counterparts.
Wei, 2015 [20]	Hong Kong	Obesity, high hemoglobin A1c, insulin resistance, hyperferritinemia, and the PNPLA3 G allele were independent factors associated with NAFLD in non-obese subjects	PNPLA3 rs738409 was more common in non-obese than obese NAFLD patients (78.4% vs. 59.8%; P = 0.001).
Feng, 2014 [21]	Harbin, China	Lean NAFLD had greater risk for central obesity, dyslipidemia, BP, DM, MetS compared to Lean control	Non-lean NAFLD had greater body fat percentage, visceral adipose index, and BP, along with IR, though similar lipids.
Niriella, 2018 [7]	Sri Lanka	Lean NAFLD more common in males with lower prevalence for HTN and central obesity at baseline. Baseline DM and weight gain during follow up greatest risk for new onset NAFLD.	Lean NAFLD had lower central obesity, HTN, and components of MetS compared to non-Lean counterparts. PNPLA3 mutation was stronger indicator of NAFLD in Lean than non-Lean NAFLD.
Kumar, 2013 [100]	India	Lean NAFLD BMI, incidence of dyslipidemia and MetS higher than normal control.	Lean NAFLD had less IR than non-lean, less likely to have MetS or diabetes, less inflammation or fibrosis, but similar proportion of patients with NASH and advanced fibrosis.

BP, blood pressure; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein; *TG*, triglycerides; *SBP*, systolic blood pressure; *IR*, insulin resistance; *MetS*, metabolic syndrome; *BMI*, body mass index; *DM*, diabetes mellitus; *OR*, odds ratio

was a better predictor for NAFLD probability in both sexes. A Korean cohort study found that sarcopenia was an independent predictor of NAFLD, and also associated with insulin resistence [34]. An analysis based on the Korea National Health and Nutrition Examination Surveys also found that individuals with sarcopenia had increased risk of NAFLD, independent of obesity, and also were more likely to have advanced fibrosis [111]. Interestingly, this study also found individuals who exercised regularly had a lower risk of NAFLD. These studies suggest a mechanism of resistance training replacing fat mass with lean mass (regardless of net weight loss) as an easily accessible, inexpensive, and targeted approach for individuals with NAFLD.

Dietary modification is another way of achieving weight reduction and decreasing hepatic fat. A Mediterranean diet may produce beneficial alterations in the gut microbiome that reinforces the gut barrier [59]. Reducing added sugars has been associated with resolution of NAFLD [54]. Montesi, et al. randomized patients with NAFLD to an intensive, individualized weight loss program which allowed participants to choose a less involved physical activity (PA) (1 h individual sessions every 2 weeks to encourage exercise) versus a more involvedcognitive behavioral therapy (CBT) program which provided weekly 2 h group counseling on nutrition and behavioral strategies based upon LEARN model [112, 113]. Both groups reduced BMI though greater in CBT (-2.04 ± 1.42 kg/m^2 vs -1.09 ± 1.68 kg/m^2, $P = 0.019$), yet both saw similar improvements in lipids, LFTs, and MetS [112]. This suggests that various approaches to lifestyle modifications can be beneficial and support shared decision making based upon patient preference. Recently, a small study which included Lean NAFLD participants, showed that an 8 week dietary intervention (with emphasis on low or middle glycemic index carbohydrates) resulted in weight loss of 5.4%, significant improvements in ALT levels, and liver steatosis on Fibroscan® [114].

10.2 Pharmaceuticals

Medications are generally reserved for patients with biopsy-proven NASH and fibrosis [23]. Currently, there are no FDA approved medical treatments for NAFLD. As of 2018, there were at least 190 compounds under investigation, and over 300 clinical trials [115]. A major barrier in drug development for NAFLD in general has been the relatively long lag time between development of steatosis and clinically important outcomes like cirrhosis, liver failure, and HCC. The lack of

