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Review Article

Nonalcoholic Fatty Liver Disease in Lean/Nonobese and Obese Individuals: A Comprehensive Review on Prevalence, Pathogenesis, Clinical Outcomes, and Treatment

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, with an estimated prevalence of 25% globally. NAFLD is closely associated with metabolic syndrome, which are both becoming increasingly more common with increasing rates of insulin resistance, dyslipidemia, and hypertension. Although NAFLD is strongly associated with obesity, lean or nonobese NAFLD is a relatively new phenotype and occurs in patients without increased waist circumference and with or without visceral fat. Currently, there is limited literature comparing and illustrating the differences between lean/nonobese and obese NAFLD patients with regard to risk factors, pathophysiology, and clinical outcomes. In this review, we aim to define and further delineate different phenotypes of NAFLD and present a comprehensive review on the prevalence, incidence, risk factors, genetic predisposition, and pathophysiology. Furthermore, we discuss and compare the clinical outcomes, such as insulin resistance, dyslipidemia, hypertension, coronary artery disease, mortality, and progression to nonalcoholic steatohepatitis, among lean/nonobese and obese NAFLD patients. Finally, we summarize the most up to date current management of NAFLD, including lifestyle interventions, pharmacologic therapies, and surgical options.

Keywords: NAFLD; Lean or nonobese nonalcoholic fatty liver disease; Obese nonalcoholic fatty liver disease; Clinical outcomes; Treatment; Incidence; Prevalence; Risk factors.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; CRP, C-reactive protein; FFA, free fatty acid; FGF 19, fibroblast growth factor 19; FIB-4, fibrosis-4; FLI, fatty liver index; GGT, gamma-glutamyl transferase; IL-6, interleukin 6; IR, insulin resistance; LXRa, liver X receptor alpha; MRI, magnetic resonance imaging; MRI-PDFF, MRI proton density fat fraction; MRS, proton magnetic resonance spectroscopy; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES III, National Health and Nutrition Examination Survey III; PNPLA3, patanin-like phospholipase domain-containing protein 3; T2DM, type 2 diabetes mellitus; TE, transient elastography; TM6SF2, transmembrane 6 superfamily 2; TNF-α, tumor necrosis factor alpha; UPP, ubiquitin-proteasome proteolytic pathway; US, ultrasound.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, with an estimated prevalence of 25% globally.[1,2] NAFLD encompasses a disease spectrum that ranges in severity from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis.[2,3] While NAFLD is usually asymptomatic, an estimated 25% of NASH patients may develop cirrhosis, and 10% will develop decompensated liver disease.[3,4] Patients with NAFLD do not typically require medical therapy and should, instead, pursue lifestyle modifications; however, NASH, especially NASH-fibrosis, are targets for liver-directed medical therapy and innovative interventions, such as clinical trials.[5,6] Although liver-related death is currently the third leading cause of death in NAFLD patients,[7–9] NASH related fibrosis is the most rapidly rising cause of liver transplantation and is projected to be the leading cause in the coming years.[10] Furthermore, fibrosis in NAFLD/NASH is expected to become the leading risk factor for liver-related mortality.[10]

NAFLD is the hepatic manifestation of MetS due to its association with obesity-induced insulin resistance, dyslipidemia, and hypertension.[11,12] Although NAFLD is strongly associated with obesity, NAFLD occurs in clinically obese and nonobese (lean) patients.[13,14] Lean/nonobese NAFLD patients can be further subdivided into two categories, (1) overweight with or without excess visceral fat or normal weight with excess visceral fat and (2) lean with no excess visceral fat mass.[13] Risk factors for lean/nonobese NAFLD include central obesity, physical inactivity, weight gain, genetic predisposition, high fructose intake, protein malnutrition, and steatogenic drug usage (amiodarone, tamoxifen, methotrexate, prednisolone).[11,14] A Mediterranean diet has

been demonstrated to help alleviate hepatic insulin sensitivity and reduce hepatic fat accumulation, while a diet consisting of high fructose and saturated fats is correlated with NAFLD development and progression.[15,16]

The definition of lean/nonobese NAFLD and body mass index (BMI) categorization are not standardized globally and have made literature interpretation difficult. Studies have shown that Asians have a higher proportion of body fat and elevated type 2 diabetes mellitus (T2DM), hyperlipidemia, and hypertension prevalence at a lower BMI than Europeans.[17,18] An estimated 8–19% of Asians with a body mass index <25 kg/m^2 have NAFLD.[18] As a result, definitions of overweight and obesity are generally more stringent than those in Western populations. Asian NAFLD patients with BMI <23 kg/m^2 and <25 kg/m^2 for non-Asians are considered lean/nonobese NAFLD patients. The BMI cutoffs for nonobese NAFLD are <25 kg/m^2 for Asian populations, and <30 kg/m^2 for non-Asian populations.[17,19,20] There is currently limited literature comparing outcomes in lean/nonobese NAFLD and obese NAFLD patients. To address this knowledge gap, we aimed to conduct a comprehensive review to explore the differences between the subgroups of NAFLD patients.

Clinical definition

NAFLD is defined as the presence of hepatic steatosis, by imaging or histology, in the absence of a secondary cause such as hepatic viral infection(s), drug-induced hepatotoxicity, excessive alcohol consumption, or hereditary disorders.[11,21,22] NAFLD encompasses a spectrum of histological states ranging in severity from simple intrahepatic fat accumulations, nonalcoholic fatty liver (NAFL), to necrotic inflammation in the presence of ballooned hepatocytes, NASH. NAFL is defined as steatosis in greater than five percent of hepatocytes without additional hepatocellular damage (i.e. ballooning of hepatocytes or cirrhosis).[11,22,23] NASH encompasses more advanced hepatic damage steatosis in greater than five percent of hepatocytes, inflammation, and hepatocyte injury with or without fibrosis. Patients with NASH can further develop NASH-cirrhosis, which is recognized by the presence of regenerative nodules enclosed by fibrous bands that results in portal hypertension and end-stage liver disease.[24]

Epidemiology

Disease prevalence

The prevalence of NAFLD has shown an upward trend over the past few decades. In a systematic review, the global prevalence of lean and nonobese NAFLD among the general population was 5.1% and 12.1%, respectively.[25] The prevalence of NAFLD among the lean patients was 10.6% and 18.3% in nonobese individuals, both lower than the 25% prevalence estimate in the general population.[25] The variability in prevalence rates between studies may be attributed to several factors, including patient selection, diagnostic criteria, BMI cutoff values, and lifestyle differences in the investigated population.

Studies have also shown regional differences in NAFLD prevalence. Those differences might be attributed to industrialization, lifestyle, diet, and genetic predisposition.[26–28] In a systematic review and meta-analysis by Lu *et al*.,[29] the prevalence of lean NAFLD was highest in Asia (4.8%), followed by Oceania (3.5%), North America (3.1%), and the lowest in Europe (2.2%). In an estimate of prevalence by country, the USA had the lowest prevalence of lean NAFLD (3.1%), whereas China had the highest prevalence (5.5%).

