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REVIEW ARTICLE

Lean NASH: distinctiveness and clinical implication

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Abstract
Introduction Non-alcoholic fatty liver (NAFL) in the absence of overweight and/or obesity, defined by the anthropometric parameter, body mass index (BMI), has been designated as 'lean NASH.' While maintaining a close pathophysiological link with metabolic syndrome (MS) and insulin resistance (IR), the presence of subtle alterations in measures of total body and regional adiposity not exceeding the designed cut-offs, are hallmarks of 'lean NASH.'
Material and methods Available literature related to non-alcoholic steatohepatitis (NASH) in lean or non-obese individuals and its pathogenesis in general published in English language journals till the time of manuscript preparation were reviewed and critically analysed.
Analysis Being a closely related but variant phenotype of NASH, its features metabolically resemble the well-characterized entity 'metabolically obese normal weight (MONW)' individuals. Apart from total body adiposity, distribution of fat in different body compartments has assumed greater pathophysiologic relevance in characterizing 'lean NASH'. Detection of NASH in stringently defined non-obese individuals, by both BMI and waist circumference indices, indicates existence of a subset of NASH in which fat compartmentalization at ectopic sites is not picked up by the anthropometric yardsticks used. Volume [Quantity] and biological behavior of the visceral and deep subcutaneous adipose tissues contribute to this variant of NASH in non-obese subjects. Genetic predisposition to IR and MS along with the environmental influences like childhood nutritional status, dietary composition and gut microbiome possibly play pathogenetic role.
Conclusion The most important concern is in the principles of nomenclature within syndromes where clinical dissimilarities exist despite biological similarities. Till a uniformly acceptable pathophysiological and/or etiology-based classification emerges, the term "lean NASH" would continue to provide us an opportunity to ponder over and refine this subset of fatty liver in non-obese people and potentially significant liver disease.

Keywords Obesity · Steatohepatitis · Adiposity · BMI · Waist circumference · Lean

Background

Non-alcoholic fatty liver (NAFL) and steatohepatitis (NASH) in the absence of overweight and obesity, defined by the anthropometric parameter body mass index (BMI), has been designated 'lean NASH.' The classical phenotype of NAFL is almost always associated with varying degrees of obesity [1]. Lean NASH is an exception in terms of its relationship with BMI, even though most of the pathophysiological changes that characterize metabolic syndrome (MS) and insulin resistance (IR) are present. Subtle alterations in measures of total body and regional adiposity not exceeding the designated cutoff values are features that indicate it is closely related to but a variation of classical NASH [2, 3]. Lean NASH was initially described in Asians. However, it has subsequently been reported from other countries, including in the West [4–7]. Remarkably, there is a shift in disease burden patterns in developing countries.

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There has been a greater prevalence of MS-associated chronic diseases in these countries—a scenario that the developed countries have long been experiencing [8]. This has led to a change in health care priorities in developing countries. MS-associated diseases in low- and middle-income countries often present with different phenotypes and also different clinical outcomes. It is under these circumstances that 'lean NASH' has grown from a regional curiosity to a distinct variant of NASH with biological plausibility. Many issues concerning the pathogenesis and natural history of NASH are still unclear. In complex diseases like NASH, alternate phenotypes are often of significant interest, as the underlying similarities in the presence of heterogeneity can provide biological clues that are often more difficult to tease out in the parent phenotype.

Evidence that LEAN NASH is a distinct phenotype

A subset of individuals, despite being obese, has preserved insulin sensitivity and does not develop adverse clinical outcomes. They are designated as 'metabolically healthy obese.' This contrasts with another group of individuals who are insulin resistant and have hyperinsulinemia, atherogenic lipid profiles, as well as hypertension, despite having normal BMIs, i.e., <25 kg/m^2 [9]. The latter are designated as metabolically obese normal weight (MONW), which is possibly closely related to lean NASH [9]. Asians, in general, have been shown to have a propensity to develop adverse metabolic clinical events at a comparatively lower BMI, and this has led to the recognition of racial and ethnic differences in body composition and fat distribution as determinants of metabolic health [10, 11].