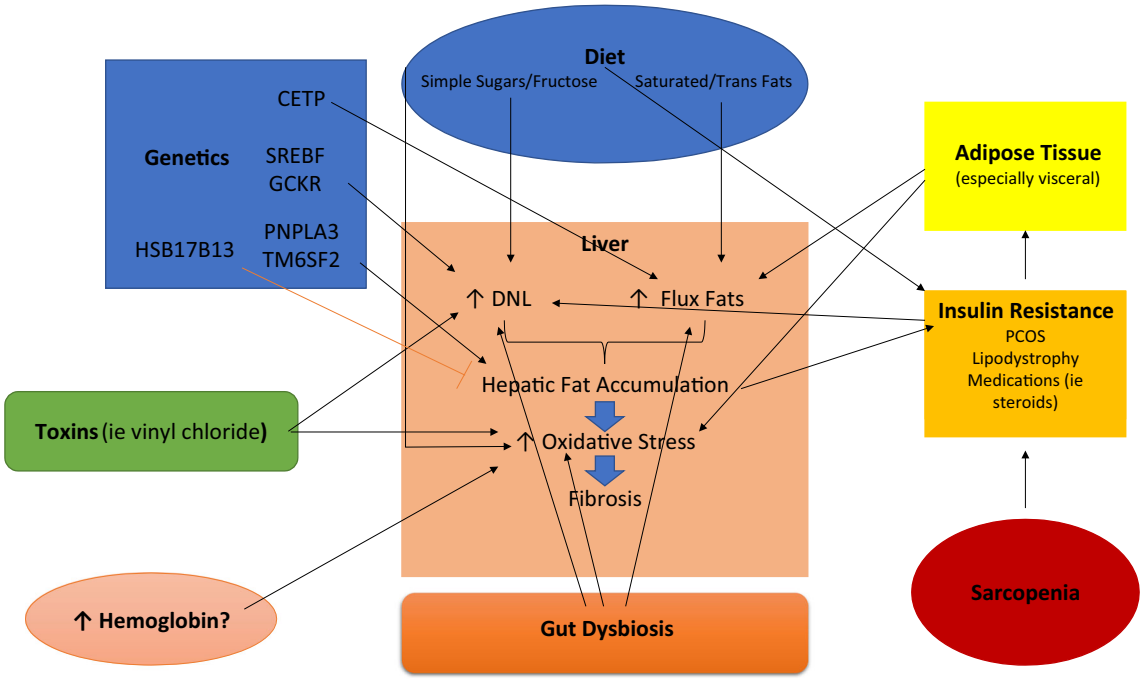

Fig. 1 Proposed mechanisms of NAFLD development and progression. Abbreviations DNL (De novo Lipogenesis)

a good animal model and noninvasive markers of fibrosis have also been barriers.

Several existing medications and supplements have been evaluated for efficacy in treating NAFLD or NASH [23]. According to AASLD guidelines on NAFLD, thiazolidinediones (TZD) and vitamin E have evidence of benefit in NASH [23]. Vitamin E has been shown to improve liver histology, but concerns remain about possible increased risk of cancer with vitamin E supplementation. The PIVENS trial compared 800 IU natural vitamin E or 30 mg pioglitazone daily to placebo [116]. Although both pioglitazone and vitamin E elicited significant improvement in histology and steatohepatitis, they did not appear to improve fibrosis. Also, all the patients in this study were overweight or obese limiting its application to lean individuals. Various studies have shown benefit of doses 300 IU daily up to 1000 IU have shown benefit, though controversy exists about potential increased risk of overall mortality ≥400 IU, though more recent studies metanalysis suggests doses up to 500 IU daily are safe [117–120]. Other risks such modest risk of hemorrhagic stroke and prostate cancer have been seen with various doses of Vitamin E even as low as 400 IU every other day [121, 122]. Therefore, risk and benefits need to be addressed with patients. Obeticholic acid, a farnesoid X receptor (FXR) agonist, regulates bile acids, and activation appears to improve hepatic fatty acid oxidation, reduce de novo lipogenesis and reduce inflammation and fibrosis. The REGENERATE trial, a phase-3 clinical trial of obeticholic acid recently published an interim analysis showing positive findings, but was not stratified by weight [123].

There is mixed evidence on the benefit of metformin, omega-3 fatty acids, glucagon like-peptide-1 (GLP-1) agonists, and Dipeptidyl peptidase 4 (DPP-4) inhibitors in reducing hepatic fat. Liraglutide is a GLP-1 agonist approved for diabetes mellitus which has several benefits besides glycemic control, including weight loss and cardioprotection. Given that cardiovascular disease is the major cause of morbidity in NAFLD patients, use of these cardioprotective medications could provide multiple benefits in patients with NAFLD and diabetes.. While these medications have not been studied in patients with Lean NAFD, Liraglutide has been shown to reverse histological evidence of inflammation in a lean guinea pig model, although did not reduce steatosis [124]. A placebo-controlled study of liraglutide in histologically-confirmed NAFLD showed significant resolution of fibrosis and less progression of fibrosis even when controlling for weight loss [125]. This study excluded those with BMI <25 kg/m^2, so whether these benefits would be seen in individuals with Lean NAFLD is unclear.

11 Outcomes

Patients with NAFLD are at risk for NASH, cirrhosis, HCC, and liver failure requiring liver transplant. Given that patients with Lean NAFLD frequently have less severe metabolic abnormalities than obese NAFLD, the question is whether they would develop the same negative outcomes. An abstract by Dela Cruz, et al. was one of the first to indicate that Lean NAFLD may not be a more benign condition [126]. In 1090

patients with biopsy-proven NAFLD, survival was significantly shorter in the Lean NAFLD (HR 11.8, CR 2.8–50.1, $p = 0.001$), despite fewer co-morbidities and less fibrosis.

12 Future directions

Does Lean NAFLD represent a continuum with Obese NAFLD or does it represent a unique pathology? This is an important question for both prevention and treatment, since different etiologies may not respond the same way to the same intervention. Previous clinical trials on NAFLD have often excluded lean individuals, or not stratified groups by BMI. Subgroup analysis by BMI may help in both targeting treatments and elucidating etiology. Ethnicity-specific BMI guidelines are also important for correctly categorizing patients as lean vs. obese.