In a study conducted in the US using data from the National Health and Nutrition Examination Survey III (NHANES III), 18.8% had NAFLD and 3.7% had lean NAFLD. The overall prevalence of NAFLD in lean subjects was 9.67%.[30] In a more recent study from the USA, 29.7% and 13.6% of NAFLD subjects were nonobese and lean, respectively.[31] The overall NAFLD prevalence in Korea is estimated to be 20.1%, with NAFLD prevalence ranging from 12.6 to 27.4% in nonobese individuals.[32,33] Furthermore, the prevalence of lean NAFLD in Korea is estimated to be 11%.[34] In a study of 1,779 Chinese individuals with a BMI <24 kg/m^2, 7.5% of individuals had ultrasound-detected liver steatosis.[35] Additionally, in a Chinese population study, NAFLD prevalence was 7.3% in nonobese subjects.[36] In a study from Hong Kong, the prevalence of NAFLD detected via proton-MRI spectroscopy was 14.8% in nonobese individuals.[37] A study from Japan showed the prevalence of nonobese NAFLD to be 12.6%.[38] In a study from rural India, the overall prevalence of NAFLD and prevalence among lean (BMI <23 kg/m^2) patients was 8.7% and 5.1%, respectively. In a study from northern Italy, the prevalence of NAFLD in a lean, non-drinking population was 16.4%. The variability in the data suggests that further studies with standardized criteria and accurate diagnostic tools are needed to provide a more accurate prevalence of lean NAFLD/NASH worldwide.

Disease incidence

Limited data on NAFLD incidence have been reported in the literature.[11,39–41] A 5 year follow-up study found the NAFLD incidence on ultrasound to be 12%.[11] Another study conducted in Israel reported a NAFLD incidence rate of 28 per 1,000 person-years.[11,41] A Japanese study of 11,500 adults reported a 5 year cumulative NAFLD incidence of 10%.[42] A study conducted in England estimated the incidence rate of NAFLD to be 29 per 1,000 person-years. The pooled regional NAFLD incidence rate was quantified to be 52.3 per 1,000 person-years (95% CI: 28.3–96.8) and 28.00 per 1,000 person-years (95% CI: 19.3–40.6) in Asia and Western countries, respectively.[11,41] In a meta-analysis of five studies, the NAFLD incidence in lean patients was (23.2 [95% CI: 7.3–48.0] per 1,000 person-years.[25] Similarly, the study found NAFLD incidence in nonobese individuals to be 24·6 (95% CI: 13.4–39.2) per 1,000 person-years. In contrast, NAFLD incidence in the obese population was 77.5 (95% CI: 28.3–150.6) per 1,000 person-years.

Diagnostic procedures in NAFLD

The diagnostic workup of NAFLD combines both invasive and noninvasive procedures. Liver biopsy is the gold standard for prognostication and diagnosis, confirming the pattern of injury, distribution and grade of steatosis, and fibrosis stage. However, this procedure is limited by its invasiveness and intra- and interobserver variability in pathological interpretations. With the rising global incidence of NAFLD, routine liver biopsy is not a feasible first-line tool in diagnosing and staging NAFLD. As a result, noninvasive diagnostic tools such as serum biomarkers/panels, elastography-based tests, and MRI-based imaging have been commonly used to detect NAFLD.[43]

Clinical prediction rules such as fibrosis-4 (FIB-4) and fatty liver index (FLI) provide viable information for risk stratification. FIB-4 is a noninvasive scoring estimate of liver scarring using age, aspartate transaminase (AST), alanine transaminase (ALT), and platelet count that is well

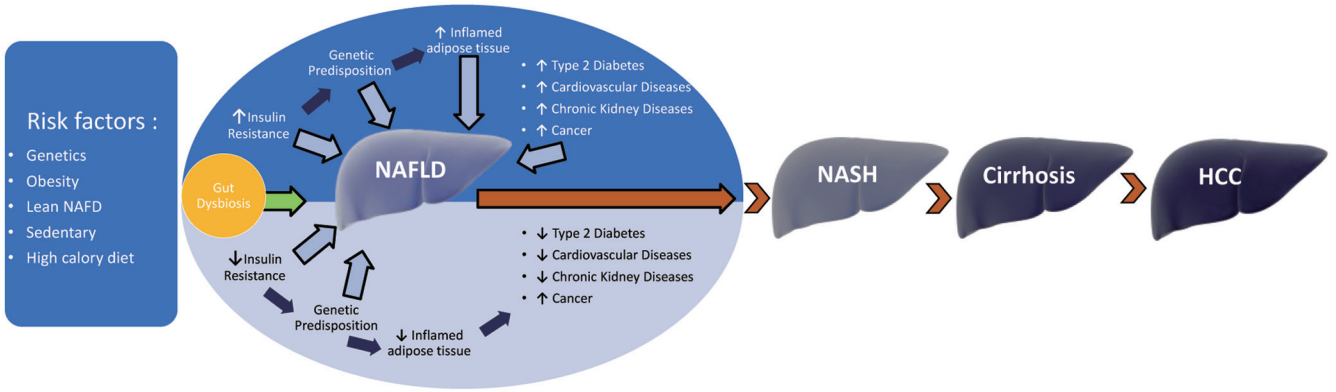

Fig. 1. Schematic representation of the pathogenesis of NAFLD and progression from NAFLD to NASH, cirrhosis, and HCC. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; HCC, Hepatocellular carcinoma.

validated, but is more useful in excluding fibrosis than identifying it.[44] The FLI uses BMI, waist circumference, gamma-glutamyl transferase (GGT), and triglyceride in its scoring estimate and has been well validated in the lean NAFLD population, with Hsu *et al*.[45] identifying FLI ≥15 as a cutoff for screening for lean NAFLD.[44,45] Serum biomarkers and blood-based panels, including NAFLD liver fat score and the SteatoTest, are noninvasive diagnostic tools used to predict and identify presence of hepatic steatosis. NAFLD liver fat score uses presence of MetS, T2DM, insulin level, AST, and ALT/AST ratio. Although it has been shown to adequately identify hepatic steatosis with an area under the curve of 0.87, the use of insulin level, which is not routinely measured, limits its use.[46] SteatoTest is a panel which combines six FibroTest elements (α2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin and ALT) as well as BMI, TGs, cholesterol, and serum glucose. It is adjusted for sex and age, has shown to have good accuracy in predicting hepatic steatosis confirmed by hepatic biopsy (area under the curve =0.80).[47] However, the test is expensive and unable to determine the degree of steatosis. Other serum biomarkers (e.g., proteomics, metabolomics, lipidomics) are currently being investigated to elucidate specific molecules that may be useful in predicting NAFLD.

