Non-alcoholic fatty liver disease in lean individuals

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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 (NAFL) to non-alcoholic steatohepatitis (NASH) 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. Excess body weight, type 2 diabetes and dyslipidaemia are classic risk factors for NAFLD. Although, it is now recognised that the condition exists in those who are not obese, especially in Asia. 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 into account the varying case definitions for the term “lean” in the West (<25 kg/m²) versus in Asia (<22 kg/m²). 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]); 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. 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. 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.
but even from rural to urban areas, especially in the Asian subcontinent. 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. 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. 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. In Asia, the prevalence of NAFLD has been reported to vary from 12.6% of unselected patients to 27% of lean individuals. 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. 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. The NHANES study reported a prevalence of NAFLD of 7.9% in lean individuals in the USA, whereas an ultrasound-based study from Italy reported a 16% prevalence of lean NAFLD.

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. Similar data have been reported from China. 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.

Pathogenesis of NAFLD in lean individuals

The broad pathogenic basis for NAFLD and its more aggressive phenotype NASH is now established. 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            | NAS              | Fibrosis               | Insulin resistance              |
| Steatohepatitis      | - Steatosis      | - Stage 0: No fibrosis | Alcohol                         |
| Indeterminate        | - Lobular inflam | - Stage 1a: Mild perisinusoidal | Lean NASH                     |
|                      | - Ballooning     | - Stage 1b: Moderate perisinusoidal | PNPLA3+                       |
|                      | SAF              | - Stage 1c: Portal/periportal | Drugs                          |
|                      | - Steatosis      | - Stage 2: Perisinusoidal and portal/periportal | Inherited disorders (e.g., Weber-Christian, hypobetalipoproteinemia) |
|                      | - Lobular inflam | - Stage 3: Bridging    | Lipodystrophy                   |
|                      | - Ballooning     | - Stage 4: Cirrhosis   | Short bowel                     |
|                      | - Fibrosis       |                        | TPN                             |

*Copyright belongs to Siddiqui, M.S., et al. Case definitions for inclusion and analysis of endpoints in clinical trials for non-alcoholic steatohepatitis through the lens of regulatory science. Hepatology. 2018. 67(5); p. 2001–2012. No changes were made to this table. DOI: https://creativecommons.org/licenses/by-nc-nd/4.0*
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 include abetalipoproteinemia, hypobetalipoproteinemia, familial combined hyperlipidemia, glycogen storage disease, Weber-Christian syndrome, and lipodystrophy. 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. The patatin-like phospholipase domain containing 3 (PNPLA3) gene and its non-synonymous gene variant, the rs738409 C/G encoding an isoleucine to 148 (I148M), was the first major gene associated with an increased risk of hepatic steatosis, particularly in non-obese individuals. Another relevant correlation is that insufficiency of phosphatidylethanolamine N-methyltransferase (PEMT) increases the risk of NASH in lean individuals.

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. In general, even within the lean population, those with NAFLD tend to consume greater calories. 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. 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 (β = 0.174, p = 0.022). 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. 

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

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. 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. 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. Another relevant correlation is that insufficiency of phosphatidylethanolamine N-methyltransferase (PEMT) increases the risk of NASH in lean 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., 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., 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., 2012 | Korea | Hospital cohort (Selected non-obese individuals) | 5,878 | 5,878 (100) | 1,611 (27.4%) | 381 (23.6%) | 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., 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., 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., 2015 | Hong Kong | General population (Urban) | 911 | 135 (51.52) | Overall 262 (28.8) Non-obese 135 (19.3) Obese 127 (17.4) | 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., 2012 | USA | National Health and Nutrition Examination Survey III (NHANES III) database | 11613 | 431 (17.20) | Overall 2492 (21.45) Non-obese 431 (3.71) Obese 127 (17.4) | NR | USG | HOMA-IR | IR and dyslipidaemia were not associated with NAFLD in non-obese. NASH was associated with MS |
| Bugianesi E et al., 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., 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., 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., 1999 | Italy | Hospital cohort | 46 | – | Not designed to see prevalence | – | USG | HOMA-IR | NAFLD was associated with IR even in non-obese individuals |
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 NASH 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/m², 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 \( 11\beta \) 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

