Non-alcoholic fatty liver disease in lean individuals

Somaya Albhaisi,[1] Abhijit Chowdhury,[2] Arun J. Sanyal[3,*]

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Summary

Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease, encompassing a spectrum from non-alcoholic fatty liver to non-alcoholic steatohepatitis, which can progress to cirrhosis. It has recently been recognised that NAFLD also occurs in individuals who are not obese, especially in Asian populations. In these patients, NAFLD manifests at lower overall body mass index thresholds in the presence of increased visceral adipose tissue. Currently, the principles of clinical management are similar to those in obese individuals, although, in specific regions and clinical situations, unique aetiologies of NAFLD must be treated specifically.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease. It encompasses a spectrum of clinical-histological phenotypes from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) which can progress to cirrhosis.[1] Excess body weight, type 2 diabetes and dyslipidaemia are classic risk factors for NAFLD.[2] Although, it is now recognised that the condition exists in those who are not obese, especially in Asia.[3] This has led to considerable debate about whether it represents a distinct condition. We critically review the existing state of knowledge about NAFLD, mainly in lean individuals, and try to distinguish between what is scientifically supported and where gaps in knowledge remain, with a view to providing guidance to both clinicians who see such patients and scientists investigating this disease.

Nomenclature and case definitions

The commonly used term "lean NASH" is both grammatically and scientifically incorrect since NASH is not "lean" and multiple aetiologies can cause NAFLD in a lean individual. Further, body weight is not part of the diagnosis of NAFLD. We therefore propose that this entity should be referred to as NAFLD in lean individuals, taking in to account the varying case definitions for the term "lean" in the West (<25 kg/m^2) versus in Asia (<22 kg/m^2).[4–6] The Liver-Forum case description, which currently represents the standard used for drug development efforts by the FDA and the EMA, requires identification of disease phenotype (fatty liver *vs.* steatohepatitis) and disease activity (by the NAFLD activity score [NAS], fibrosis stage and aetiology [Table 1])[7]; in lean individuals one or more aetiologies may be present and reported accordingly.

Aetiologies of NAFLD in lean individuals

There are multiple causes of NAFLD in those who are not overweight or obese (Box 1). The distribution of these causes varies with regional variances in the prevalence of these conditions and the type of clinical centre where such patients are seen. A detailed description of these conditions is beyond the scope of this paper and interested readers are referred to recent reviews on the individuals.[5,70,82,110,111] It is recognised that many individuals have none of these conditions, especially in populations that are predominantly lean such as those in Asia. However, the existing literature finds that the pathobiology tracks that seen in obese individuals in such cases, and thus does not represent a unique aetiology but rather a clinical sub-phenotype of "garden-variety" NAFLD associated with increasing adiposity, particularly in the visceral compartment (Table 2). The majority of lean patients have underlying insulin resistance and there is no strong rationale to include this as a unique aetiology.

Epidemiology of NAFLD in lean individuals

The prevalence of NAFLD in lean individuals varies widely among studies.[8] The variability is driven by a number of factors such as varying case definitions for NAFLD, varying methods used to diagnose NAFLD, varying study design, ascertainment bias and true differences from region to region. It is now apparent that there are not only differences from country to country

[1]Dept of Internal Medicine, VCU School of Medicine, Richmond, VA 23298-0341
[2]Dept of Hepatology, Indian Institute of Liver and Digestive Sciences, Sonarpur, West Bengal 700150, India
[3]Div. of Gastroenterology, Hepatology and Nutrition, Dept. of Internal Medicine, VCU School of Medicine, Richmond, VA 23298-0341

* Corresponding author. Address: Physiology and Molecular Pathology, MCV Box 980341, Richmond, VA 23298-0341; Tel.: +1 (804) 828 6314, fax: +1 (804) 828 2992.
E-mail address: arun.sanyal@vcuhealth.org (A. Sanyal).

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but even from rural to urban areas, especially in the Asian subcontinent.[9] Unfortunately, the published literature does not systematically evaluate the presence of specific aetiologies that can drive NAFLD in lean individuals and future studies are needed to define the role of specific aetiologies within these populations.

Overall, the global trends of NAFLD prevalence in lean individuals track the march of the obesity pandemic globally.[10] Even within the normal body mass index (BMI) range, there is an ongoing increase of obesity worldwide, which is linked to expanded, dysfunctional, inflamed adipose tissue.[11] In cross-sectional studies, 7–20% of individuals with NAFLD have a lean habitus (Table 2). Initially described in Asian populations and considered as a "third world phenotype", this subset of NAFLD has since been described in other populations, including in Europe and the USA.[9,12] In Asia, the prevalence of NAFLD has been reported to vary from 12.6% of unselected patients to 27% of lean individuals.[13–15] A magnetic resonance (MR) spectroscopy-based study from Hong Kong reported a 19% prevalence of fatty liver in non-obese individuals, compared to 61% in people with higher BMI.[17] Lean, non-alcoholic, non-diabetic, non-smoking Asian Indians – in comparison to age-, sex- and BMI-matched Caucasians, Hispanics, Blacks and Eastern Asians – have been reported to have a 2-fold increased prevalence of hepatic steatosis, reflecting a poorer metabolic status in these individuals. [18] The NHANES study reported a prevalence of NAFLD of 7.9% in lean individuals in the USA,[4,19] whereas an ultrasound-based study from Italy reported a 16% prevalence of lean NAFLD.[16]

In a population-based study that included 565 adults from Hong Kong, with repeat proton MR spectroscopy carried out at a mean interval of 47 months, 71% of individuals were lean at baseline (<23). A total of 7.9% had developed incident fatty liver at follow-up, which was associated with increasing BMI as well as waist circumference and triglycerides while remaining below the BMI boundaries for obesity.[20] Similar data have been reported from China.[15,21] In general, these data suggest a 3–5% annual incidence rate for NAFLD in lean individuals, which is mostly associated with expansion of fat mass and increasing adiposity, underscoring the common linkage between adiposity and insulin resistance across various BMI strata among those with NAFLD.