Noninvasive diagnostics further include abdominal ultrasound (US), elastography-based tests such as vibration-controlled transient elastography (TE), or magnetic resonance-based imaging (MRI). According to a meta-analysis comparing ultrasound findings to histopathologic findings, abdominal ultrasound had a sensitivity of 85% and a specificity of 94% for moderate to severe fatty liver diagnosis.[48] However, pitfalls of ultrasound include dependence on the ultrasound technician and decreased accuracy in patients with morbid obesity or hepatic steatosis of less than 20%.[48]

TE is a more sensitive method than ultrasound alone for detecting liver steatosis with low-fat content. The controlled attenuation parameter (CAP) measurement by TE allows for the quantification of liver fat via evaluation of ultrasound attenuation in the liver. As a result, this method is more sensitive than ultrasound alone and can detect histopathological grade 1 steatosis (5–33% fat content in the liver) with a sensitivity of 69% and a specificity of 82%.[48] MRI-based diagnostic tools for quantifying liver steatosis include MRI Elastography (MRE), MRI proton density fat fraction (MRI-PDFF), and proton magnetic spectroscopy (MRS). MRE has been shown to demonstrate a higher diagnostic accuracy compared to TE for the detection of individual stages of fibrosis.[49,50] However, other studies have found MRE to be superior to TE in specific degrees of fibrosis.[51,52] Therefore, these modalities need further statistical validation and are less commonly used due to expensive equipment.[48]

Pathophysiology

In previous years, the prevailing dogma regarding NAFLD pathogenesis revolved around a two hit hypothesis in which insulin resistance (IR) serves as the first hit by inducing lipid accumulation in hepatocytes and thereby increasing the vulnerability of the liver to a second hit that can cause hepatic injury, inflammation, and fibrosis.[53,54] Recent evidence suggests that NAFLD is a multifactorial disease resulting from a complex interaction of multiple risk factors such as insulin resistance, fat distribution/metabolic dysfunction, gut microbiota dysbiosis, dietary factors, physical inactivity, sarcopenia, and genetic predisposition (Fig. 1).[55,56] While lean NAFLD shares several pathophysiological mechanisms with obese NAFLD, multiple studies have proposed unique roles of the aforementioned risk factors in lean NAFLD pathogenesis.[57,58]

IR

IR plays a major role in the development of obese NAFLD, but recent evidence shows that it also plays a major role in developing lean NAFLD.[59–61] Studies in lean individuals highlighted that IR is more commonly observed in NAFLD patients than in healthy subjects and revealed that higher intrahepatic triglyceride content is associated with increased IR in skeletal muscles, hepatocytes, and adipose tissue regardless of BMI.[57,59–61] IR contributes to hepatic steatosis by accumulating excess free fatty acids (FFAs) in the liver via enhanced de novo lipogenesis, decreased oxidation, and increased uptake.[61–63] Studies have shown that a significant proportion of lean NAFLD patients have insulin resistance in the absence of other metabolic risk factors.[59,61] However, other studies have revealed a far lower degree of insulin resistance in the lean NAFLD population.[30,64] The discordance between the presence or absence of insulin resistance in this population may be explained by other factors, such as genetic predisposition, that may confer susceptibility to NAFLD without insulin resistance. Gastaldelli *et al*.[65] showed severe insulin resistance in adipose tissue in patients with NASH independent of the degree of obesity. Additionally, another study found lean patients with NAFLD to have insulin resistance and dysfunctional adipose tissue.[57] Further studies are warranted to better

understand insulin resistance in this population and how the underlying mechanisms may be different compared to obese NAFLD patients.

Fat distribution and metabolic dysfunction

Abdominal fat distribution is a critical factor implicated in metabolic dysfunction. A higher visceral-to subcutaneous fat ratio is associated with an increased risk of NAFLD development and progression to fibrosis.[56] The findings are supported by a recent biopsy-based study of 250 lean living liver donors that found that the severity of NAFLD was positively correlated with visceral fat accumulation.[66] The specific inflammatory pathways implicated in lean NAFLD pathophysiology have yet to be elucidated, with multiple studies debating the role of key cytokines in the progression of the disease.[57,67,68] Similar to obesity-related NAFLD, one study found that lean individuals with NAFLD present decreased adiponectin levels, an anti-inflammatory hormone with an insulin-sensitizing effect.[57,69] Additionally, animal models provide preliminary evidence implicating interleukin 6 (IL6) overexpression in the pathogenesis of NAFLD regardless of weight.[68] However, other studies have found that alterations in tumor necrosis factor alpha (TNF- α), IL6, and leptin levels are not significantly different between nonobese NAFLD subjects and healthy controls.[57] Further research is needed to elucidate the true impacts of cytokines in lean NAFLD pathophysiology.

Gut microbiota dysbiosis

The gut microbiome and bile acids contribute significantly to metabolic homeostasis, and emerging evidence implicates the dysfunction of these entities in NAFLD pathogenesis. A change in the microbial environment marks gut microbial dysbiosis through an increase in pathogenic bacteria and a decrease in the number of beneficial bacteria.[70] This dysbiosis is hypothesized to contribute to NAFLD through multiple mechanisms, including increased gut permeability, endotoxemia, endogenous ethanol production, increased energy harvest from food, and alterations in choline and bile acid metabolism, all resulting in liver inflammation and steatosis.[70] Recent studies highlight that lean NAFLD subjects have a distinct gut microbiota profile from obese ones.[56] In a study conducted in a Chinese population, lean NAFLD subjects demonstrated a reduced population of Firmicutes, including Lachnospiraceae, Ruminococcaceae, Lactobacillaceae, and an increase in lipopolysaccharide-producing Gram-negative bacteria.[71] Chen *et al*.[72] similarly reported a distinct microbiome profile in a Caucasian population of lean NAFLD patients who were found to have an increased population of Ruminococcaceae compared to obese NAFLD patients and an increased population of Dorea and decreased populations of Marvinbryantia and Christensellenaceae compared with healthy controls. Furthermore, compared to their non-lean counterparts, the lean NAFLD subjects included in this study displayed an obesity-resistant phenotype partially mediated by higher total bile acid and fibroblast growth factor 19 (FGF19) levels.[72] Gut microbiome and bile acid alterations may predispose individuals to develop NAFLD at a lower BMI, and further research into microbiome modulation is required to better understand its role as both a potential biomarker and a therapeutic option in NAFLD patients.[73]

Dietary factors

High fructose and cholesterol diets play an essential role in developing NAFLD. In the body, fructose has both lipogenic and proinflammatory effects as fructose is rapidly phosphorylated inside cells, depleting intracellular ATP stores. High uric acid production induces mitochondrial oxidative stress triggering both lipogenesis and impaired fatty acid oxidation.[74] Intake of fructose, primarily in soft drinks containing high fructose corn syrup, is strongly associated with NAFLD development and progression. A study found soft drink consumption to be significantly associated with hepatic steatosis independent of metabolic factors.[75] Expanding further, a systematic review discovered a dose-dependent relationship between the amount of sugar-sweetened beverages per week and NAFLD, with a relative risk of 1.56 for seven cups per week and a relative risk of 1.10 for one cup per week.[76] Fructose has a role in the development of lean/nonobese NAFLD. Nonobese NAFLD subjects have been found to consume higher amounts of added sugar, such as soft drinks and juices, compared to healthy controls.[77] This connection is supported by a study on nonobese NAFLD cases with no underlying metabolic risk factors, which revealed that 80% of the NAFLD patient consume more than 50 g of added sugar per day versus 20% in the healthy control group.[77]