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### Table 2 (continued)

| Author; Year | Country | Population | Sample size (n) | Proportion of non-obese among NAFLD individuals⁰ | Prevalence of NAFLD; 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.,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.,103 | 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 |

⁰Non-obese defined as BMI <25 kg/m²; ¹Unadjusted prevalence; ²Non-obese defined as BMI <25 kg/m² 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.
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. 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 accumulation of risk factors before progressing to obesity. This includes:

- **Metabolic/caloric imbalance**
  - Imbalanced (high carbohydrate) diet
  - Physical inactivity
  - Relative calorie excess

- **Anthropometric risk**
  - Modest increase in BMI/adiposity within normal range
  - Increased adipocyte size and altered behaviour

- **Dysmetabolic state**
  - Impaired insulin sensitivity in adipose tissue, muscular tissue and liver
  - Increased flux/turnover of free fatty acids
  - Liver targeted lipotoxicity

- **Dysregulated Gut-Liver interaction**
  - Development of ‘NASHogenic’ gut microbiome
  - Increased gut permeability to microbial products
  - Liver targeted lipotoxicity

- **Genetic predisposition for NASH**
  - PNPLA3
  - Metabolic conditioning in foetal life
  - Thrifty genotype

**Development of overt NASH in non-obese individuals with different histological phenotypes**

- Steatosis
- Hepatic steatosis
- Steatohepatitis
- Fibrosis

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

**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. 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; 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.

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. 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. 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. 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.

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.

**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.

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. 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, and hypertriglyceridemia, indicating that lyso-PCs may play a role in NAFLD development. 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. 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. 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. 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. 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. There are no published data to indicate that there are unique inflammatory pathways 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.

**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. 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. Diabetic Asian Indians have significantly higher volumes of total abdominal fat (19.4%), total intra-abdominal fat (49.7%), intra-peritoneal fat (47.7%) and retroperitoneal fat (70.7%) compared to non-diabetic controls.

**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. They also had higher serum ferritin, haemoglobin and haematocrit, compared to obese patients without NAFLD. Previous studies suggested that elevated serum ferritin, haemoglobin and triglyceride levels may be markers of liver disease in lean individuals.

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/m²) with NAFLD had higher levels of triglycerides, higher fasting blood glucose, and more subcutaneous fat than those without NAFLD.

**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. Wolman disease can be diagnosed by pathognomonic birefringent cholesterol crystals, although they are not always seen. Foamy histiocytes and increased small droplet steatosis should raise suspicions of a partial lysosomal acid lipase deficiency. With respect to common NAFLD findings, lean patients are identical to obese counterparts. 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.\textsuperscript{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 pre-defined 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 multi-ethnic NAFLD cohort from the USA revealed that liver disease progression was less rapid in non-obese individuals.\textsuperscript{66} 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”.\textsuperscript{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 validated instruments that are currently available for quantitative assessment of NAFLD.\textsuperscript{74} The tool for quantitative assessment of NAFLD, MR proton density fat fraction (MR-PDFF) has emerged as an excellent non-invasive reference tool for quantitative assessment of NAFLD.\textsuperscript{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.\textsuperscript{75} Multiple studies in Asia have shown variable thresholds for the diagnosis of individuals, an association was suggested between the severity of NAFLD and cardiovascular disease.\textsuperscript{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.\textsuperscript{72} However, this is an artefact caused by the over-representation 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.\textsuperscript{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.\textsuperscript{67} A recent study by Hagström \textit{et al.}\textsuperscript{70} 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.\textsuperscript{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.\textsuperscript{75} Table 3 shows the comparison of histological features between lean and non-lean individuals with fatty liver disease.