Key points

Although non-alcoholic fatty liver disease (NAFLD) is usually associated with obesity, patients who are not obese can also present with NAFLD.

This subset of individuals, known to have 'lean NAFLD' or 'non-obese NAFLD', is growing increasingly prevalent.

NAFLD in lean patients appears to be more common among Asians.

Risk factors for NAFLD in lean patients include high body fat, body weight gain even within normal weight limits, high fructose and high cholesterol intake, and genetic risk factors.

Although NAFLD in lean individuals is generally considered a less severe form of liver disease than NAFLD in obese patients, this conception has recently been challenged.

Lifestyle modification, including diet and physical activity remains the mainstay in the management of patients with non-obese NAFLD.

Pathogenesis of NAFLD in lean individuals

The broad pathogenic basis for NAFLD and its more aggressive phenotype NASH is now established.[83] NAFLD typically develops in a systemic milieu characterised by diet-induced adiposity, increased gut permeability and altered microbiome, insulin resistance, systemic inflammation and an acute phase reaction where the liver is exposed to excess metabolic substrates (lipids and carbohydrates), pro-inflammatory bacterial products and cytokines (Fig. 1). These factors cause hepatocellular stress pathway activation, resulting in cell death and activation of inflammatory signalling. Sustained inflammation drives fibrogenic remodelling towards cirrhosis. Simultaneously, regenerative signals are activated. Disease progression reflects a balance between factors driving the disease towards cirrhosis or restoration of normal function and structure. In the following sections, we review these core concepts in the context of NAFLD in lean individuals.

Table 1. Standardised format for comparison of study populations across trials.

Phenotype	Disease activity	Disease stage	Aetiology/associations
Steatosis Steatohepatitis Indeterminate	NAS - Steatosis - Lobular inflammation - Ballooning SAF - Steatosis - Lobular inflammation - Ballooning - Fibrosis	Fibrosis - Stage 0: No fibrosis - Stage 1a: Mild perisinusoidal - Stage 1b: Moderate perisinusoidal - Stage 1c: Portal/periportal - Stage 2: Perisinusoidal and portal/periportal - Stage 3: Bridging - Stage 4: Cirrhosis	Insulin resistance Alcohol Lean NASH PNPLA3+ Drugs Inherited disorders (*e.g.*, Weber-Christian, hypobetalipoproteinemia) Lipodystrophy Short bowel TPN Jejunoileal bypass

PNPLA3, patatin-like phospholipase domain containing 3; TPN, total parenteral nutrition.

Box 1. Causes of NAFLD in non-obese individuals.

1. **Genetic disorders:**
   a. Abetalipoproteinemia
   b. Lipodystrophies
   c. Cholesterol ester storage disease
   d. Wolman disease
   e. Wilson's disease
   f. *PNPLA3* mutation*
2. **Metabolic:**
   a. Insulin resistance and increased visceral adiposity (most common cause)
3. **Infectious-Inflammatory disorders:**
   a. Hepatitis C (especially genotype 3)
   b. HIV
   c. Celiac disease
   d. Small intestinal bacterial overgrowth
4. **Drugs:**
   a. Amiodarone
   b. Tamoxifen
   c. Diltiazem

NAFLD, non-alcoholic fatty liver disease.

Genetics

NAFLD occurs in 2 genetic contexts. First, there are specific genetic disorders, particularly associated with adipose tissue or affecting specific metabolic pathways that result in fat accumulation in the liver despite physiological levels of lipid flux through the liver. These genetic disorders[92] include abetalipoproteinemia,[93] hypobetalipoproteinemia,[94] familial combined hyperlipidemia,[95] glycogen storage disease,[96] Weber–Christian syndrome,[97] and lipodystrophy.[98] There are also genetic traits that normally do not result in the development of NAFLD but, in the context of diet-induced expansion of adipose tissue mass, increase susceptibility and are linked to increased risk or protection from disease development (Box 2). The patatin-like phospholipase domain containing 3 (*PNPLA3*) gene and its non-synonymous gene variant, the rs738409 C/G encoding an isoleucine to methionine substitution at the amino acid position 148 ($I^{148}M$), was the first major gene associated with NASH. This variant is associated with the development of NASH rather than NAFL and its progression to cirrhosis and hepatocellular carcinoma. The mechanisms by which it promotes steatohepatitis and hepatocellular carcinoma remain unknown. The prevalence of this mutation is variable; it is very common in the Hispanic communities and in certain Asian countries but not others.[5] A variant of the ApoC3 has been linked to the development of NAFLD in South Indian males but these data have not been corroborated in other populations.[22]