Consumption of a high-cholesterol diet may lead to NAFLD in lean subjects despite modest total caloric intake. Multiple studies found that cholesterol intake was significantly higher in nonobese NAFLD patients than in their obese NAFLD counterparts.[78,79] cholesterol may promote apoptosis of hepatocytes and macrophages, formation of reactive oxygen species, and lipid peroxidation.[80,81] Cholesterol metabolites, such as oxysterols, serve as endogenous ligands for the liver X receptor alpha (LXRa), which ultimately increases de novo lipogenesis and hepatic steatosis.[82] Increased expression of LXRa has been found in patients with nonobese NAFLD, compared with obese patients.[83,84]

Physical inactivity

Physical inactivity or sedentary lifestyle is associated with both lean/nonobese and obese NAFLD. Physical exercise plays an important role in a variety of molecular pathways regulating metabolic homeostasis, such as AMP-activated protein kinase, glucose transporter 4. Some studies have pointed to specific genetic polymorphisms (e.g., PNPLA3 alleles) that are more likely to benefit from lifestyle modifications such as physical activity.[85] Although physical inactivity or sedentary lifestyle is closely linked to sarcopenia, MetS, obesity, cardiovascular diseases, etc., which are all predispositions to NAFLD, increased physical activity has shown beneficial effects on NAFLD independent of weight loss.[86] Another study showed an inverse relationship between physical activity and the prevalence of NAFLD in a dose-dependent manner, which was independent of visceral adiposity and insulin resistance.[87] One study showed that prolonged sitting time, which is usually related with high caloric intake and unhealthy dietary practices, and decreased physical activity are independent risk factors for NAFLD.[88] Further research is needed to assess the role of physical activity and sedentary lifestyles in NAFLD pathophysiology and the impact of their interplay with other closely associated risk factors.

Sarcopenia

Sarcopenia is marked by low skeletal muscle mass with reduced function and is thought to contribute to the pathogenesis of lean/nonobese NAFLD, with multiple studies identifying lower skeletal muscle mass in lean individuals with NAFLD

as compared to patients with obesity.[89,90] The relationship between NAFLD and sarcopenia is explained by crosstalk between the liver and muscle, where insulin resistance and sarcopenia have been found to create a vicious cycle that harms both organs. insulin resistance contributes to the loss of lean body mass by activating the ubiquitin-proteasome proteolytic pathway (UPP) in skeletal muscle. Initially, insulin resistance reduces the activity of PI3K, which then reduces the levels of phosphorylated Akt.[58] The decreased level of phosphorylated Akt induces the expression of E3 ubiquitin-conjugating enzymes, activating the UPP and decreasing skeletal muscle mass.[58] Because muscle has a primary role in insulin-mediated glucose disposal, the decrease in muscle mass causes reduced glucose uptake and metabolism.[91]

Sarcopenia is further propagated by chronic inflammation caused by abnormal cytokine production in NAFLD. Chronic exposure to IL-6 and C-reactive protein levels (CRP) leads to increased muscle catabolism and atrophy, and elevated levels of TNF-α induce ceramide accumulation that has been observed to contribute to muscle cell atrophy.[92–94] In addition, visceral adipose tissue and sarcopenia act together in NAFLD pathogenesis, where NAFLD patients with a decreased muscle mass and increased visceral adipose tissue are found to have worsened steatosis and increased progression of liver fibrosis.[95] Moreover, several studies have reported the association of sarcopenia with NAFLD pathogenesis and progression independent of obesity.[96,97] A study from Korea investigating a large cohort of obese and nonobese subjects elucidated a strong inverse relationship between skeletal muscle index and NAFLD, where the prevalence of NAFLD in sarcopenic subjects was higher compared to non-sarcopenic subjects, irrespective of the presence of obesity or the MetS.[97]

Genetic predisposition

As discussed, genetic predisposition to nonobese NAFLD has been identified as a component of NAFLD development and progression. Several genes have been identified as known NAFLD variants. The rs738409 single nucleotide polymorphism in patanin-like phospholipase domain-containing protein 3 (*PNPLA*3) has been linked with NAFLD development and progression.[57] *PNPLA3* encodes a protein expressed in both adipocytes and hepatocytes. The protein is found in the endoplasmic reticulum and surface of lipid. It has acyl hydrolase activity, which plays a role in the hydrolysis of major glycolipids, including mono, diacylglycerol, and triacylglycerol. Mutation in the rs738409 polymorphism, known as the G allele, has been shown to decrease the enzymatic activity, resulting in increased hepatic fat contents and increased hepatic inflammation and thus increasing the severity of NAFLD.[60,98–100] A recent meta-analysis has shown that this polymorphism is more prevalent in nonobese and lean NAFLD patients than in both obese NAFLD and nonobese controls.[101] Interestingly, the prevalence of the rs738409 [G] allele in PNPLA3 varies among ethnicities. Romeo *et al*.[98] found that the rs738409 [G] allele frequency was directly associated with the prevalence of NAFLD in different ethnic groups. In a population of Hispanic, African American, and European American individuals, the G allele was most common in Hispanics, followed by European-Americans, and lowest among African Americans. Another allele of PNPLA3, or rs6006460 [T], was associated with lower hepatic fat content and was most common in African Americans, the group at lowest risk of NAFLD. Studies in the Asian population have shown a higher prevalence of the PNPLA3 risk allele than European and African subjects.[102]

Another gene variant identified is the rs58542926 encoding a Glu157Lys substitution in the transmembrane 6 superfamily 2 (*TM6SF2*) gene. The substitution has been shown to be associated with increased hepatic triglyceride content and NAFLD disease severity; however, the finding does not show as strong an association as the PNPLA3 mutation.[103] Sterol regulatory element-binding factor 2 (SREBF-2) is another genetic marker that has been identified as a potential contributor to the pathogenesis of NAFLD. Studies have shown that the rs133291 polymorphism in the SREBF-2 gene impacts lipid and glucose metabolism, as the nuclear transcription factor is responsible for regulating genes involved in cholesterol metabolism.[104] Studies by Musso *et al*.[104,105] demonstrated that the SREBF-2 gene polymorphism might be used to predict the 7-year incidence of NAFLD in nonobese or non-diabetic patients without MetS. In their study, SREBF was able to predict the 7-year incidence of NAFLD in the former group, and it conferred an increased risk of NASH in the biopsy-proven NAFLD group. Although the SREBF-1c polymorphism is associated with impaired glucose and lipoprotein metabolism, further evidence is needed to elucidate this association to better understand how it may aid in NAFLD prognostication. Cholesteryl transfer protein, apolipoprotein C3, glucokinase regulatory gene (GCKR), and membrane-bound O-acyl transferase domain-containing 7 (MBOAT7) genes are additional genes identified in the literature that may lead to NAFLD predisposition.[100,106]

Clinical outcomes in lean vs. obese NAFLD/NASH

Regardless of lean or obese status, patients with NAFLD experience poor outcomes, metabolic irregularities, and liver disease progression. In this section, we have reviewed the literature and compared and contrasted NAFLD/NASH in lean/nonobese patients and patients with obesity (Figs. 2 and 3).