Further studies on lifestyle modifications are needed in this population. Potential areas of research include the effect of macronutrient content, development of culturally sensitive diet recommendations where traditional diets are high in simple carbohydrates (i.e. rice), and effects of different types of exercise on liver steatosis, liver enzymes, and fibrosis. In the era of personalized medicine, genetic risk markers may help identify both patients at risk, and those who would benefit from certain treatments over others. For example, patients with polymorphisms in PNPLA3 appear to respond better to exercise as well as lower carbohydrate diets.

13 Conclusions

NAFLD is likely a disorder which requires multiple "hits" for development and progression of the disease. It is classically associated with obesity, but Lean NAFLD represents a unique subset of patients that due to the interaction of genetics, lifestyle, diet, age, the microbiome, underlying medical conditions, environmental exposures, medications, and other factors are at risk of developing steatosis, inflammation, and NAFLD at a lower BMI. Despite the generally milder clinical phenotype, patients with Lean NAFLD are still at risk for cirrhosis, hepatocellular carcinoma, and liver failure.

Although the metabolic syndrome is associated with both Lean and Overweight/Obese NAFLD, Lean NAFLD appears to have a greater association with genetic risk factors suggesting less metabolic adaptability at a given weight. In addition, increased visceral fat with or without sarcopenia further contributes to less metabolic adaptability and greater risk of NAFLD at lower weights. Given that the global burden of NAFLD is huge, upwards of 50% in certain populations, it is important to continue research into screening, prognosis, and treatment of Lean NAFLD.

Compliance with ethical standards

Conflict of interest disclosure SM, AW, MCG, KN, SS, and TJ have no conflicts of interest to report. RJ and ML have equity with Colorado Research Partners LLC that is developing inhibitors of fructose metabolism. RJ also has equity with XORTX Therapeutics that is developing novel xanthine oxidase inhibitors. RJ also has consulted for Astra Zeneca and Horizon Pharma. RJ and ML are inventors on several patents and patent applications related to fructose metabolism.

References

1. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nature Reviews Gastroenterology and Hepatology. 2018;15(1):11–20. https://doi.org/10.1038/nrgastro.2017.109.
2. Younossi ZM, Loomba R, Rinella ME, et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2018;68(1):361–71. https://doi.org/10.1002/hep.29724.
3. Pais R, Barritt AS, Calmus Y, et al. NAFLD and liver transplantation: current burden and expected challenges. J Hepatol. 2016;65(6):1245–57. https://doi.org/10.1016/j.jhep.2016.07.033.
4. Sookoian S, Pirola CJ. Systematic review with meta-analysis: risk factors for non-alcoholic fatty liver disease suggest a shared altered metabolic and cardiovascular profile between lean and obese patients. Aliment Pharmacol Ther. 2017;46(2):85–95. https://doi.org/10.1111/apt.14112.
5. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73(1):202–9. https://doi.org/10.1016/j.jhep.2020.03.039.
6. Fouad Y, Waked I, Bollipo S, Gomaa A, Ajlouni Y, Attia D. What's in a name? Renaming 'NAFLD' to 'MAFLD'. Liver Int. 2020;40(6):1254–61. https://doi.org/10.1111/liv.14478.
7. Niriella MA, Kasturiratne A, Pathmeswaran A, et al. Lean nonalcoholic 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(3):314–22. https://doi.org/10.1007/s12072-018-9916-4.
8. Nishida C, Barba C, Cavalli-Sforza T, et al. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157–63. https://doi.org/10.1016/S0140-6736(03)15268-3.
9. Timothy Garvey W, Mechanick JI, Brett EM, et al. AACE/ACE guidelines american association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocrine Practice. 2016;22(3). https://doi.org/10.4158/EP161365.GL.
10. Kim MK, Lee WY, Kang JH, et al. 2014 clinical practice guidelines for overweight and obesity in Korea. Endocrinol Metab. 2014;29(4):405–9. https://doi.org/10.3803/EnM.2014.29.4.405.
11. Naderian M, Kolahdoozan S, Sharifi AS, et al. Assessment of lean patients with non-alcoholic fatty liver disease in a middle income country; Prevalence and its association with metabolic disorders: A cross-sectional study. Archives of Iranian Medicine. 2017;20(4):211–7 0172004/AIM.005.