Recently, a variant of the 17β hydroxy steroid dehydrogenase gene was found to be protective against NAFLD.[23] We have further demonstrated that a single nucleotide polymorphism (SNP) at rs6834314, which is closely associated with this gene, is associated with an increased risk of NAFLD but decreased cell injury.[24,112] Another SNP, rs62305723 (encoding a P260S mutation) is significantly associated with decreased ballooning and inflammation. There is a paucity of literature on these variants in lean populations, particularly in Asia where this phenotype is the predominant clinical phenotype. *TM6SF2* is another gene where variants have been linked to disease severity and effects on lipid trafficking out of the liver.[25] Another gene polymorphism that could play a role in NAFLD is the rs12979860 polymorphism in the *IFNL3* gene, which has been shown to be associated with increased hepatic inflammation and fibrosis in non-obese patients with NAFLD.[106] Cholesteryl ester transfer protein (CETP) plays an important role in the transport of cholesterol from peripheral tissue back to the liver. Two SNPs on the *CETP* gene, namely rs12447924 and rs12597002, have been found to be associated with an increased risk of hepatic steatosis, particularly in non-obese individuals.[107] Another relevant correlation is that insufficiency of phosphatidylethanolamine N-methyltransferase (PEMT) increases the risk of NASH in lean individuals.[108]

Diet and other environmental influences

There is a general paucity of high-quality literature on diet in lean individuals with NAFLD. This is partly due to a lack, in many parts of the world, of validated questionnaires that capture the varying dietary habits of individuals. Furthermore, translation of food intake from questionnaires to calculation of specific nutrient intake is challenging. Despite these limitations, in a Chinese population, no substantial qualitative differences in diet were noted between those who were lean and had NAFLD versus obese individuals with NAFLD.[26] In general, even within the lean population, those with NAFLD tend to consume greater total calories.[27] Sedentary lifestyle is known to be associated with an increased prevalence of insulin resistance, however in lean individuals the role of a sedentary lifestyle has not yet been well established. We suspect that the role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome may be a contributing factor.[100] A cross-sectional epidemiological study in Chinese workers, investigating the association between sitting time and NAFLD, found that longer sitting time (>7.1 hours/day) was associated with a higher prevalence of NAFLD (odds ratio 1.09; 95% CI 1.04–1.67) after adjusting for confounders. Further multivariate linear regression analyses showed that sitting time independently correlated with BMI ($\beta = 0.174$, $p = 0.022$).[99] Another case-control study in a Chinese population looked at the dose-response association between physical activity and NAFLD. The study reported that physical activity was inversely associated with the risk of NAFLD in a dose-dependent manner in men, after adjusting for BMI, hypertension, diabetes, fasting blood glucose and sedentary time (>3,180 mean exercise time min/week *vs.* ≤1,440 mean exercise time

Table 2. Prevalence and metabolic status of NAFLD in non-obese individuals.

Author; Year	Country	Population	Sample size (n)	Proportion of non-obese among NAFLD individuals[a]	Prevalence of NAFLD[b] ; n (%)	Prevalence of MS among non-obese NAFLD persons; n (%)	Mode of diagnosis of NAFLD	Mode of diagnosis of IR/MS	Status of IR/MS in non-obese NAFLD
Riquelme A *et al.*,[10] 2009	Chile	Urban population (Hispanics)	832	NR	195 (23.4%)	NR	USG	HOMA-IR	HOMA-IR >2.16 significantly associated with NAFLD (OR 2.97)
Kwon YM *et al.*,[86] 2012	Korea	Hospital cohort	29,994	3,014 (49.9)	Overall 6,039 (20.1) Non-obese 3,014 (12.6) Obese 3,025 (50.1)	NR	USG	HOMA-IR	NAFLD was associated with higher risk of components of MS regardless of gender and obesity
Sinn DH *et al.*,[85] 2012	Korea	Hospital cohort (Selected non-obese individuals)	5,878	5,878 (100)	1,611 (27.4%)	381 (23.64)	USG	HOMA2-IR ≥1.5 and NCEP-ATP III criteria	IR in 13.6% (n = 801) MS in 6.5% (n = 381) NAFLD, not MS predicted IR
Xu C *et al.*,[15] 2013	China	Hospital cohort (Employee Health Checkup)	6,905	6,905 (100)	502 (7.27 %)	NR	USG	NR	Components of MS were separately associated with NAFLD
Das K *et al.*,[17] 2010	West Bengal, India	General population (Rural)	1,911	90 (54%)[c]	167 (8.7%)	43 (26%)[b]	US and CT		Components of MS like FBG and TG were higher in non-obese NAFL than control. HOMA-IR was comparable
Wei JL *et al.*,[5] 2015	Hong Kong	General population (Urban)	911	135 (51.52)	Overall 262 (28.8) Non-obese 135 (19.3) Obese 127 (60.5)	51 (37.8)	Proton MRS	HOMA-IR, IDF and NCEP-ATP III criteria	HOMA-IR, BMI and WC predicted NAFLD in non-obese individuals
Younossi Z M *et al.*,[4] 2012	USA	National Health and Nutrition Examination Survey III (NHANES III) database	11613	431 (17.29)	Overall 2492 (21.45) Non-obese 431 (3.71) Obese 127 (17.74)	NR	USG	HOMA-IR	IR and dyslipidaemia were not associated with NAFLD in non-obese. NASH was associated with MS
Bugianesi E *et al.*,[87] 2005	Italy	Selected non-obese, non-diabetic NAFLD subjects	12	–	Not designed to see prevalence	NR	Liver histology	Euglycemic Insulin clamp	Features of IR were present in all individuals
Feldman A *et al.*,[31] 2016	Austria, Switzerland	Subjects selected from Salzburg Colon Cancer Prevention Initiative study	187	55 (29.41)	Not designed to see prevalence	NR	USG	HOMA-IR OGTT	Lean NAFLD showed significant impairment in glucose tolerance
Musso G *et al.*,[88] 2008	Italy	Healthy individuals	197	NR	Not designed to see prevalence	NR	USG with elevated ALT	HOMA-IR, OGTT, NCEP-ATP III criteria	NAFLD was more significantly associated with IR than with ATP III criteria
Marchesini G *et al.*,[89] 1999	Italy	Hospital cohort	46	–	Not designed to see prevalence	–	USG	HOMA-IR	NAFLD was associated with IR even in non-obese individuals