Evidence of a non-obese phenotype of NAFLD was first reported from Asian countries (Table 1) [4, 5]. There was no difference in the pattern of metabolic abnormalities observed among those with normal weight, overweight, and obesity. Even in those with normal weight (non-obese group), the presence of central obesity and expanded visceral fat was associated with NAFL [5].

The 'lean NASH' paradigm received its conceptual fillip in a cross-sectional multiethnic study involving young, anthropometrically lean, nonsmoking, sedentary volunteers [11]. Asian Indian male were shown to have a lower mean insulin sensitivity index and higher mean homeostasis model assessment-insulin resistance (HOMA-IR) values along with correspondingly higher hepatic triglyceride (TG) content in comparison to their Caucasian, Black, and Hispanic counterparts. In addition, adipocytokine profiles were different in Asian Indian male, particularly IL-6 levels, indicating a state of a relatively higher degree of inflammatory activation. Besides, larger size of the adipocytes is demonstrated in South Asian male in comparison to Caucasians along with higher levels of non-esterified fatty acid and leptin and lower levels of adiponectin [10]. All this evidence suggests that MONW and lean NASH might represent the non-obese counterpart of the 'sick fat cell syndrome' of obesity and IR.

A more robust description of lean NASH, as a distinct phenotype, came from a community-based epidemiological study in West Bengal, India. The study revealed the prevalence of NAFL to be 8.7 % [12]. The study population was rural, physically active, and predominantly poor, with an average BMI of 19.6 ± 6.6 kg/m^2. Overweight and central obesity were present in 7 and 11 %, respectively. Histological changes in biopsied individuals showed that one third (31 %) of the subjects with NAFLD and elevated ALT levels had significant inflammatory activity (NAFLD activity score ≥ 5) that qualified as NASH, and 2.4 % had cirrhosis. Those who were non-obese/lean (BMI < 25 kg/m^2 with WC <90 cm in male and <80 cm in female) with NAFL had higher BMIs and levels of subcutaneous fat, fasting blood glucose (FBG), and TG in comparison to the non-obese control group. While these biological similarities with the classical phenotype strengthen the notion that both are part of the same disease, 'lean NASH' qualifies as an alternate phenotype with a distinct relationship with adiposity, albeit with some differences. Recently, genome-wide association studies (GWAS) have identified several loci that influence adiposity and fat distribution [13]. Thus, a convergence of clinical, epidemiological and genetic data would suggest that the ethnic differences in body fat distribution and relative adiposity are critical in determining the obesity phenotypes as well as their relationship with defined clinical syndromes like NASH (Fig. 1).

Pathogenesis

Adiposity, BMI and lean NASH

Availability of excess calories due to socioeconomic affluence and sedentary lifestyles leads to obesity, with the excess energy being stored as fat. Accumulation of fat in the liver, the cardinal feature of NAFL, also occurs in this setting and is an expression of an expanded adipose tissue mass in the body. The prevalence of NAFL in a population has a good correlation with measures of obesity. In addition, progression from NAFL to NASH is also higher with increasing degrees of obesity—indicating the intimate relationship between overall fat mass and NASH prevalence and outcomes [1].

In general, adipose tissue is not only expanded in MS-related conditions, but is also more likely to be dysfunctional, triggering inflammatory responses that set into motion the diffuse functional changes that occur in MS and in NASH as part of its hepatic manifestation [14]. The large mass of fat tissue in the body, despite its diffuse nature and existence in multiple localizing compartments, is now regarded as an organ by itself. Adipose tissues in

Table 1 Summary of the studies reporting metabolic abnormalities in lean/non-obese subjects