**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 \textit{et al.}\textsuperscript{69} (Bangladesh) | 56/164        | --                | --              |
| Margariti \textit{et al.}\textsuperscript{64} (Greece) | 8/48          | --                | --              |
| Leung \textit{et al.}\textsuperscript{84} (USA)   | 72/235        | \textit{less severity} | Less prevalent, \textit{less severity} |
| Dela Cruz \textit{et al.}\textsuperscript{70} (USA) | 125/965       | \textit{less severity} | \textit{less 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/JCTH201700068 and can also be viewed on the Journal’s website at http://www.jctnet.com".

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steatosis using the XL versus the M probe in lean individuals.\textsuperscript{76,77} Specific cut-offs have also been proposed for different BMI strata.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. Albhai 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, Direc, Exhalen and Hemoshear. He has served as a consultant to Astra Zeneca, Nitto Denko, Arde-lyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Fibro- gen, Janssen, Gilead, Lilly, Poxel, Artham, Cymahay, Boehringer Ingelheim, Novo Nordisk, Birdrock, Novartis, Pfizer, Janssen and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affinune, Chemomab, Nordic Bioscience and Bristol Myers Squibb. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck, Astra Zeneca, Malnickrodt, 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.

**References**

[1] Sattar N, Forrest E, Preiss D. Non-alcoholic fatty liver disease. BMJ 2014;349:g4596.
[2] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20.
[3] Kojima S, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty liver in Japan over the past 12 years: analysis of clinical background. J Gastroenterol 2003;38:954–961.
[4] Younossi ZM, Stepanova M, Negro F, Hallaj S, Younossi Y, Lam B, et al. Nonalcoholic fatty liver
Non-alcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore) 2012;91:319–327.

[5] Tabibian JH, Kim MY, Hwang ES, Park YH, Jeon HE, Lee SG, et al. Prevalence and Severity of Nonalcoholic Fatty Liver Disease in Non-Obese Patients: A Population Study Using Proton-Magnetic Resonance Spectroscopy. Am J Gastroenterol 2015;110:1306–1314 quiz 1315.

[6] Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol 2017;67:862–873.

[7] Siddiqui MS, Harrison SA, Abdelmalek MF, Ansteet QM, Bedossa P, Castera L. et al. Case definitions for inclusion and analysis of endpoints in clinical trials for nonalcoholic steatohepatitis through the lens of regulatory science. Hepatology 2018;67:2001–2012.

[8] Chowdhury A, Younossi ZM. Global Epidemiology and Risk Factors for Nonalcoholic Fatty Liver Disease. In: Chalasani N, & Szabo G, editors. Alcoholic and Non-Alcoholic Fatty Liver Disease. Cham: Springer. p. 21–40.

[9] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymr M. Global epidemiology of nonalcoholic fatty liver disease:Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.

[10] Riquelme A, Arrese M, Soza A, Morales A, Baudrand R, Perez-Ayuso RM, et al. Non-alcoholic fatty liver disease and its association with obesity, insulin resistance and increased serum levels of C-reactive protein in Hispanics. Liver Int 2009;29:82–88.

[11] Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1689 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377–1396.

[12] Vos B, Lazarovici P, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–285.

[13] Deurenberg-Yap M, Schmidt G, van Staveren WA, Deurenberg P. The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. Int J Obes Relat Metab Disord 2000;24:1011–1017.

[14] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymr M. Global epidemiology of nonalcoholic fatty liver disease:Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.

[15] Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1689 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377–1396.

[16] Vos B, Lazarovici P, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–285.

[17] Deurenberg-Yap M, Schmidt G, van Staveren WA, Deurenberg P. The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. Int J Obes Relat Metab Disord 2000;24:1011–1017.

[18] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymr M. Global epidemiology of nonalcoholic fatty liver disease:Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.

[19] Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1689 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377–1396.

[20] Vos B, Lazarovici P, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–285.