Table 2 (*continued*)

Author; Year	Country	Population	Sample size (n)	Proportion of non-obese among NAFLD individuals[a]	Prevalence of NAFLD[b] ; n (%)	Prevalence of MS among non-obese NAFLD persons; n (%)	Mode of diagnosis of NAFLD	Mode of diagnosis of IR/MS	Status of IR/MS in non-obese NAFLD
Kim H J *et al.*,[82] 2004	Korea	Clinic attendee	768	74 (41)	180	NR	USG	HOMA-IR	NAFLD was associated with components of MS in non-obese individuals
Fracanzani *et al.*,[110] 2017	Italy	Hospital cohort	669	143 (21.38)	Not designed to see prevalence	17 (14)	Liver histology	HOMA-IR	Adipose tissue insulin resistance was higher in patients with NASH than in patients without even when analysed in lean and overweight/obese patients separately

[a]Non-obese defined as BMI <25 kg/m^2; [b] Unadjusted prevalence; [c] Non-obese defined as BMI <25 kg/m^2 and waist circumference <80 cm (female) /<90 cm (male); ATP III, Adult Treatment Panel III; BMI, body mass index; CT, computed tomography; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment - insulin resistance; IDF, International Diabetes Federation; IR, insulin resistance; MRS, magnetic resonance spectroscopy; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NCEP, National Cholesterol Education Programme; NR, not reported; OGTT, oral glucose tolerance test; TG, triglyceride; USG, ultrasonography; WC; waist circumference.

min/week: odds ratio 0.61, 95% CI 0.41–0.92, p for trend = 0.02).[109]

Microbiome and metabolomics

There is now a substantial body of literature indicating a key role for the intestinal microbiome in the regulation of metabolic homeostasis.[28] The composition of the microbiome is affected by age, gender, race, hormonal status and diet. Multifaceted changes occur in the microbiome with the onset of obesity, including increased *Proteobacteria* and an altered *Firmicutes* to *Bacteroidetes* ratio.[29] The only available study on the gut microbiome in lean NAFLD included a relatively small sample of individuals in Brazil. It revealed a trend towards qualitative differences compared to the obese NAFLD group, with a 3-fold lower abundance of *Fecalibacterium* and *Ruminococcus* species, and a relative deficiency in *Lactobacillus*.[30]

There is limited literature on metabolomics in lean NASH. A study among lean Caucasians showed that NAFLD in lean individuals might have a distinct metabolomic profile, with lysophosphatidylcholine, phosphatidylcholine, tyrosine and valine levels being different from those in the obese NAFLD group.[31] However, these studies are underpowered and did not adjust for multiple confounders. Therefore, they require confirmation in independent data sets from the same and other regions of the world. Importantly, it is unclear how these changes relate to the development and progression of NAFLD.

Non-hepatic end-organs that impact the development of NAFLD in lean individuals

There is a close and direct relationship between adiposity and the development of NAFLD. It is further recognised that the BMI does not capture all aspects of adiposity and can be normal despite increased total body adipose tissue. Several decades ago, it was shown that in apparently normal individuals with a BMI of 22 kg/m^2, Asian males had significantly higher total body and visceral adipose tissue.[81] The visceral adipose tissue size, including both intra-abdominal and epicardial fat compartments, are well known risk factors for cardiometabolic disease.[32,33] It has been proposed that visceral adipose tissue preferentially express 11β hydroxylase, a key enzyme in steroid synthesis which may explain a greater propensity for insulin resistance to develop in this compartment.[34,35] Inhibitors of this enzyme have been shown to have a modest effect on hepatic steatosis.[36]

Adipocyte size and biological behaviour are additional determinants of metabolic disorders.[37,38] A study examined the relationship between body fat characteristics and insulin resistance in South Asian men (n = 29) compared to Caucasians (n = 18). They found that insulin resistance was related to large subcutaneous adipocyte size rather than intraperitoneal fat mass, indicating that truncal fat may play a bigger role than visceral fat excess.[39] Larger adipocytes have a more pro-inflammatory gene expression profile. Adipocyte turnover studies have indicated that the overall size of the adipocyte mass has a higher set-point