12. Petta S, Gastaldelli A, Rebelos E, et al. Pathophysiology of non alcoholic fatty liver disease. International Journal of Molecular Sciences. 2016;17(12). https://doi.org/10.3390/ijms17122082.
13. Wattacheril J, Sanyal AJ. Lean NAFLD: an underrecognized outlier. Curr Hepatol Reports. 2016;15(2):134–9. https://doi.org/10.1007/s11901-016-0302-1.
14. Lonardo A, Nascimbeni F, Maurantonio M, Marrazzo A, Rinaldi L, Adinolfi LE. Nonalcoholic fatty liver disease: evolving paradigms. World J Gastroenterol. 2017;23(36):6571–92. https://doi.org/10.3748/wjg.v23.i36.6571.
15. Conjeevaram Selvakumar PK, Kabbany MN, Lopez R, Rayas MS, Lynch JL, Alkhouri N. Prevalence of suspected nonalcoholic fatty liver disease in lean adolescents in the United States. J Pediatr Gastroenterol Nutr. 2018;67(1):75–9. https://doi.org/10.1097/MPG.0000000000001974.
16. Das KK, Das KK, Mukherjee PS, et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology. 2010;51(5):1593–602. https://doi.org/10.1002/hep.23567.
17. Younossi ZM, Stepanova M, Negro F, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine. 2012;91(6):319–27. https://doi.org/10.1097/MD.0b013e3182779d49.
18. Sinn DH, Kang D, Cho SJ, et al. Lean non-alcoholic fatty liver disease and development of diabetes: a cohort study. Eur J Endocrinol. 2019;181(2):185–92. https://doi.org/10.1530/EJE-19-0143.
19. 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(12):1852–8. https://doi.org/10.1038/ajg.2012.314.
20. Wei JL, Leung JCF, Loong TCW, 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;110(9):1306–14. https://doi.org/10.1038/ajg.2015.235.
21. Feng RN, Du SS, Wang C, et al. Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population. World J Gastroenterol. 2014;20(47):17932–40. https://doi.org/10.3748/wjg.v20.i47.17932.
22. Cho HC. Prevalence and factors associated with nonalcoholic fatty liver disease in a nonobese Korean population. Gut and Liver. 2016;10(1):117–25. https://doi.org/10.5009/gnl14444.
23. Chalasani N, Younossi Z, Lavine JE, 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;67(1):328–57. https://doi.org/10.1002/hep.29367.
24. Marchesini G, Day CP, Dufour JF, et al. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402. https://doi.org/10.1016/j.jhep.2015.11.004.
25. Association AD. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of medical care in diabetesd 2019. Diabetes Care. 2019;42(Supplement 1):S34–45. https://doi.org/10.2337/dc19-S004.
26. Vos MB, Abrams SH, Barlow SE, 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;64(2):319–34. https://doi.org/10.1097/MPG.0000000000001482.
27. Estrada E, Eneli I, Hampl S, et al. Children's hospital association consensus statements for comorbidities of childhood obesity. Child Obes. 2014;10(4):304–17. https://doi.org/10.1089/chi.2013.0120.
28. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120(Suppl 4). https://doi.org/10.1542/peds.2007-2329C.
29. Eslam M, Sarin SK, Wong VWS, et al. The asian pacific association for the study of the liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int. 2020. https://doi.org/10.1007/s12072-020-10094-2.
30. Jensen T, Wieland A, Cree-Green M, Nadeau K, Sullivan S. Clinical workup of fatty liver for the primary care provider. Postgrad Med. 2019;131(1):19–30. https://doi.org/10.1080/00325481.2019.1546532.
31. Kotronen A, Peltonen M, Hakkarainen A, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology. 2009;137(3):865–72. https://doi.org/10.1053/j.gastro.2009.06.005.
32. Cuthbertson DJ, Weickert MO, Lythgoe D, et al. External validation of the fatty liver index and lipid accumulation product indices, using 1H-magnetic resonance spectroscopy, to identify hepatic steatosis in healthy controls and obese, insulin-resistant individuals. Eur J Endocrinol. 2014;171(5):561–9. https://doi.org/10.1530/EJE-14-0112.
33. Kaya E, Bakir A, Kani HT, Demirtas CO, Keklikkiran C, Yilmaz Y. Simple noninvasive scores are clinically useful to exclude, not predict, advanced fibrosis: a study in turkish patients with biopsy-proven nonalcoholic fatty liver disease. Gut Liver. 2020;14(4):486–91. https://doi.org/10.5009/gnl19173.
34. Shah AG, Lydecker A, Murray K, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7(10):1104–12. https://doi.org/10.1016/j.cgh.2009.05.033.
35. Eren F, Kaya E, Yilmaz Y. Accuracy of Fibrosis-4 index and non-alcoholic fatty liver disease fibrosis scores in metabolic (dysfunction) associated fatty liver disease according to body mass index: failure in the prediction of advanced fibrosis in lean and morbidly obese individuals. Eur J Gastroenterol Hepatol. 2020.
36. Hsu CL, Wu FZ, Lin KH, et al. Role of fatty liver index and metabolic factors in the prediction of nonalcoholic fatty liver disease in a lean population receiving health checkup. Clinical and Translational Gastroenterology. 2019;10(5). https://doi.org/10.14309/ctg.0000000000000042.
37. Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6. https://doi.org/10.1186/1471-230X-6-33.
38. Bertot LC, Adams LA. The natural course of non-alcoholic fatty liver disease. International Journal of Molecular Sciences. 2016;17(5). https://doi.org/10.3390/ijms17050774.
39. Denkmayr L, Feldman A, Stechemesser L, et al. Lean patients with non-alcoholic fatty liver disease have a severe histological phenotype similar to obese patients. J Clin Med. 2018;7(12):562. https://doi.org/10.3390/jcm7120562.
40. Rinaldi L, Valente G, Piai G. Serial liver stiffness measurements and monitoring of liver-transplanted patients in a real-life clinical practice. Hepatitis Monthly. 2016;16(12). https://doi.org/10.5812/hepatmon.41162.
41. Yilmaz Y. NAFLD in the absence of metabolic syndrome: different epidemiology, pathogenetic mechanisms, risk factors for disease progression? Semin Liver Dis. 2012;32(1):14–21.
42. Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. JHEP Reports. 2019;1(4):329–41. https://doi.org/10.1016/j.jhepr.2019.08.002.