MetS

NAFLD is strongly associated with metabolic syndrome (MetS) features, which represent at least three of the following conditions: elevated triglycerides, blood pressure, glucose, waist, or low high-density lipoprotein (HDL) cholesterol. MetS conditions confer a higher risk for cardiovascular disease, dyslipidemia, insulin resistance, and T2DM. A higher MetS severity score, which is a validated tool that combines and describes the extent of all 5 metabolic abnormalities, has shown to be linked to higher risk of mortality from all causes, heart disease, diabetes, and hypertension.[107] A study in the US concluded that lean (BMI <25 kg/M^2) NAFLD patients compared with lean, healthy subjects, had a higher prevalence of the following MetS conditions: IR, T2DM, hypercholesterolemia, and hypertension.[30] Several studies have reported that lean subjects with NAFLD have a higher risk of T2DM, dyslipidemia, hypertension, and cardiovascular outcomes than obese subjects with NAFLD.[108–113]

A study from South Korea showed a higher prevalence of MetS conditions in nonobese (BMI <25 kg/m^2) NAFLD patients compared with obese NAFLD patients after adjusting for confounders.[33] Similarly, Lee *et al*.[114] reported a higher prevalence of MetS components in nonobese (BMI <25 kg/m^2) NAFLD patients than obese NAFLD patients. On the other hand, a study conducted on NAFLD patients in Italy showed that lean (BMI <25 kg/M^2) NAFLD patients had a lower prevalence of hypertension, T2DM, and MetS compared to overweight (25 kg/m^2≤BMI<30 kg/m^2) and obese (BMI ≥30 kg/m^2) NAFLD patients.[115] Obese (BMI >25 kg/m^2) patients with NAFLD had a higher prevalence

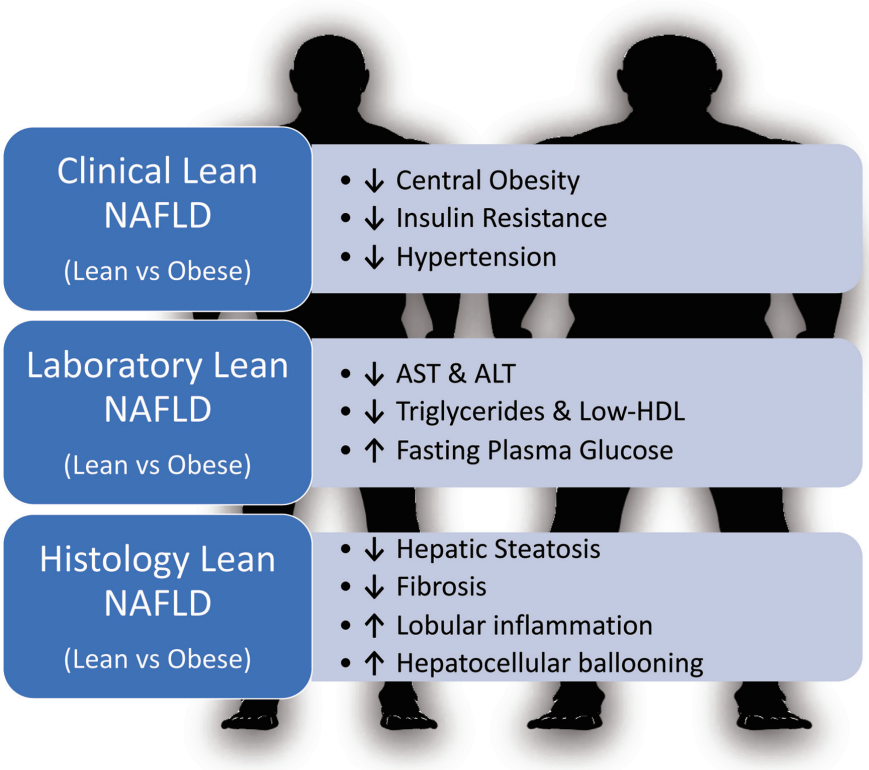

Fig. 2. Comparison of clinical, laboratory, and histology in lean/nonobese NAFLD and obese NAFLD. NAFLD, nonalcoholic fatty liver disease; ALT, alanine transaminase; AST, aspartate transaminase; HDL, High-density lipoprotein.

of MetS than their nonobese counterparts in 2 studies conducted in China.[116,117] Additionally, Akyuz *et al*.[118] reported a lower prevalence of MetS in lean (BMI <25 kg/m^2) NAFLD compared to overweight NAFLD patients in a prospective study in Turkey. Several studies have suggested that lean/nonobese NAFLD represents a metabolic phenotype somewhere in the spectrum between healthy individuals and NAFLD patients with obesity.[119,120] We will attempt to further delineate and summarize the data by metabolic condition.

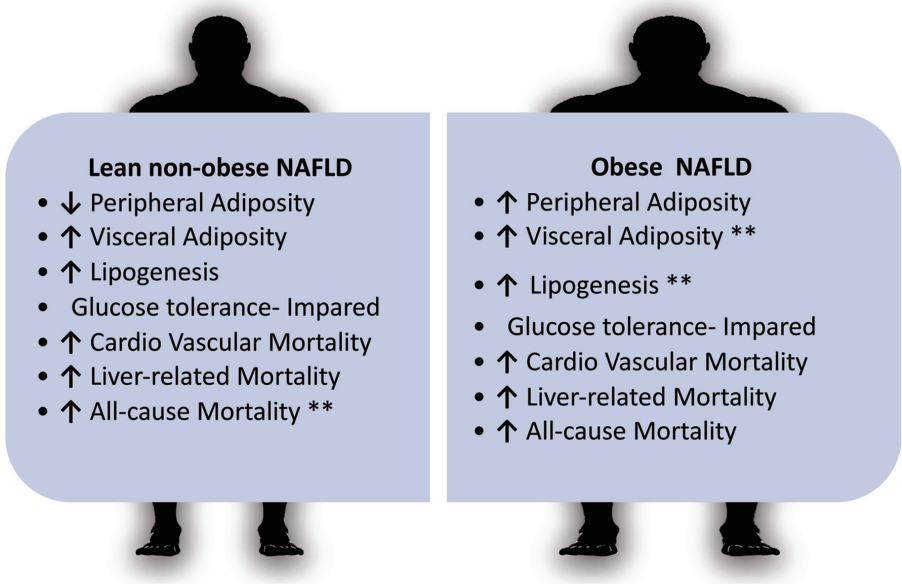

Fig. 3. Comparison of phenotypes and clinical outcomes between lean/nonobese and obese NAFLD. **Significant differences. NAFLD, nonalcoholic fatty liver disease.