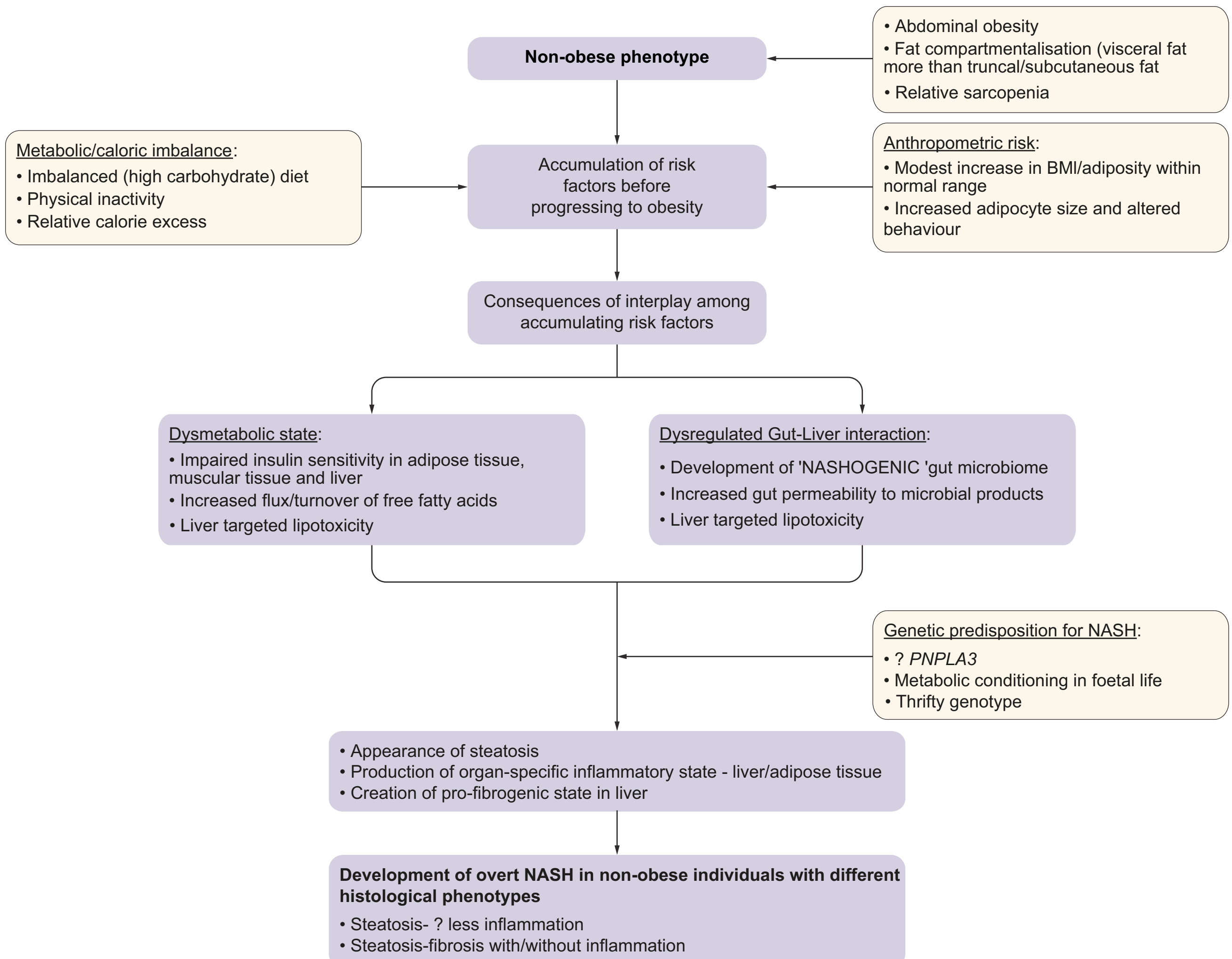

Fig. 1. Pathophysiological concepts underlying development of NASH in non-obese individuals. BMI, body mass index; NASH, non-alcoholic steatohepatitis.

at turnover equilibrium in obese individuals than in lean individuals during childhood and adolescence, although the turnover in adulthood is similar in both lean and obese individuals. In adulthood, hypertrophy is the principal mechanism for expansion of the adipose tissue mass.

The age-dependence of mechanisms by which adipose tissue mass expands may be relevant in various socio-economic contexts. For example, in economically developing nations, access to excess calories often occurs in adulthood following long periods of childhood malnutrition, whereas dietary excess and diet-induced obesity often develop during childhood in the West. The precise mechanisms by which these differing mechanisms contribute to altered adipocyte biology, lipid trafficking, insulin sensitivity and propensity for adipose tissue inflammation in lean versus obese individuals remain to be defined.

The skeletal muscle compartment is another important determinant of metabolic homeostasis. In the post-prandial state, it is the site of glucose clearance from the circulation, which is impaired in the insulin resistant state.[40] This provides more glucose for hepatic uptake where it can be converted to glycogen, undergo glycolysis followed by oxidation, or be used for *de novo* lipogenesis. In the fasting state, the liver generates glucose via gluconeogenesis and the skeletal muscle increases fat oxidation.[41] This ability to switch metabolic substrate is critical for metabolic homeostasis and its failure is linked to the development of insulin resistance. Sarcopenia is commonly present along with increased adipose tissue mass in patients with NAFLD.[42]

Multiple studies in Asia and Europe revealed a relationship between low muscle mass and the

Box 2. Genetic variants in lean NAFLD.

1. A single variant in the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*), the rs738409
2. Cholesteryl ester transfer protein (*CETP*) : Two single-nucleotide polymorphisms (rs12447924 and rs12597002)
3. A single nucleotide polymorphism in transmembrane 6 superfamily member 2 (*TM6SF2*) rs58542926 C
4. The interferon (*IFN*) lambda 4 rs368234815 TT
5. Deficiency of the phosphatidylethanolamine N-methyltransferase (*PEMT*)

NAFLD, non-alcoholic fatty liver disease.

increased risk of NAFLD.[103,104] Decreased muscle mass may impact NASH by impairing fat utilisation and reducing the body's ability to clear glucose. Beta cell function is another key element in the development of the systemic milieu in which NAFLD develops. Beta cell mass and function are supported by glucagon-like peptide 1 (GLP1) and the intestinal incretin response is an important mechanism of cross-talk between the intestine and pancreas. Bile acids produced by the liver can also modulate beta cell function via both FXR and TGR5-mediated mechanisms [43]; importantly, the bile acid profile changes early in diet-induced obesity and switches to a profile with poorer affinity for FXR and TGR5. It is not known if there are clinically or pathophysiologically important differences between lean and obese individuals with respect to their beta cell status.