References	Country	Population (*n*)	Subject with BMI <25 kg/m^2 (*n*)	Non-obese Subjects with NAFLD	Definition of leanness/non-obese used	Prevalence of abdominal obesity in lean NAFLD	Prevalence of metabolic abnormalities in lean NAFLD	Risk factors for NAFLD in non-obese subjects	Ref no.
Chen et al. [4]	Taiwan	General population ($n = 3,245$)	1,444	61 (4.2 %)	BMI < 25 kg/m^2	NR	FPG ≥126 mg/dl in 9 TG ≥150 mg/dl in 34	Age 40–64 years, elevated ALT and TG ≥150 mg/dl	7
Das et al. [12]	India	General population ($n = 1,911$)	1,777	90	BMI < 25 kg/m^2 WC <90 cm (male) and <80 cm (female)	–	Mean ± SD FBG 86 ± 25 mg/dl Mean ± SD TG 118.2 ± 66.3 mg/dl	Higher BMI (OR 1.2; 95 % CI 1.1–1.4; $p < 0.01$), higher biceps skinfold thickness (OR 1.2; 95 % CI 1.1–1.3; $p < 0.01$)	24
Kim et al. [2]	Iceland	General population ($n = 2,495$)	941	NR	BMI < 25 kg/m^2	NR	NR	Significant association between VAT and MS in lower BMI (<25 and 25–29.9 kg/m^2)	6
Margariti et al. [7]	Greece	NAFLD patients attending Liver clinic ($n = 162$)	19	–	BMI < 25 kg/m^2	33 %	MS 20 % diabetes 5 %	–	10
Younossi et al. [6]	US	National Health and Nutrition Examination Survey (NHANES III) ($n = 11,613$)	4,475	431 (7.39 %)	BMI < 25 kg/m^2	8.05 %	Diabetes 6.72 % hypercholesterolemia 62.65 %	Younger age, female gender	9
Kim et al. [5]	Korea	Clinic based medical check-up ($n = 786$)	460	74 (16 %)	BMI < 25 kg/m^2	35 %	Hypertriglyceridemia 60.8 % IFG 8.1 %	Male gender, higher WC, TG and IR	8

BMI body mass index, *WC* waist circumference, *NAFLD* non-alcoholic fatty liver disease, *FPG* fasting plasma glucose, *FBG* fasting blood glucose, IFG impaired fasting glucose, *TG* triglyceride, *MS* metabolic syndrome, *IR* insulin resistance, *VAT* visceral adipose tissue, *OR* odds ratio, *CI* confidence interval, *SD* standard deviation, *NR* not reported

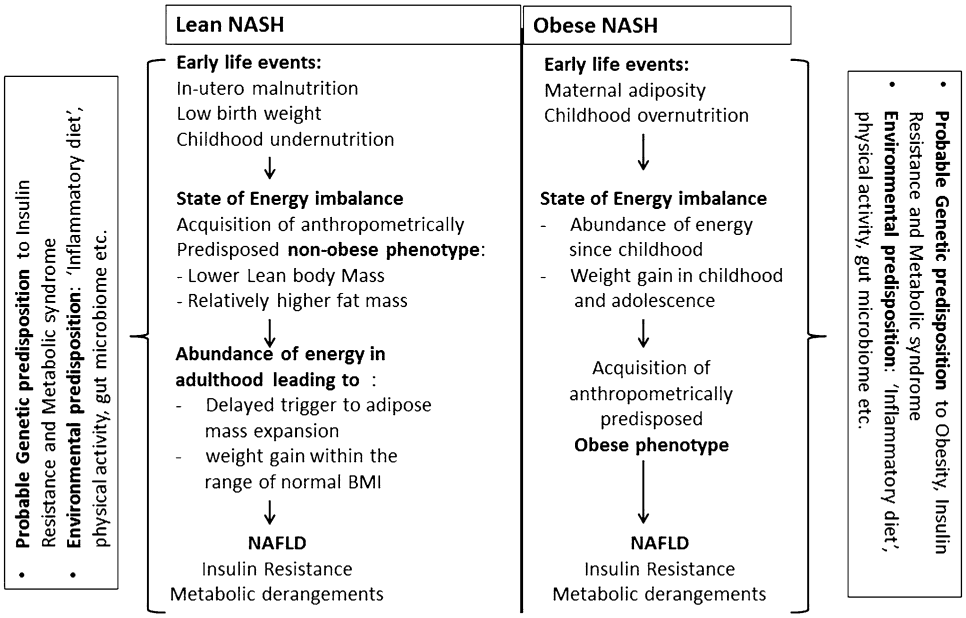

Fig. 1 Comparative pathophysiological hypothesis of 'lean NASH'

different locations maintain a functionally harmonious relationship and cross-talk with each other, responding to different perturbations of the metabolic–inflammatory milieu in the body, and therefore, they become relevant in health and disease [14]. In light of this, measures of adiposity have all along been a key element in the definition of MS and also relevant to evaluation of NASH.