43. Li C, Guo P, Okekunle AP, et al. 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 Gastroenterology and Hepatology (Australia). 2019;34(1):256–62. https://doi.org/10.1111/jgh.14360.
44. Jensen T, Abdelmalek MF, Sullivan S, et al. Fructose and sugar: a major mediator of non-alcoholic fatty liver disease. J Hepatol. 2018;68(5):1063–75. https://doi.org/10.1016/j.jhep.2018.01.019.
45. Parks EJ, Skokan LE, Timlin MT, Dingfelder CS. Dietary sugars stimulate fatty acid synthesis in adults. J Nutr. 2008;138(6):604S–15S. https://doi.org/10.1093/jn/138.6.1039.
46. Ouyang X, Cirillo P, Sautin Y, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. J Hepatol. 2008;48(6):993–9. https://doi.org/10.1016/j.jhep.2008.02.011.
47. Abdelmalek MF, Suzuki A, Guy C, et al. Increased fructose consumption is associated with fibrosis severity in patients with non-alcoholic fatty liver disease. Hepatology. 2010;51(6):1961–71. https://doi.org/10.1002/hep.23535.
48. Ishimoto T, Lanaspa MA, Rivard CJ, et al. High-fat and high-sucrose (western) diet induces steatohepatitis that is dependent on fructokinase. Hepatology. 2013;58(5):1632–43. https://doi.org/10.1002/hep.26594.
49. Lanaspa MA, Ishimoto T, Li N, et al. Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome. Nat Commun. 2013;4:1–8. https://doi.org/10.1038/ncomms3434.
50. Lanaspa MA, Kuwabara M, Andres-Hernando A, et al. High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. Proc Natl Acad Sci U S A. 2018;115(12):3138–43. https://doi.org/10.1073/pnas.1713837115.
51. Roncal-Jimenez CA, Lanaspa MA, Rivard CJ, et al. Sucrose induces fatty liver and pancreatic inflammation in male breeder rats independent of excess energy intake. Metab Clin Exp. 2011;60(9):1259–70. https://doi.org/10.1016/j.metabol.2011.01.008.
52. Slone D, Taitz LS, Gilchrist GS. Aspects of carbohydrate metabolism in kwashiorkor. Br Med J. 1961;1(5218):32–4. https://doi.org/10.1136/bmj.1.5218.32.
53. Williams CD. Kwashiorkor: a nutritional disease of children associated with a maize diet. 1935. Lancet 1935;ii:1151–1152 Reprinted in Bulletin of the World Health Organization. 2003;81(12):912–913. https://doi.org/10.1590/S0042-96862003001200011
54. Assy N, Nasser G, Kamayse I, et al. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. Can J Gastroenterol. 2008;22(10):811–6. https://doi.org/10.1155/2008/810961.
55. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): a population based study. J Hepatol. 2007;47(5):711–7. https://doi.org/10.1016/j.jhep.2007.06.020.
56. Lanaspa MA, Sanchez-Lozada LG, Choi YJ, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. J Biol Chem. 2012;287(48):40732–44. https://doi.org/10.1074/jbc.M112.399899.
57. Bergheim I, Weber S, Vos M, et al. Antibiotics protect against fructose-induced hepatic lipid accumulation in mice: role of endotoxin. J Hepatol. 2008;48(6):983–92. https://doi.org/10.1016/j.jhep.2008.01.035.
58. Cho YE, Kim DK, Seo W, Gao B, Yoo SH, Song BJ. Fructose promotes leaky gut, Endotoxemia, and liver fibrosis through ethanol-inducible cytochrome P450-2E1–mediated oxidative and nitrative stress. Hepatology. 2019. https://doi.org/10.1002/hep.30652.
59. Safari Z, Gérard P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). Cell Mol Life Sci. 2019;76(8):1541–58. https://doi.org/10.1007/s00018-019-03011-w.
60. Yun Y, Kim HN, Lee E ju, et al. Fecal and blood microbiota profiles and presence of nonalcoholic fatty liver disease in obese versus lean subjects. PLoS ONE. 2019;14(3). https://doi.org/10.1371/journal.pone.0213692
61. Chen F, Esmaili S, Rogers GB, et al. Lean NAFLD: a distinct entity shaped by differential metabolic adaptation. Hepatology. January 2020:hep.30908. https://doi.org/10.1002/hep.30908
62. Ma J, Zhou Q, Li H. Gut microbiota and nonalcoholic fatty liver disease: Insights on mechanisms and therapy. Nutrients. 2017;9(10). https://doi.org/10.3390/nu9101124.
63. Kolodziejczyk AA, Zheng D, Shibolet O, Elinav E. The role of the microbiome in NAFLD and NASH. EMBO Molecular Medicine. 2019;11(2). https://doi.org/10.15252/emmm.201809302.
64. Adejumo AC, Alliu S, Ajayi TO, et al. Cannabis use is associated with reduced prevalence of non-alcoholic fatty liver disease: A cross-sectional study. PLoS ONE. 2017;12(4). https://doi.org/10.1371/journal.pone.0176416
65. Kim D, Kim W, Kwak MS, Chung GE, Yim JY, Ahmed A. Inverse association of marijuana use with nonalcoholic fatty liver disease among adults in the United States. PLoS ONE. 2017;12(10). https://doi.org/10.1371/journal.pone.0186702.
66. Farooqui MT, Khan MA, Cholankeril G, et al. Marijuana is not associated with progression of hepatic fibrosis in liver disease: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2019;31(2):149–56. https://doi.org/10.1097/MEG.0000000000001263.
67. Purohit V, Rapaka R, Shurtleff D. Role of cannabinoids in the development of fatty liver (steatosis). AAPS Journal. 2010;12(2):233–7. https://doi.org/10.1208/s12248-010-9178-0.
68. Lin YC, Lian I bin, Kor CT, et al. Association between soil heavy metals and fatty liver disease in men in Taiwan: A cross sectional study. BMJ Open. 2017;7(1). https://doi.org/10.1136/bmjopen-2016-014215
69. Cave M, Falkner KC, Ray M, et al. Toxicant-associated steatohepatitis in vinyl chloride workers. Hepatology. 2010;51(2):474–81. https://doi.org/10.1002/hep.23321.
70. Cotrim HP, de Freitas LAR, Freitas C, et al. Clinical and histopathological features of NASH in workers exposed to chemicals with or without associated metabolic conditions. Liver Int. 2004;24(2):131–5. https://doi.org/10.1111/j.1478-3231.2004.0897.x.
71. Kumarendran B, O'Reilly MW, Manolopoulos KN, et al. Polycystic ovary syndrome, androgen excess, and the risk of non-alcoholic fatty liver disease in women: A longitudinal study based on a United Kingdom primary care database. Myers JE, ed. PLOS Medicine. 2018;15(3):e1002542. https://doi.org/10.1371/journal.pmed.1002542
72. Cree-Green M, Rahat H, Newcomer BR, et al. Insulin resistance, Hyperinsulinemia, and mitochondria dysfunction in nonobese girls with polycystic ovarian syndrome. Journal of the Endocrine Society. 2017;1(7):931–44. https://doi.org/10.1210/js.2017-00192.
73. Pang Q, Zhou L, Jin H, Man ZR, Liu HC. Letter: non-alcoholic fatty liver disease and polycystic ovary syndrome-evidence for low vitamin D status contributing to the link. Aliment Pharmacol Ther. 2017;46(5):566–7. https://doi.org/10.1111/apt.14159.
74. Kim JJ, Kim D, Yim JY, et al. Polycystic ovary syndrome with hyperandrogenism as a risk factor for non-obese non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2017;45(11):1403–12. https://doi.org/10.1111/apt.14058.