Insulin resistance as a key element in the development of NAFLD in lean individuals

Insulin resistance is defined operationally by the relationship between circulating insulin and glucose under steady state conditions. This is frequently measured by the homeostatic model for insulin resistance (HOMA-IR). While this is useful in epidemiological studies, this measure provides only limited information in individual patients and is subject to considerable laboratory-to-laboratory variability in insulin measurements. The gold-standard for the assessment of insulin resistance is therefore a euglycemic hyperinsulinaemic clamp.[44]

Lean individuals with NAFLD have a higher HOMA-IR and circulating triglyceride levels compared to lean individuals without NAFLD, confirming the relationship between NAFLD and insulin resistance.[4,45] The mechanisms of insulin resistance in lean individuals are generally considered to be similar to those in obese individuals. In a case-control study, serum free fatty acid (FFA) profiles were significantly higher in patients with NAFLD than healthy controls; these FFA profiles were positively associated with almost all metabolic indicators, especially blood glucose, lipid and liver enzymes.[101] The study observed 14:0 and 16:1 as unique FFAs of prominent diagnostic importance for the early screening of NAFLD. Lean and overweight patients with NAFLD had similar concentrations of all FFAs, but obese patients with NAFLD presented significantly higher levels of all types of FFA.[101] A study that analysed data from the NASH-CRN found a significant interaction between HOMA-IR and ethnicity (p <0.001) even after excluding diabetic participants. HOMA-IR was not a significant risk factor for NASH among Latinos, but it was a significant risk factor among non-Latino Whites.[102]

Even in children, some studies have shown that there is an association between intrauterine growth retardation and development of paediatric NAFLD – independent of and in addition to insulin resistance – independently of age, sex, BMI, and genetic inheritance.[105]

Development of steatosis and steatohepatitis

The precise mechanism of development of steatosis and steatohepatitis depends on the specific aetiology underlying the development of the condition in a lean individual. Hepatic steatosis results when triglyceride synthesis exceeds its utilisation and export. Lean individuals with increasing adiposity and insulin resistance are likely to recapitulate this pathophysiology, although the contribution of specific nutrients such as fructose in specific settings remains largely unexplored.

Beta sitoterolemia is associated with increased uptake of dietary cholesterol and may lead to fatty liver disease; in animal models, cholesterol loading leads to more severe NAFLD.[46]

The progression to steatohepatitis involves activation of cell stress signalling as a consequence of delivery of a toxic load of lipids within the hepatocyte. Several studies have attempted to determine if there are unique metabolites associated with NASH in lean individuals. It has been postulated that the levels of phosphatidylcholines, sphingolipid and lysophosphatidylcholines (lyso-PCs) can distinguish individuals with lean NAFLD.[47] Amino acid and acyl-carnitine profile may also differentiate between lean and obese individuals with NAFLD. Lower lyso-PC concentrations were found in lean NAFLD. Low levels of lyso-PCs have been linked to obesity,[48] and hypertriglyceridemia,[49] indicating that lyso-PCs may play a role in NAFLD development.[31] It was also found that the levels of short-chain acyl-carnitines C3 and C4 were lower in lean individuals with NAFLD than in obese individuals, suggestive of relatively preserved mitochondrial function.[50] Also, studies have reported higher concentrations of lysine and lower concentrations of alanine, tyrosine and valine in lean individuals with NAFLD than in obese individuals with NAFLD.[31] These studies await independent validation.

The hallmark of NASH is the development of hepatocellular ballooning, which is associated with disruption of cytoskeletal architecture and accumulation of ubiquitinated compounds that cannot be eliminated because of proteasomal dysfunction.[51] However, ubiquitin staining is present even in cells that are not ballooned, suggesting that the histological manifestation of ballooning is a late feature that follows progressive intracellular architectural and proteasomal dysfunction. There are currently no data to indicate that unique mechanisms come into play in the development of hepatocellular ballooning in lean individuals with steatohepatitis.

The inflammatory response in NASH is initiated both by extrahepatic and intrahepatic cues.

Extrahepatic drivers of inflammation include circulating inflammatory cytokines and cytotoxic lipids, as well as activation of toll-like receptors in response to gut-derived products.[52] Intracellular stress and injury secondary to activation of oxidative stress, mitochondrial dysfunction and endoplasmic reticulum stress result from activation of intracellular inflammatory pathways by modified cell proteins and lipids. Inflammasome activation has been demonstrated in the liver of humans with NASH.[53] There are no published data to indicate that there are unique inflammatory paths that are linked to a lean body habitus or a specific aetiology of NASH. Fibrosis and fibrogenic remodelling of the liver are also downstream events in response to activation of stellate cells. There are also no data to indicate the presence of unique stellate cell pathways in lean individuals with NASH. Thus, currently it is believed that progressive NASH in lean individuals involves activation of pathways similar to those in obese individuals and that disease progression is linked to quantitative differences involving genetic, dietary, molecular and cellular changes in various organs in a given individual.