BMI is the most simple and commonly used measure of total body adiposity in clinical as well as epidemiological studies. It has shown a linear relationship with overall mortality in a population, primarily by virtue of its association with MS [15]. Lean NASH shares the metabolic features and hepatic pathology in the absence of linearity of association with adiposity, as seen in classical NASH [16].

Compartmentalization of adipose tissue: the context of 'lean NASH'

BMI is regarded as a surrogate of body fat content. There is complex interaction among different body compartments such as adipose tissue, skeletal muscle, and osseous elements. Adipose tissue is the most dynamic of all these components [17]. However, it has been observed that the sensitivity of a specific BMI cutoff value to identify the correlation between the degree of fatness and increased risk of health hazards varies across different populations as well as among individuals with different energy reserves [18]. Asian Indians, in particular, show a higher prevalence of abdominal obesity reflected in higher waist:hip ratios (WHRs) and higher truncal subcutaneous fat, especially deep subcutaneous adipose tissue, even when they have 'normal' BMIs [3, 19] (Fig. 2). These features, along with shorter height and lower lean body mass, lead to a higher propensity to develop IR and MS at a lower BMI [3]. In addition, comparable to obese subjects, non-obese subjects who gain weight despite being within the range of normal BMI or currently normal weight individuals who were obese in the past are found to have increased risk of NAFL and type 2 diabetes [20, 21]. This emphasizes the need to consider BMI within a dynamic frame rather than as a single-point observation. Another limitation of BMI is that it falls short of capturing the subtle changes in amount and disposition/distribution of fat tissue that occur in lean NASH, thus making it a suboptimal marker of adiposity in this setting. Despite all these considerations, a WHO expert committee rejected a proposition to revise the current BMI cutoff values for metabolic health risks as a general principle, but acknowledges the heterogeneity in the strength of racial, ethnic, and individual differences in BMI in such settings [18]. Family and twin studies have shown that BMI, as a marker of obesity, has a 40–70 % component of heritability [13]. Subsequent GWASs have identified several loci, particularly fat mass and obesity associated (FTO) gene and MC4R, as potential genetic determinants of BMI [13]. Although the strength of such associations has generally been modest, they emphasize the complex nature of the interaction between genetic and environmental factors in determining the degree and pattern of adiposity.

Apart from total body adiposity, the distribution of fat in different body compartments has assumed greater relevance in the pathophysiology of lean NASH. An expanded fat mass in the visceral adipose tissue (VAT) compartments has been observed in MONW subjects [9]. WC and WHR, as measures of central adiposity or VAT, show strong linear correlation with overall adiposity, as defined by BMI and also correlate more precisely with intra-abdominal fat, defined by abdominal MRI, in higher degrees of adiposity [22]. Therefore, WC has been incorporated into the

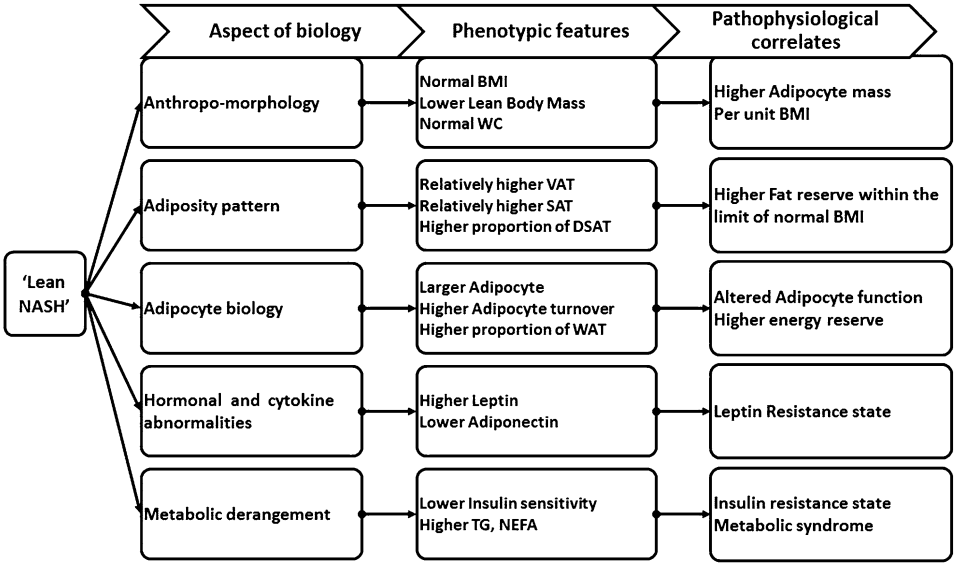

Fig. 2 Disease biology of 'lean NASH'