[21] Deurenberg-Yap M, Schmidt G, van Staveren WA, Deurenberg P. The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. Int J Obes Relat Metab Disord 2000;24:1011–1017.
Caussy C, Reeder SB, Sirlin CB, Loomba R. Noninvasive, Quantitative Dela Cruz AC, Bugianesi E, George J, Day C, Liaquat H, Charatcharoenwitwan X, Xu C, Yu C, Li Y. Role of NLRP3 Inflammasome in the Progression HH AK. Lysosomal acid lipase deficiency: a form of non-obese fatty liver Leung JC, Loong TC, Wei JL, Wong GL, Chan AW, Choi PC, et al. Histological Wattacheril J, Chalasani N. Nonalcoholic fatty liver disease (NAFLD): is it Zheng W, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K, et al. Can the same controlled attenuation parameter cut-offs be used for M patients with non alcoholic fatty liver disease. Gastroenterology Liver Int 2017;37:97–103. Dudeja V, Misra A, Pandey RM, Devina G, Kumar G, Vikram NK. BMI does not accurately predict overweight in Asian Indians in northern Br J Nutr 2001;86:105–112. Banerji MA, Fardini N, Attiri L, Chailken RL, Lebovitz HE. Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. J Clin Endocrinol Metab 1999;84:137–144. Misra A, Anoop S, Gulati S, Mani K, Bhattacharjee SM, Pandey RM. Body Fat Pattern, Hepatic Fat and Pancreatic Volume of Non-Obese Asian Indians with Type 2 Diabetes in North India: A Case-Control Study. PLoS One 2015;10:e0140447. Bernhardt P, Kratzer W, Schmidberger J, Graeter T, Gruener B, Group ES. Laboratory parameters in lean NAFLD: comparison of subjects with lean NAFLD with obese subjects without hepatic steatosis. BMC Res Notes 2018;11:101. Agarwal Y, Yesal AA, Yilmaz Y. Characterization of lean patients with non- cholic fatty liver disease: potential role of high hemoglobin levels. Scand J Gastroenterol 2015;50:341–346. Jiayi Zeng, J Chen B. Hemoglobin combined with triglyceride and ferritin in predicting non-alcoholic fatty liver. J Gastroenterol Hepatol 2014;29:1508–1514. Sterling RK, Smith PG, Brunt EM. Hepatic steatosis in human immunode- ernergy virus: a prospective study in patients without viral hepatitis, dia- betes, or alcohol abuse. J Clin Gastroenterol 2013;47:182–187. SAFAR Zadeh E, Lungu AA, Cochran EK, Brown RJ, Ghany MG, Hellinger T, et al. The liver diseases of lipodystrophy: the long-term effect of leptin treatment. J Hepatol 2013;59:131–137. Bernstein DL, Hulten H, Blader MG, Desnick RJ. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol 2013;58:1230–1243. HH AK. Lysosomal acid lipase deficiency: a form of non-obese fatty liver disease (NFLD). Expert Rev Gastroenterol Hepatol 2017;11:911–92. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalco- holic fatty liver disease. Hepatology 2005;41:1313–1321. Leung JC, Loong TC, Wei JL, Wong GL, Chan AW, Choi PC, et al. Histologi- cal severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology 2017;65:54–64. Chalasani N, Szabo G. Alcoholic and non-alcoholic fatty liver disease: Bench to Bedside. Springer International Publishing, 2015, https://doi.org/10.1007/978-3-319-20538-4. Wattacheril J, Chalasani N. Nonalcoholic fatty liver disease (NAFLD); is it really a serious condition? Hepatology 2012;56:1580–158. Feng RN, Du SS, Wang C, Li YC, Liu LY, Guo FC, et al. Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population. World J Gastroenterol 2014;20:17932–17940. Sung KC, Ryan MC, Wilson AM. The severity of nonalcoholic fatty liver disease is associated with increased cardiovascular risk in a large cohort of non-obese Asian subjects. Atherosclerosis 2009;203:581–586. Zheng W, McIlernan DF, Rolland B, Zhang X, Inoue M, Matsuo K, et al. Association between body-mass index and risk of death in more than 1 million Japanese. N Engl J Med 2011;364:719–729. De la Cruz AC, Bugianesi E, George J, Day C, Li Y, Lebovitz HE, Charatcharoenwitwan X, et al. Characteristics and long term prognosis of lean patients with non alcoholic fatty liver disease. Gastroenterology 2014;146:9–909. Causby C, Reeder SB, Sirlin CB, Loomba R. Noninvasive, Quantitative Assessment of Liver Fat by MRI-PDFH as an Endpoint in NAS Clinical Trials. Hepatology 2010;52:763–772. Mikolasevic I, Orlic L, Franic N, Hauser G, Stimac D, Milic S. Transient elastography (FibroScan (R)) with controlled