Clinical profile of NAFLD in lean individuals

The clinical profile

A priori, one would expect the distribution of causes of NAFLD in lean individuals to vary with both geography and the clinical site. Thus, in Europe, coeliac disease and *PNPLA3* mutations may be over-represented in these populations. Unfortunately, the existing studies from the USA or Europe have not systematically evaluated the distribution of specific aetiologies within the lean population. Thus, this remains a gap in current knowledge. The situation in economically developing nations is similarly confounded with the additional possibility of malnutrition-induced insulin resistance or recurrent gastrointestinal infections in some cases, particularly in rural impoverished regions or regions with poor water quality. Furthermore, with economic development, there has also been a surge of adiposity even within the normal BMI category, and lean individuals with NAFLD often have increased visceral adipose tissue and sarcopenia.[54]

Symptoms, signs and comorbidity profile

There are no specific presenting symptoms or signs of NAFLD in most patients. Fatigue, right upper quadrant discomfort, incidental identification of abnormal liver enzymes or hepatic steatosis noted on imaging done for unrelated reasons or during abdominal surgery remain the most common methods of presentation. There are no data to indicate that lean individuals with NAFLD have a different profile with respect to symptoms. Impairment of activities of daily living do not usually occur until cirrhosis develops.

As seen in obese populations, the prevalence of comorbidities that are over-represented in the NAFLD population such as type 2 diabetes, hypertension and dyslipidaemia are similarly over-represented in lean populations who have not been systematically screened for rare disorders. Medications for diabetes, hypertension, dyslipidaemia, depression and opioids are amongst the most common concomitant drugs used in patients with NASH in the West.[55] There are no data from Asia on either the pill burden or distribution of concomitant medications in large unselected groups of individuals with NAFLD.

The physical findings in those with NAFLD and a lean habitus depend on the presence of an underlying lipodystrophic disorder and the general increase noted in visceral adipose tissue seen across multiple studies from different Asian countries.[13,56,57] Diabetic Asian Indians have significantly higher volumes of total abdominal fat (19.4%), total intra-abdominal fat (49.7%), intraperitoneal fat (47.7%) and retroperitoneal fat (70.7%) compared to non-diabetic controls.[58]

Laboratory abnormalities

It has been reported that compared to obese patients without NAFLD, lean patients with NAFLD have a similar degree of dyslipidaemia and hypertriglyceridaemia.[59] They also had higher serum ferritin, haemoglobin and haematocrit, compared to obese patients without NAFLD.[59] Previous studies suggested that elevated serum ferritin, haemoglobin and triglyceride levels may be markers of liver disease in lean individuals.[60,61] An epidemiological study from India reported on a poor rural community in which non-obese and lean patients (average BMI 19.6 ± 6.6 kg/m^2) with NAFLD had higher levels of triglycerides, higher fasting blood glucose, and more subcutaneous fat than those without NAFLD.[17]

Histological spectrum of disease

The liver histology may be considered in 2 ways: i) common features of NAFLD, and ii) findings suggestive of a unique aetiology. The histological spectrum of NAFLD in HIV and lipodystrophies has been reviewed elsewhere.[62,63] Wolman disease can be diagnosed by pathognomonic birefringent cholesterol crystals, although they are not always seen.[64] Foamy histiocytes and increased small droplet steatosis should raise suspicions of a partial lysosomal acid lipase deficiency.[65] With respect to common NAFLD findings, lean patients are identical to obese counterparts.[66] The histological studies on NAFLD in common unspecified lean populations are summarized in Table 3. A study on patients with advanced liver disease undergoing liver biopsy showed that NAFLD in lean individuals was the most common cause of cryptogenic liver disease.[14]

Natural history and progression to cirrhosis

There is a remarkable paucity of rigorously obtained prospective adjudicated data on the natural history of NAFLD using standardised predefined case definitions, criteria for follow-up assessments and masked assessment of histology. This is also true for NAFLD in lean individuals and our current understanding of disease progression is based on retrospective cross-sectional analyses of existing datasets, which are susceptible to all of the biases associated with such data. A multiethnic NAFLD cohort from the USA revealed that liver disease progression was less rapid in non-obese individuals.[67] Although the proportion of those with advanced fibrosis was similar, liver failure, hepatocellular carcinoma and overall mortality were lower in those with non-obese versus obese NAFLD. These results suggest that there are additional factors which may influence clinical decompensation rates. We hypothesize that obese individuals who have specific alterations in the microbiome, bile acid profile and intestinal permeability may be more susceptible to bacterial translocation and systemic inflammation and thus decompensate more easily than lean individuals. This of course remains to be verified experimentally.

Clinical outcomes

Clinically meaningful outcomes are defined by how an affected individual "feels, functions or survives".[68] There are no data on patient reported outcomes (PRO) in lean individuals with NAFLD and current PRO instruments have not been developed to regulatory specifications. While activities of daily living are an established PRO, there are no published data on the subject. However, these are not impacted until cirrhosis develops in most chronic liver diseases. The situation is further confounded by background obesity which does impair activities of daily living.

In Western populations, there is an excess of cardiovascular, cancer and liver related mortality in those with NAFLD.[69] A Chinese study identified NAFLD without obesity to be a significant risk factor for diabetes mellitus and metabolic syndrome.[70] In a large cohort of non-obese Asian individuals, an association was suggested between the severity of NAFLD and cardiovascular disease.[71]

Survival in lean individuals with NAFLD continues to be debated. A pooled analysis found a U-shaped association between BMI and the risk of death in East Asian populations, as has been seen in many Western populations. Studies have shown that among Asians, the risk of death is more strongly affected by a low BMI than by a high BMI, when compared with Europeans.[72] However, this is an artefact caused by the overrepresentation of undernutrition in Asian cohorts with a BMI that is low by Asian standards, a cohort which is underrepresented in Europeans. In 2014, a study found that the cumulative survival was significantly shorter in lean patients with NAFLD compared to non-lean patients with NAFLD over a follow-up period of 133 months.[73] Even after adjustment in a Cox regression model with only lean NAFLD, this difference in survival remained significant (hazard ratio (HR) 11.8; 95% CI 2.8–50.1; p = 0.001). Surprisingly, they reported a lower fibrosis stage in the lean population, suggesting extrahepatic causes for increased mortality. Another study performed in Hong Kong came to opposite conclusions.[67] A recent study by Hagström *et al.*[91] reported that lean patients are at higher risk of developing severe liver disease (HR 2.69; p = 0.007) compared to patients with NAFLD and a higher BMI (HR 1.11; p= 0.74), independent of available confounders.