NASH Non-alcoholic Steatohepatitis; BMI Body Mass Index; WC Waist Circumference; VAT Visceral adipose Tissue; SAT Subcutaneous Adipose Tissue; DSAT Deep Subcutaneous Adipose Tissue; WAT White Adipose Tissue; TG Triglyceride; NEFA Non-Esterified Fatty Acid.

definition of MS to improve the biological relevance of the measurement. However, these anthropometric measures of overall and central adiposity lack uniformity in their precision and efficiency for identifying health hazards across varying degrees of adiposity [18]. Studies in non-obese subjects report a varying relationship between WC and progressive liver disease. A study in an occidental population found no association between NASH-related fibrosis and WC, although an association between WC and risk of having a NAFL is consistently observed across other ethnicities, including Asians [16].

NAFL and even NASH have since been reported in individuals who are stringently non-obese (applying both BMI and WC criteria) [12]. This indicates the existence of a subset of NASH subjects that either has NASH unassociated with MS or, more likely, has fatty liver disease in which fat compartmentalization and distribution at ectopic sites are not picked up by the anthropometric yardsticks used, i.e., BMI and WC. Moreover, fat tissue in the body is in a state of flux under environmental influences. It has been proposed that its compartmental redistribution to deep subcutaneous adipose tissue (DSAT), in contrast to superficial subcutaneous adipose tissue (SSAT), might be pathogenetically important, since DSAT is metabolically more active and is similar to VAT [19]. Thus, such differences in body composition may contribute to the relatively subtle association of adiposity with NASH in lean people (Fig. 2).

Delayed trigger to adipocyte expansion: an intuitive hypothesis for lean NASH

Recent research has shown that the size of adipocytes and their biological behavior are critical issues in the pathogenesis of MS [23]. Adipocytes set the tone of the metabolic and low-grade inflammatory state that occurs in MS and NASH [14]. There is an inter-individual variation in adipocyte size among lean and obese individuals [23]. Asian Indians have been shown to have larger adipocytes compared to Caucasians and other ethnic groups [10]. Furthermore, gene expression profiling of human adipocytes of different sizes from the same adipose tissue sample has identified that large adipocytes have a markedly higher gene expression than small adipocytes. The majority of these genes were immune related, often with important roles in the maintenance as well as regulation of cell structure, or with unknown functions [24]. In light of these, the functional plasticity and expandability of adipose tissue have become the subject of extensive research studying the pathogenesis of NASH. All individuals possess a maximum, but limited, capacity for adipose expansion, which is determined by both genetic and environmental factors. Once the adipose tissue expansion limit has been reached, it ceases to store energy efficiently, and lipids begin to accumulate in other tissues [23]. Such ectopic lipid accumulation in non-adipocyte cells results in lipotoxic insults that include IR, tissue damage, and inflammation.

Adipocyte turnover studies indicate that the overall size of the adipocyte mass is set at a higher level of equilibrium in childhood and adolescence in obese subjects, with turnover in adulthood similar to that in lean adults [23]. It is possible that the age of the switch to adipocyte mass expansion by either hypertrophy or hyperplasia may be critically different in classical vs. lean NASH. In developing nations, weight gain is mostly an adult phenomenon. In these developing countries where lean NASH is more prevalent, early life nutritional stress is often followed by

relative abundance in adulthood. Moreover, lifestyle changes classically associated with MS and NASH occur in adulthood in these lean individuals. This contrasts with the setting of the developed nations where the switch to adiposity occurs in childhood and adolescence [25]. Thus, a relatively late trigger to adipocyte expansion and meta-inflammatory perturbations may underlie the phenotypic differences between obese and lean NASH.