attenuation parameter in the assessment of liver steatosis and fibrosis in patients with nonalco- holic fatty liver disease - Where do we stand? World J Gastroenterol 2016;22:7236–7251. Chan WK, Nickstam NR, Mahadeva S, Wong VW, Cheng JY, Wong GI. Can the same controlled attenuation parameter cut-offs be used for M and XL probes for diagnosing hepatic steatosis? J Gastroenterol Hepatol 2018;33:1787–1794. Gervino VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalco- holic fatty liver disease. Hepatology 2010;51:454–462. Durango E, Dietrich C, Seitz HK, Kunz CU, Pomier-Layrargues GT, Duarte- Rojo A, et al. Direct comparison of the FibroScan XL and M probes for assessment of liver fibrosis in obese and nonobese patients. Hepat Med 2013;7:43–52. Wang Y, Fan Q, Wang T, Ren J, Wang H, Zhang T. Controlled attenuation parameter for assessment of hepatitis steatosis grades: a diagnostic meta- analysis. Int J Clin Exp Med 2015;8:17654–17663. Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD. J Gastroenterol 2018;53:362–376. Yvsavisvan H. Nonalcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol 2014;2:901–910. Kim HJ, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, et al. Metabolic signifi- cance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med 2004;164:2169–2175. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ, Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24:908–918. Margaritis A, Deutsch M, Manolakopoulos S, Tiniakos D, Papadopoulos GV. The severity of histologic liver lesions is independent of body mass index in patients with nonalcoholic fatty liver disease. J Clin Gastroenter- ology 2014;48:280–286. Sinn DH, Gwak CY, Park HN, Kim JE, Min YW, Kim KM, et al. Ultrasono- graphically detected non-alcoholic fatty liver disease is an independent predictor for identifying patients with insulin resistance in non-obese, non-diabetic middle-aged Asian adults. Am J Gastroen- terol 2012;107:561–567. Kwon YM, Oh SW, Hwang SS, Lee C, Kwon H, Chung GE. Association of nonalcoholic fatty liver disease with components of metabolic syndrome according to body mass index in Korean adults. Am J Gastroenterol 2012;107:1852–1858. Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassidy M, Baldi S, et al. In insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. Diabetes 2005;48:634–642. Musso G, Gambino R, Bo S, Uberti B, Birolli G, Pagano G, et al. Should non- alcoholic fatty liver disease be included in the definition of metabolic syn- drome? A cross-sectional comparison with Adult Treatment Panel III criteria in nonobese nondiabetic subjects. Diabetes Care 2008;31:562–568. Marchesini G, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullo- rough AJ, et al. Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med 1999;107:450–455. Alam S, Gupta UD, Alam M, Kabir J, Chowdhury ZR, Alam AK. Clinical, anthropometric, biochemical, and histological characteristics of nonobese nonalcoholic fatty liver disease patients of Bangladesh. Indian J Gastroenterol 2013;33:452–457. Hjorth Mørch H, Nasr P, Ekelund M, Hammar U, Stal P, Hultcrantz R, et al. Risk for development of severe liver disease in lean patients with nonalco- holic fatty liver disease: A long-term follow-up study. Hepatol Commun 2018;2:48–52. Kneeman JM, Misraji J, Corey KE. Secondary causes of nonalcoholic fatty liver disease. Therap Adv Gastroenterol 2012;5:199–207. Zeissig S, Dougan SK, Barral DC, Junker Y, Chen Z, Kaser A, et al. Primary deficiency of microsomal triglyceride transfer protein in human abetalipo- proteinemia is associated with loss of CD1 function. J Clin Invest 2010;120:2889–2899. Harada N, Satojiya Y, Takanami K, Kusano S, Ikeda T, Uchida K, et al. Recurrent familial hypobetalipoproteinemia-induced nonalcoholic fatty liver disease after living donor liver transplantation. Liver Transpl 2014;20:605–809. de Bruin TW, Georgiev AM, Brouwers MC, Hettink AM, van der Kallen CJ. Radiological evidence of nonalcoholic fatty liver disease in Chinese male workers: a cross- sectional study. BMJ Open 2016;6:e011939.
Conte C, Fabbrini E, Kars M, Mittendorfer B, Patterson BW, Klein S. Multi-organ insulin sensitivity in lean and obese subjects. Diabetes Care 2012;35:1316–1321.