Diagnostic approach

It is important to look for and treat specific aetiologies of NAFLD in lean individuals, when present. In others, the diagnostic approach is focused on identification of excess fat in the liver and the risk of outcomes, which is linked to the fibrosis stage. Comorbidities should be carefully evaluated and managed since they contribute substantially to mortality in this population.

MR proton density fat fraction (MR-PDFF) has emerged as an excellent non-invasive reference tool for quantitative assessment of NAFLD.[74] The use of the continuous attenuation parameter (CAP) along with transient elastography provides a widely available and relatively inexpensive option to identify hepatic steatosis.[75] Multiple studies in Asia have shown variable thresholds for the diagnosis of

Table 3. Comparison of histological features between lean and non-lean individuals with fatty liver disease.

Study	Lean/non-lean	Steatosis in lean	Fibrosis in lean
Alam *et al.*[90](Bangladesh)	56/164	↔	↔
Margariti *et al.*[84] (Greece)	8/48	↔	↔
Leung *et al.*[67] (USA)	72/235	↓severity	Less prevalent, ↓severity
Dela Cruz *et al.*[73] (USA)	125/965	↓severity	↓severity

Adapted from Kumar, R. and S. Mohan, Non-alcoholic Fatty Liver Disease in Lean Subjects: Characteristics and Implications. *J Clin Transl Hepatol*, 2017. 5(3): p. 216-223. "This article has been published in Journal of Clinical and Translational Hepatology at doi:10.14218/JCTH.2017.00068 and can also be viewed on the Journal's website at http://www.jcthnet.com".

steatosis using the XL versus the M probe in lean individuals.[76,77] Specific cut-offs have also been proposed for different BMI strata.[78] The CAP is both sensitive and specific for the diagnosis of pathological steatosis, but it is not very accurate for distinguishing between varying degrees of severity of steatosis.[79]

Transient elastography using the Fibroscan® has provided the largest amount of data in this regard and the liver stiffness measured by this method is related to mortality risk. 2D-MR elastography is modestly superior to transient elastography and is another option, where available and cost-effective. MR elastography is not impacted by the physical characteristics outside the liver. Thus, while a liver biopsy is the reference standard, MR elastography is used mainly when there is diagnostic uncertainty and is increasingly being relegated to the role of a research tool.

Principles of management

There is scarce data on the management of NAFLD/NASH in lean individuals. Specific aetiologies of NASH should be treated when found. However, in the remaining individuals, the principles of management are similar to those in obese individuals. This is based on the excess adipose tissue, markers of insulin resistance and systemic inflammation, dyslipidaemia seen in lean individuals with NAFLD versus those without NAFLD. We recommend the following approach, realising that it reflects a low grade of evidence. Where available, simple tools such as a DEXA scan enable body composition analysis, which serves as an independent objective guide to therapeutic success in terms of decreasing adiposity. Overall caloric intake should be tailored to local guidelines and individual patient needs, to reduce adipose tissue mass and maintain or restore muscle mass. Metabolic health may also be boosted by attention to duration and quality of sleep.[113,114] Individuals with snoring or severe early morning fatigue should be evaluated for sleep apnoea. Weight loss and physical fitness are interlinked and a combination of dietary changes and physical activity are most likely to succeed. Dietary recommendations should ideally be provided in a social and cultural context where they are acceptable.

Pharmacological therapy is restricted for those with active NASH and at least stage 2 fibrosis. The specific drugs available and current drug development efforts have been extensively reviewed and are not distinct for those who are lean.[80] However, many trials exclude individuals who are lean. It is hoped that phase IV studies, following drug approval, will include such individuals, to determine whether specific treatments are also effective in this population. Evidence on effective pharmacotherapy in lean patients with NASH remains lacking. Not only pharmacological therapy, but also the impact of changes in physical activity and caloric intake need further study in this particular population.

Conclusion

In summary, individuals who are lean may also develop NAFLD. This is particularly true in populations that are mostly lean, as seen in Asia. However, the development of NAFLD is associated with increasing adiposity, biochemical evidence of insulin resistance and an acute phase reaction, and increased risk of type 2 diabetes. These individuals thus represent a subset where the disease manifests at lower overall BMI thresholds but where there is increased visceral adipose tissue. In addition, in specific regions and clinical situations, there are other unique aetiologies for NAFLD that must be considered which require specific treatments.

Conflicts of Interest

Dr. Albhaisi has no conflicts of interest. Dr.Chowdhury has no conflicts of interest. Dr. Sanyal is President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz and Hemoshear. He has served as a consultant to Astra Zeneca, Nitto Denko, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Fibrogen, Jannsen, Gilead, Lilly, Poxel, Artham, Cymabay, Boehringer Ingelhiem, Novo Nordisk, Birdrock, Novartis, Pfizer, Jannsen and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affimune, Chemomab, Nordic Bioscience and Bristol Myers Squibb. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck, Astra Zeneca, Malinckrodt, Cumberland and Novartis. He receives royalties from Elsevier and UptoDate.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhepr.2019.08.002.

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