Dyslipidemia

Obese and lean/nonobese NAFLD patients often have dyslipidemia and other characteristics of MetS, which contributes to the high risk of mortality because of cardiovascular disease and further hepatic dysfunction in both populations. In both the lean/nonobese and overweight/obese populations, NAFLD was found to be associated with higher levels of triglycerides, low-density lipoprotein (LDL), and total cholesterol compared to their non-NAFLD controls.[35] Li *et al*.[121] showed that obese (BMI >25 kg/M^2) patients had a higher prevalence of elevated serum triglyceride levels compared to nonobese with NAFLD in a Chinese population. Similarly, serum triglycerides were higher in obese (BMI >25 kg/m^2) and overweight (BMI 25–29 kg/m^2) NAFLD patients compared with lean patients in Japan and Spain.[122,123] Shao *et al*.[124] and Alam *et al*.[125] reported lower serum total cholesterol and triglycerides in nonobese (BMI <25 kg/m^2) patients compared to obese (BMI >25 kg/m^2) patients with NAFLD. Several studies have shown that obese or overweight NAFLD is associated with lower serum high-density cholesterol (HDL-C) compared to lean NAFLD patients.[57,123,125,126]

IR

Although insulin resistance is associated with both lean/nonobese and obese NAFLD, the degree of glycemic abnormalities among the two populations differs. Fasting plasma glucose (FPG), insulin, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) have been used to assess the degree of insulin resistance in patients with NAFLD. Li *et al*.[121] reported a higher proportion of Chinese patients with elevated FPG in obese (BMI >25 kg/m^2) compared with nonobese NAFLD patients. Similarly, Wang *et al*.[127] showed a higher FPG in obese women (BMI >28 kg/m^2) with NAFLD compared to nonobese/lean women with NAFLD in a study conducted in China. Shao *et al*.[124] reported lower FPG in nonobese (BMI <25 kg/m^2) Chinese NAFLD patients compared to obese NAFLD patients. Yoshitaka *et al*.[126] reported lower FPG levels in lean (BMI <23 kg/m^2) compared with overweight Japanese NAFLD patients. In studies conducted in Japan,[122] Bangladesh,[125] and Austria,[57] obese (BMI >25 kg/m^2) NAFLD patients had higher FPG, insulin, and HOMA-IR index compared with nonobese NAFLD patients. Nonobese/lean (BMI <23 kg/m^2) NAFLD patients in India had lower serum insulin, HOMA-IR index, and prevalence of T2DM compared with obese (BMI >25 kg/m^2) patients with NAFLD.[64] In a study conducted in Spain, overweight (BMI: 25–29 kg/m^2) NAFLD patients had a higher HOMA-IR compared with lean NAFLD patients.[123] The aforementioned studies are in agreement with the cross-sectional NHANES III study in which lean (BMI <25 kg/m^2) NAFLD patients had lower FPG and HOMA-IR and less frequently had T2DM compared with overweight/obese NAFLD patients.[30]

Cardiovascular disease

Hypertension

Hypertension is a common comorbidity in patients with NAFLD, regardless of lean or overweight/obese classification. The prevalence of hypertension is significantly higher in lean NAFLD patients than lean patients without NAFLD.[30] The presence of NASH further increases the prevalence of hypertension.[128] In a hospital-based study, Lee *et al*.[114] reported that nonobese (BMI <25 kg/m^2) NAFLD patients had a higher prevalence of MetS and hypertension compared to obese NAFLD. On the other hand, multiple studies conducted in Italy[115] and China[116,117] reported a lower prevalence of hypertension in lean/nonobese (BMI <25 kg/m^2) compared with overweight or obese NAFLD patients. In a case-control study conducted in Sri Lanka[99] and a study conducted in Japan,[126] lean (BMI <23 kg/m^2) NAFLD patients had a lower prevalence of hypertension compared to non-lean NAFLD patients. A meta-analysis of 45 studies reported a lower prevalence of hypertension in lean/nonobese NAFLD population as compared with non-lean/obese patients with NAFLD.[26]

Coronary artery disease

NAFLD is associated with cardiovascular disease, including hypertension, coronary artery disease, cardiomyopathy, cardiac arrhythmias, and patients are at increased risk of cardiovascular mortality. A meta-analysis of 16 observational studies including 24,043 patients with a median seven-year follow-up showed that patients with NAFLD had a 64% higher risk of developing fatal or non-fatal cardiovascular events compared with non-NAFLD patients.[129] Yoshitaka *et al*.[126] reported a higher risk (hazard ratio 10.4) of cardiovascular events in lean (BMI <23 kg/m^2) NAFLD patients compared with lean non-NAFLD patients, independent of potential confounders. In an analysis of the NHANES III survey, lean NAFLD patients had a higher risk of cardiovascular-related mortality (hazard ratio 2.38) compared with lean non-NAFLD patients after adjusting for potential confounding variables.[112] Patients with NAFLD are at an increased risk of developing atherosclerotic disease. A meta-analysis including 25,837 patients demonstrated a higher risk of clinical coronary artery disease compared with non-NAFLD patients.[130] NASH was found to be an independent predictor of high-risk coronary plaques, which may explain the higher risk of coronary events in this population.[131] In a retrospective study, lean NAFLD patients, reported higher atherosclerotic cardiovascular disease (ASCVD) scores (defined as ASCVD >10%), 51.6% compared with 39.8% in obese NAFLD and 25.5% in patients without NAFLD.[66] On the other hand, Fracanzani *et al*.[115] reported that lean NAFLD patients had significantly thinner carotid intima-media, which is indicative of a decreased atherosclerotic burden, compared to obese NAFLD. Data regarding cardiovascular mortality and atherosclerotic burden among lean/nonobese vs. obese NAFLD patients are scarce and more longitudinal data comparing the NAFLD cohorts are needed.

Risk of mortality

There is still a debate whether patients with NAFLD are at an increased risk of mortality compared to those without. A recent meta-analysis including 498,501 patients showed that patients with NAFLD had an elevated risk of all-cause mortality (hazard ratio 1.34) compared with patients without NAFLD.[132] There are fewer studies that have studied the differences in mortality among obese/non-lean vs. nonobese/lean NAFLD patients. Compared with lean non-NAFLD patients, lean (BMI <25 kg/m^2) NAFLD had a 50% increase in all-cause mortality (hazard ratio 1.54) after adjustment for potential confounding variables.[112] A cohort study of 646 patients with biopsy-proven NAFLD showed patients with lean (BMI <25) had no increased risk of mortality compared with patients who were overweight (BMI 25.0–29.9 kg/m^2) or obese (BMI >30 kg/m^2).[133] On the other hand, a meta-

analysis conducted in the US showed lean/nonobese NAFLD individuals had a higher 15-year cumulative all-cause mortality (51.7%) compared with obese NAFLD (27.2%) and non-NAFLD (20.7%) patients.[31] Another study in the US that included 483 patients with biopsy-confirmed NAFLD, reported a higher all-cause mortality in lean (BMI <25 kg/m^2) compared to non-lean patients during a follow-up of 133 months. Another study reported a higher risk of mortality in lean (BMI <25 kg/m^2) compared with obese NAFLD patients. Lean NAFLD was an independent risk factor (hazard ratio 11.8) for higher all-cause mortality after adjustment for potential confounders.[134]