Feng Q, Liu W, Baker SS, Li H, Chen C, Liu Q, et al. Multi-targeting therapeutic mechanisms of the Chinese herbal medicine QHD in the treatment of non-alcoholic fatty liver disease. Oncotarget 2017;8:27820–27838.

Bambha K, Belt P, Abraham M, Wilson LA, Pabet M, Ferrell L, et al. Ethnicity and nonalcoholic fatty liver disease. Hepatology 2012;55:769–780.

Lee YH, Kim SJ, Song K, Park JY, Kim DY, Ahn SH, et al. Sarcopenia is associated with significant liver fibrosis independently of obesity and insulin resistance in nonalcoholic fatty liver disease: Nationwide surveys (KHNANES 2008-2011). Hepatology 2016;63:776–786.

Petta S, Ciminnisi S, Di Marco V, Cabibi D, Camma C, Licata A, et al. Sarcopenia is associated with severe liver fibrosis in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2017;45:510–518.

Nobili I, Marcellini M, Marchesini G, Vanni E, Manco M, Villani A, et al. Intrauterine growth retardation, insulin resistance, and nonalcoholic fatty liver disease in children. Diabetes Care 2007;30:2638–2640.

Petta S, Valenti L, Tuttolomondo A, Dongiovanni P, Pipitone RM, Camma C, et al. Interferon lambda 4 rs368234815 TT>deltaG variant is associated with liver damage in patients with nonalcoholic fatty liver disease. Hepatology 2017;66:1885–1893.

Adams LA, Marsh JA, Ayonrinde OT, Olynyk JK, Ang WQ, Belin L, et al. Cholesterol ester transfer protein gene polymorphisms increase the risk of fatty liver in females independent of adiposity. J Gastroenterol Hepatol 2012;27:1520–1527.

Nakatsuka A, Matsuyama M, Yamaguchi S, Katayama A, Eguchi J, Murakami K, et al. Insufficiency of phosphatidylethanolamine N-methyltransferase is risk for lean non-alcoholic steatohepatitis. Sci Rep 2016;6:21721.

Li Y, He F, He Y, Pan X, Wu Y, Hu Z, et al. Dose-response association between physical activity and non-alcoholic fatty liver disease: a case-control study in a Chinese population. BMJ Open 2019;9:e026854.

Fracanzani AL, Petta S, Lombardi R, Pisano G, Russello M, Consonni D, et al. Liver and Cardiovascular Damage in Patients With Lean Nonalcoholic Fatty Liver Disease, and Association With Visceral Obesity. Clin Gastroenterol Hepatol 2017;15:1604–1611 e1601.

Honda Y, Yoneda M, Kessoku T, Ogawa Y, Tomeno W, Imajo K, et al. Characteristics of non-obese non-alcoholic fatty liver disease: Effect of genetic and environmental factors. Hepatol Res 2016;46:1011–1018.

Rotman Y, Koh C, Zmuda JM, Kleiner DE, Liang TJ, Nash CRN. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. Hepatology 2010;52:894–903.

Taheri S, Lim L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 2004;1:e62.

Cizza G, Jang P, Rother KL, Csako G. Sleep Extension Study G. Hawthorne effect with transient behavioral and biochemical changes in a randomized controlled sleep extension trial of chronically short-sleeping obese adults: implications for the design and interpretation of clinical studies. PLoS One 2014;9:e104176.