75. Del Campo JA, Gallego-Duran R, Gallego P, Grande L. Genetic and epigenetic regulation in nonalcoholic fatty liver disease (NAFLD). Int J Mol Sci. 2018;19(3).
76. Petersen KF, Dufour S, Hariri A, et al. Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease. N Engl J Med. 2010;362(12):1082–9. https://doi.org/10.1056/NEJMoa0907295.
77. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008;40(12):1461–5. https://doi.org/10.1038/ng.257.
78. Abul-Husn NS, Cheng X, Li AH, et al. A protein-truncating *HSD17B13* variant and protection from chronic liver disease. N Engl J Med. 2018;378(12):1096–106. https://doi.org/10.1056/NEJMoa1712191.
79. Fracanzani AL, Petta S, Lombardi R, et al. Liver and cardiovascular damage in patients with lean nonalcoholic fatty liver disease, and association with visceral obesity. Clinical Gastroenterology and Hepatology. 2017;15(10):1604–1611.e1. https://doi.org/10.1016/j.cgh.2017.04.045.
80. Feldman A, Eder SK, Felder TK, et al. Clinical and metabolic characterization of lean Caucasian subjects with non-alcoholic fatty liver. Am J Gastroenterol. 2017;112(1):102–10. https://doi.org/10.1038/ajg.2016.318.
81. Trépo E, Romeo S, Zucman-Rossi J, Nahon P. PNPLA3 gene in liver diseases. J Hepatol. 2016;65(2):399–412. https://doi.org/10.1016/j.jhep.2016.03.011.
82. Pingitore P, Romeo S. The role of PNPLA3 in health and disease. Biochim Biophys Acta Mol Cell Biol Lipids. 2019;1864(6):900–6. https://doi.org/10.1016/j.bbalip.2018.06.018.
83. Shen J, Wong GLH, Chan HLY, et al. PNPLA3 gene polymorphism and response to lifestyle modification in patients with non-alcoholic fatty liver disease. Journal of Gastroenterology and Hepatology (Australia). 2015;30(1):139–46. https://doi.org/10.1111/jgh.12656.
84. Nishioji K, Mochizuki N, Kobayashi M, 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). https://doi.org/10.1371/journal.pone.0140427
85. Honda Y, Yoneda M, Kessoku T, et al. Characteristics of non-obese non-alcoholic fatty liver disease: effect of genetic and environmental factors. Hepatol Res. 2016;46(10):1011–8. https://doi.org/10.1111/hepr.12648.
86. Fan JG, Kim SU, Wong VWS. New trends on obesity and NAFLD in Asia. J Hepatol. 2017;67(4):862–73. https://doi.org/10.1016/j.jhep.2017.06.003.
87. Kozlitina J, Smagris E, Stender S, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2014;46(4):352–6. https://doi.org/10.1038/ng.2901.
88. Wong VWS, Wong GLH, Tse CH, Chan HLY. Prevalence of the TM6SF2 variant and non-alcoholic fatty liver disease in Chinese. J Hepatol. 2014;61(3):708–9. https://doi.org/10.1016/j.jhep.2014.04.047.
89. Luukkonen PK, Tukiainen T, Juuti A, et al. Hydroxysteroid 17-β dehydrogenase 13 variant increases phospholipids and protects against fibrosis in nonalcoholic fatty liver disease. JCI Insight. 2020;5(5). https://doi.org/10.1172/jci.insight.132158.
90. Kim D, Kim WR. Nonobese fatty liver disease. Clin Gastroenterol Hepatol. 2017;15(4):474–85. https://doi.org/10.1016/j.cgh.2016.08.028.
91. Adams LA, Marsh JA, Ayonrinde OT, et al. Cholesteryl ester transfer protein gene polymorphisms increase the risk of fatty liver in females independent of adiposity. Journal of Gastroenterology and Hepatology (Australia). 2012;27(9):1520–7. https://doi.org/10.1111/j.1440-1746.2012.07120.x.