Progression of NAFLD to NASH

NAFLD, which can initially present as simple steatosis, can progress to NASH, cirrhosis, and hepatocellular carcinoma (HCC). Several studies have reported outcomes regarding the degree of injury and fibrosis and the risk of developing NASH, cirrhosis, and HCC in NAFLD patients. One study from Bangladesh found no significant histologic difference between lean and obese NAFLD patients.[125] Kumar *et al*.[64] reported a lower NAFLD activity score in lean NAFLD patients compared to obese NAFLD. The proportion of patients with hepatic fibrosis was lower in the lean population than in the obese NAFLD population. However, the prevalence of NASH was statistically similar in lean (28%) and obese (38%) NAFLD patients. In a prospective cohort study from China involving 307 NAFLD patients, lean/nonobese (BMI <25 kg/m^2) had a lower NAFLD activity score (3.3±1.3 vs. 3.8±1.2; p=0.019) and lower fibrosis stage (1.3±1.5 vs. 1.7±1.4; p=0.004). Interestingly, during 49 months of follow-up, death, HCC, and liver failure only occurred in the obese population.[117] Studies from Japan,[122] Belgium,[135] and Turkey[118] have shown lower histological severity in lean NAFLD patients compared with obese NAFLD patients. In a study with patients with a similar liver fat content as measured by 1H-MRS, lean NAFLD patients had a lower liver stiffness compared to obese NAFLD patients.[37] In a retrospective cohort study including 646 biopsy-proven NAFLD patients in Sweden, lean (BMI <25 kg/m^2) NAFLD patients had a lower fibrosis stage and lower prevalence of NASH but had a higher risk of cirrhosis, decompensated cirrhosis, and HCC compared to the overweight (25 kg/m^2≤BMI<30 kg/m^2) patients. Similar to the previous study, obese NAFLD had the highest mortality.[133]

In a meta-analysis including eight studies[64,115,117–119,122,125,136] and 2,702 patients (493 lean NAFLD patients vs. 2,209 overweight/obese NAFLD patients), lean NAFLD patients had a significantly lower NAFLD activity score and fibrosis score compared with overweight/obese NAFLD patients.[137] Interestingly, in a meta-analysis of five studies including 1,886 patients, lean NAFLD patients had significantly lower steatosis scores compared to overweight/obese NAFLD. Data from six studies (n=1,679 participants) reported a lower prevalence of NASH in lean NAFLD patients compared to their overweight/obese counterparts.[137] On the other hand, a biopsy-based study of a Greek population showed that the prevalence of NASH and degree of inflammation and fibrosis were statistically similar between patients with normal and increased BMI.[136] A biopsy-based study in Austria demonstrated a higher rate of NASH in lean patients compared with overweight but similar to obese NAFLD patients. The rate of cirrhosis was higher in lean patients compared to overweight and obese NAFLD patients. Weight loss due to cirrhosis may be present and may obscure whether lean NAFLD is a risk factor for cirrhosis.[138] Further studies are warranted to elucidate the mechanism and pathways that lead to liver disease progression in both lean and obese NAFLD populations.

Treatment of lean/nonobese vs. obese NAFLD

Lifestyle modification

Weight loss: Lifestyle interventions, including exercise and dietary modifications, have been an important and effective component in the treatment of NAFLD and remain the first-line therapy for NAFLD. The American Association for the Study of Liver Disease (AASLD) reports that a 3–5% reduction in body weight via calorie restriction and, or increased physical activity could reduce NAFLD in patients with obesity.[11] A prospective study showed that the degree of histological improvement was correlated with weight loss. A weight reduction of 3–5% effectively improved steatosis, while a decrease of 5–7% showed improvement in hepatic inflammation. Weight reductions of >7% and >10% showed improvement in histopathologic features of NASH including hepatic steatosis, ballooning, and lobular inflammation, and improvement in fibrosis and portal inflammation.[139]

Weight loss is effective in both lean and obese NAFLD populations. Studies from Korea[140] and Turkey[141] showed that a 5% reduction in body weight led to a significant decrease in steatosis in lean NAFLD patients. In a study involving 333 patients with NAFLD with a mean follow-up of 28.7 months, weight change was an independent predictor of disease progression or resolution. In the population who experienced disease progression, lean patients had a more significant weight gain compared to patients with obesity. However, in patients who experienced NAFLD resolution, lean patients showed a smaller degree of weight loss compared with obese NAFLD patients.[142] Weight loss has shown to be effective in the improvement of NAFLD and NASH in lean and obese populations and is the foundation of treatment for patients with NAFLD regardless of BMI.

Dietary modification: Although several diets have been studied in patients with NAFLD/NASH, the Mediterranean diet has been the most studied, and adherence to the diet has shown a reduction in the risk and progression of NAFLD via antioxidant and anti-inflammatory mechanisms linked to the consumption of monounsaturated and omega-3-fatty acids, and phytosterols found in the diet.[143,144] The Mediterranean diet consists of fresh vegetables, legumes, fruit, minimally processed whole grains, fish, and foods rich in omega-3-fatty acids, such as olive oil, nuts, and seeds. It includes minimal to low consumption of dairy and red or processed meats.[145] The EASL-EASD-EASO clinical practice guidelines recommend the Mediterranean diet for NAFLD patients.[146] In patients with NAFLD, the Mediterranean diet has been shown to reduce hepatic steatosis and insulin resistance without weight loss compared to a low-fat, high carbohydrate diet.[147] Interestingly, an increase in the Mediterranean diet score, which is a measure of Mediterranean diet consumption, was shown to be associated with a reduction in liver fat accumulation and severity. Each standard deviation increase in the score reduced the odds for incident fatty liver by 26%.[148]

Other dietary changes, such as coffee consumption, sugar, and calorie-deficits, have been studied in patients with NAFLD/NASH. As mentioned previously, weight loss has been shown to improve hepatic steatosis and lead to a dose-dependent improvement of NAFLD in lean/nonobese and overweight/obese patients. A hypocaloric diet should be considered in patients with NAFLD to achieve the aforementioned results associated with a total body weight loss. NAFLD/NASH and certain MetS conditions, such as insulin resistance, are associated with an increased intake of fructose and high fructose corn syrup products.[149] In patients with NAFLD, higher amounts of fructose intake via sugar-sweetened beverages are associated with increased hepatic fibrosis, inflammation, and hepatocellular ballooning.[150] On

the other hand, fructose found in fruits was not associated with NAFLD. Therefore, patients with NAFLD should restrict fructose intake via artificial sweeteners or high fructose corn syrup but do not need to limit fruit consumption. In several studies, coffee consumption has been shown to play a protective role in NAFLD.[151,152] However, it requires further investigation in lean NAFLD patients.