92. Musso G, Cassader M, Bo S, de Michieli F, Gambino R. Sterol regulatory element-binding factor 2 (SREBF-2) predicts 7-year NAFLD incidence and severity of liver disease and lipoprotein and glucose dysmetabolism. Diabetes. 2013;62(4):1109–20. https://doi.org/10.2337/db12-0858.
93. Santoro N, Caprio S, Pierpont B, van Name M, Savoye M, Parks EJ. Hepatic *de novo* lipogenesis in obese youth is modulated by a common variant in the GCKR gene. J Clin Endocrinol Metab. 2015;100(8):E1125–32. https://doi.org/10.1210/jc.2015-1587.
94. Petta S, Miele L, Bugianesi E, et al. Glucokinase regulatory protein gene polymorphism affects liver fibrosis in non-alcoholic fatty liver disease. PLoS ONE. 2014;9(2). https://doi.org/10.1371/journal.pone.0087523
95. Gao H, Liu S, Zhao Z, et al. Association of GCKR gene polymorphisms with the risk of nonalcoholic fatty liver disease and coronary artery disease in a chinese northern han population. Journal of Clinical and Translational Hepatology. 2019;X(X):1–7. https://doi.org/10.14218/jcth.2019.00030.
96. Mohammadi S, Farajnia S, Shadmand M, Mohseni F, Baghban R. Association of rs780094 polymorphism of glucokinase regulatory protein with non-alcoholic fatty liver disease. BMC Research Notes. 2020;13(1). https://doi.org/10.1186/s13104-020-4891-y.
97. Lin YC, Chang PF, Chang MH, Ni YH. Genetic variants in GCKR and PNPLA3 confer susceptibility to nonalcoholic fatty liver disease in obese individuals. Am J Clin Nutr. 2014;99(4):869–74. https://doi.org/10.3945/ajcn.113.079749.
98. Gambarin-Gelwan M, Kinkhabwala S. V., Schiano TD, Bodian C, Yeh HC, Futterweit W. prevalence of nonalcoholic fatty liver disease in women with polycystic ovary syndrome. Clin Gastroenterol Hepatol. 2007;5(4):496–501. https://doi.org/10.1016/j.cgh.2006.10.010.
99. Gonzalez-Cantero J, Martin-Rodriguez JL, Gonzalez-Cantero A, Arrebola JP, Gonzalez-Calvin JL. Insulin resistance in lean and overweight nondiabetic Caucasian adults: Study of its relationship with liver triglyceride content, waist circumference and BMI. PLoS ONE. 2018;13(2). https://doi.org/10.1371/journal.pone.0192663.
100. Kumar R, Rastogi A, Sharma M, et al. 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 Journal of Endocrinology and Metabolism. 2013;17(4):665. https://doi.org/10.4103/2230-8210.113758.
101. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology. 2003;37(4):917–23. https://doi.org/10.1053/jhep.2003.50161.
102. Fracanzani AL, Valenti L, Bugianesi E, et al. Risk of nonalcoholic steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease and low visceral adiposity. J Hepatol. 2011;54(6):1244–9. https://doi.org/10.1016/j.jhep.2010.09.037.
103. Keating SE, Hackett DA, Parker HM, et al. Effect of aerobic exercise training dose on liver fat and visceral adiposity. J Hepatol. 2015;63(1):174–82. https://doi.org/10.1016/j.jhep.2015.02.022.
104. st. George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Independent effects of physical activity in patients with nonalcoholic fatty liver disease. Hepatology 2009;50(1):68–76. https://doi.org/10.1002/hep.22940.
105. Winn NC, Liu Y, Rector RS, Parks EJ, Ibdah JA, Kanaley JA. Energy-matched moderate and high intensity exercise training improves nonalcoholic fatty liver disease risk independent of changes in body mass or abdominal adiposity — a randomized trial. Metab Clin Exp. 2018;78:128–40. https://doi.org/10.1016/j.metabol.2017.08.012.

106. Kim HK, Park JY, Lee KU, et al. Effect of body weight and lifestyle changes on long-term course of nonalcoholic fatty liver disease in Koreans. Am J Med Sci. 2009;337(2):98–102.
107. Rabøl R, Petersen KF, Dufour S, Flannery C, Shulman GI. Reversal of muscle insulin resistance with exercise reduces postprandial hepatic *de novo* lipogenesis in insulin resistant individuals. Proc Natl Acad Sci U S A. 2011;108(33):13705–9. https://doi.org/10.1073/pnas.1110105108.
108. Holt HB, Wild SH, Wareham N, et al. Differential effects of fatness, fitness and physical activity energy expenditure on whole-body, liver and fat insulin sensitivity. Diabetologia. 2007;50(8):1698–706. https://doi.org/10.1007/s00125-007-0705-1.
109. Devries MC, Samjoo IA, Hamadeh MJ, Tarnopolsky MA. Effect of endurance exercise on hepatic lipid content, enzymes, and adiposity in men and women. Obesity. 2008;16(10):2281–8. https://doi.org/10.1038/oby.2008.358.
110. Zelber-Sagi S, Buch A, Yeshua H, et al. Effect of resistance training on non-alcoholic fatty-liver disease a randomized-clinical trial. World J Gastroenterol. 2014;20(15):4382–92. https://doi.org/10.3748/wjg.v20.i15.4382.
111. 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(3):341–6. https://doi.org/10.3109/00365521.2014.983160.
112. Montesi L, Caselli C, Centis E, et al. Physical activity support or weight loss counseling for nonalcoholic fatty liver disease? World J Gastroenterol. 2014;29:10128–36. https://doi.org/10.3748/wjg.v20.i29.10128.
113. Moscatiello S, Di Luzio R, Bugianesi E, et al. Cognitive-behavioral treatment of nonalcoholic fatty liver disease: a propensity score-adjusted observational study. Obesity (Silver Spring). 2011;19(4):763–70.
114. 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. December 2019. https://doi.org/10.1097/meg.0000000000001656.
115. Thiagarajan P, Aithal GP. Drug development for nonalcoholic fatty liver disease: landscape and challenges. Journal of Clinical and Experimental Hepatology. 2019;9(4):515–21. https://doi.org/10.1016/j.jceh.2019.03.002.
116. Sanyal AJ, Chalasani N, Kowdley K v., et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362(18):1675–1685. doi:https://doi.org/10.1056/NEJMoa0907929.
117. Abner EL, Schmitt FA, Mendiondo MS, Marcum JL, Kryscio RJ. Vitamin E and all-cause mortality: a meta-analysis. Curr Aging Sci. 2011;4(2):158–70.
118. El Hadi H, Vettor R, Rossato M. Vitamin E as a treatment for nonalcoholic fatty liver disease: reality or myth? Antioxidants (Basel). 2018;7(1).
119. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142(1):37–46.
120. Pacana T, Sanyal AJ. Vitamin E and nonalcoholic fatty liver disease. Curr Opin Clin Nutr Metab Care. 2012;15(6):641–8.
121. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the selenium and vitamin E cancer prevention trial (SELECT). JAMA. 2011;306(14):1549–56.
122. Schurks M, Glynn RJ, Rist PM, Tzourio C, Kurth T. Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials. BMJ. 2010;341:c5702.
123. Younossi ZM, Ratziu V, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2019;394(10215):2184–96. https://doi.org/10.1016/S0140-6736(19)33041-7.
124. Ipsen DH, Rolin B, Rakipovski G, et al. Liraglutide decreases hepatic inflammation and injury in advanced lean non-alcoholic Steatohepatitis. Basic Clin Pharmacol Toxicol. 2018;123(6):704–13. https://doi.org/10.1111/bcpt.13082.
125. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387(10019):679–90. https://doi.org/10.1016/S0140-6736(15)00803-X.
126. Cruz AC dela, Bugianesi E, George J, et al. 379 Characteristics and long-term prognosis of lean patients with nonalcoholic fatty liver disease. Gastroenterology. 2014;146(5):S-909. https://doi.org/10.1016/s0016-5085(14)63307-2