Physical activity: As mentioned previously, weight loss is linked to NAFLD improvement and remission. Physical activity likely accentuates the therapeutic benefits of weight loss. Still, it has been shown to improve NAFLD independently of weight loss via a reduction in hepatic steatosis, insulin resistance, hepatic lipogenesis, adipocyte lipolysis, and fatty acid delivery to the liver.[153] The EASL–EASD–EASO guidelines recommend 150 to 200 min/week of moderate-intensity aerobic exercise in three to five sessions.[146] The AGA recommends a goal of 150 to 300 min of moderate-intensity or 75 to 150 min of vigorous-intensity aerobic exercise per week with resistance training as a complement to the aerobic exercises.[154] Li *et al*.[86] found that the benefits of physical activity were dose-dependent and that moderate and vigorous levels of intensity in physical activity had beneficial effects on NAFLD, regardless of energy intake and sedentary time. A meta-analysis reported both resistance and aerobic exercise was able to show a reduction in hepatic steatosis in NAFLD patients with a similar period of exercise, duration, and frequency.[155] These results suggest that patients in poor cardiorespiratory shape or those unable to tolerate or participate in aerobic exercises should opt for resistance exercises, especially if it will lead to continued adherence.

Surgical intervention

Bariatric surgery is an effective method for weight loss. Research behind its therapeutic benefits in NAFLD/NASH is limited to the obese population. Bariatric surgery is currently recommended in patients with a BMI ≥40 kg/m^2 and no comorbidities or a BMI of 35–39.9 kg/m^2 with comorbidities such as diabetes, hypertension, or NAFLD/NASH.[156] It has been shown to improve obesity-related diseases such as T2DM, dyslipidemia, obstructive sleep apnea, hypertension, and reduce the risk of cardiovascular diseases. Interestingly, bariatric surgery in NAFLD patients with severe obesity was associated with a significant reduction in the risks of any cancer and obesity-related cancers.[157]

Roux-en-Y gastric bypass (RYGB) and laparoscopic gastrectomy (LSG) are most commonly performed among the available surgical methods. In a meta-analysis including 15 studies with 766 paired liver biopsies, the pooled proportion of patients with improvement or resolution in steatosis was 91.6% [95% confidence interval (CI), 82.4–97.6%)], in steatohepatitis was 81.3% (95% CI, 61.9–94.9%), in fibrosis was 65.5% (95% CI, 38.2–88.1%), and for complete resolution of nonalcoholic steatohepatitis was 69.5 (95% CI, 42.4–90.8%) after undergoing bariatric surgery.[158] In a review of 12 studies including 496 patients with paired liver biopsies who underwent RYGB or LSG, the average NASH resolution rate was 87.4% (LRYGB: 91.9%, LSG: 80%) in a mean follow-up period of 14.5 months. Furthermore, both surgical techniques led to significant improvement or resolution of liver fibrosis.[159] Lassaily *et al*.[160] reported resolution of NAFLD/NASH in most patients and significant regression of liver fibrosis. Cazzo *et al*.[161] reported a significant reduction in mean NAFLD fibrosis score and a resolution rate of 55% of severe fibrosis in a 12 month observation in patients who underwent RYGB. Several studies have shown significant improvement in NAFLD activity score, steatosis, inflammation, and liver ballooning in a 1-year observation period following RYGB.[162,163] In patients with morbid obesity who had undergone LSG, Cabre *et al*.[164] showed that patients' histology and liver function significantly improved via mechanisms that reduced oxidative stress and inflammation. In a study from Egypt that included 81 patients who underwent LSG, a significant reduction in steatosis, liver fibrosis, lobular inflammation, and hepatocyte ballooning was observed in the postoperative biopsies (p<0.001 each). An 18-month observation showed significant improvement in postoperative liver function tests (AST, ALT, GGTP).[165] In a Swedish study, bariatric surgery was associated with lower serum AST and ALT at 2- and 10-year follow-up with a reduction in ALT levels proportional to the degree of weight loss.[166]

Endoscopic bariatric and metabolic treatment (EBMT), such as intragastric balloon and endoscopic sleeve gastroplasty, is safer and less invasive compared to bariatric surgery. In a meta-analysis including 18 studies and 863 patients, EBMT was shown to significantly reduce liver fibrosis, hepatic steatosis, and histologic NAFLD activity score. EBMT was shown to significantly improve other metabolic parameters, including insulin resistance, waist circumference, and weight reduction.[167] Although results are promising, further studies are warranted.

Pharmacologic intervention

Although lifestyle modifications are effective and should be considered the first line in managing patients with NAFLD/NASH, pharmacological treatments should be considered. Several factors may help optimize medical therapy, including lean vs. obese status, stage of disease/fibrosis, etc. Thiazedinediones, such as pioglitazone, are PPAR-γ agonists and exhibit anti-inflammatory properties, improving insulin sensitivity and hepatic fatty acid oxidation. In a randomized controlled trial, pioglitazone improved hepatic steatosis, ballooning, and inflammation in patients with NASH.[168] Vitamin E is an antioxidant able to inhibit lipid peroxidation and improve lipid metabolism. In the PIVENS trial (Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis), vitamin E resulted in significant improvement in ALT levels, liver steatosis, and inflammation but did not significantly improve fibrosis. Patients in this study were overweight or obese, and therefore, the results cannot be applied to lean/nonobese individuals.[169] Liraglutide, a GLP-1 agonist, has been studied in obese and diabetic NAFLD patients, leading to improvement and less fibrosis progression.[170] However, the effects of the drug have not been studied in lean NAFLD patients. Several agents are currently in phases II and III, and further investigation is necessary to delineate further which population of NAFLD patients may benefit from specific pharmacologic interventions.

Other interventions

Poor quality of sleep and short sleep duration have been associated with an increased incidence of NAFLD.[171,172] A significant proportion of lean NAFLD patients have been linked to poor sleep quality.[173] Patients with NAFLD should receive recommendations for more rest and other measures that may improve sleep quality.

Conclusions

NAFLD has predominantly been a disease associated with

obesity and other metabolic conditions. However, the prevalence of NAFLD in lean/nonobese subjects is growing worldwide, heightening the importance of understanding the differences between lean and obese patients. A standardized definition delineating obese and lean NAFLD is necessary to understand the pathophysiology and disease outcomes more precisely. Patients with NAFLD, regardless of BMI, are associated with a genetic predisposition, increased visceral adiposity, insulin resistance, sarcopenia, gut dysbiosis, and poor diet/exercise habits. Lean NAFLD patients displayed MetS conditions compared to lean non-NAFLD patients. Among patients with NAFLD, patients with obesity were typically found to have a higher prevalence and degree of MetS conditions, such as dyslipidemia, insulin resistance, and hypertension, compared to lean subjects. Patients with NAFLD have a higher overall cardiovascular mortality risk compared to non-NAFLD patients. However, the differences among obese and lean NAFLD patients were inconclusive, and further research is required. Obese NAFLD patients are typically associated with a greater degree of hepatic steatosis, inflammation, and fibrosis than lean patients. Still, data on advanced liver diseases, such as cirrhosis and HCC are relatively mixed. Lifestyle modifications remain the first line of treatment in NAFLD, regardless of BMI or body weight. Future therapies include PPAR-γ, such as pioglitazone, GLP-1, vitamin E, and many other options currently in clinical trials are being studied. Further understanding of the mechanisms and pathways of NAFLD in both lean and obese cohorts is necessary to optimize our current clinical practice and decision-making in this patient population.

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Conflict of interest

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