Genes, diet, and intestinal flora: lean NASH perspective

Available information on the genetics of NASH is heavily weighted in favor of an association with PNPLA3 variants. There is significant uniformity in the strength of this association across different races. On the other hand, variant alleles of APOC3 loci have been shown to address the ethnic-specific differences in NAFL. Although its association has been reported with NAFLD and IR in Asian Indians, this has subsequently not been replicated in other studies. Particularly concerning were the negative results from the Dallas Heart Study cohort, a population with a predominance of obesity [26, 27]. In addition, identification of FTO and LAMA-1 gene variants that have shown stronger genetic predisposition to diabetes, MS, and IR in non-obese subjects has raised the possibility of a variant genetic basis for lean NASH [28]. While genetic factors in lean NASH need to be delineated, dietary factors, particularly consumption of a 'more inflammatory diet' characterized by higher levels of cholesterol, transfatty acid, and carbohydrates including sucrose, by the Asians can lead to a deranged cellular energy balance and may contribute to NAFLD [29].

Apart from these genetic, dietary, and lifestyle influences, the resident intestinal flora seems to be another critical determinant in the genesis of NASH and MS. It plays an important role in substrate availability from the diet and modifies the host's metabolic milieu, immune function, and inflammation. Most relevantly, gut microbial 'enterotypes' have been demonstrated to change with the countries' progression from being socioeconomically developing to developed, and there are distinct differences in the composition of gut microbes with respect to microbial diversity, differential enrichment of microbial genes, and metabolic functions in obese and non-obese persons [30]. In addition to this complex pathophysiological interplay, the maternal nutritional status during the gestational period, low birth weight (LBW), and malnutrition in early life have been related to MS and its consequences in adult life. Given the prevalence of LBW to the extent of 23 %, growth retardation in young children to the extent of 60 %, and high prevalence of maternal malnutrition in developing countries like India, these features may also contribute to the genesis of the phenotype called 'lean NASH' [3].

'Lean NASH' in the present clinical perspective: issues in clinical diagnosis and assessment

'Lean NASH,' i.e., the presence of fatty liver in lean/non-obese subjects, is evolving as a clinical entity, and more information is needed before its characteristics, outcome, and management can be crystallized for guiding clinical case management. As of now, we should consider NASH in the differential diagnosis of unexplained liver disease even if the anthropometric parameters are within normal range or are subtly abnormal. Relevant clinical scenarios would include unexplained liver enzyme elevation and chronic hepatitis/chronic liver disease including hepatocellular carcinoma of unclear etiology, particularly in a setting of diabetic or impaired glucose tolerance. Metabolic abnormalities found in 'lean NASH' are similar to those seen in the classical phenotype, i.e., 'obese NASH,' and should be analyzed in detail. Standard diagnostic criteria, particularly the histology, management strategy, and surveillance protocol for NASH, are also applicable to lean subjects (Fig. 3). It needs to be emphasized that a stringent definition of leanness/non-obesity is to be adopted in future research protocols for identification of 'lean NASH' (Fig. 3). A number of noninvasive modalities including biomarkers have been evaluated and validated for the diagnosis and severity assessment of NAFLD/NASH, mostly in obese subjects [31, 32]. Different panels of markers include BMI or other anthropometric measurements to develop prediction models for the presence of NASH and presence of fibrosis in NASH [31–33]. In most such cases, BMI has been used as a categorical covariate and found to have predictive value above a definite cutoff value that indicates obesity. Hence, performance characteristics of such prediction models and biomarkers need to be evaluated specifically in non-obese subjects. A major departure, however, would emerge in the management of lean NASH. Behavioral therapy protocols for weight loss, one of the most impacting treatment modalities in classical obese NASH, are not relevant in this phenotype for obvious reasons. On the other hand, lean NASH is more biological, and the emerging therapeutic targets such as those acting by modifying insulin resistance, signaling of pathways of inflammation, and fibrosis as well as alterations in gut flora may find a wider role here.

Lean NASH: biologically distinct or a transitional nomenclature? Clinical implication

The lean NASH story is gradually being revealed. However, several issues remain unanswered. The most important concern is with the principles of nomenclature within syndromes where clinical dissimilarities exist despite biological similarities. It is relevant to raise the question as to whether it is epistemologically correct to classify subsets within a disease based on observed anthropometric parameters (e.g., BMI and

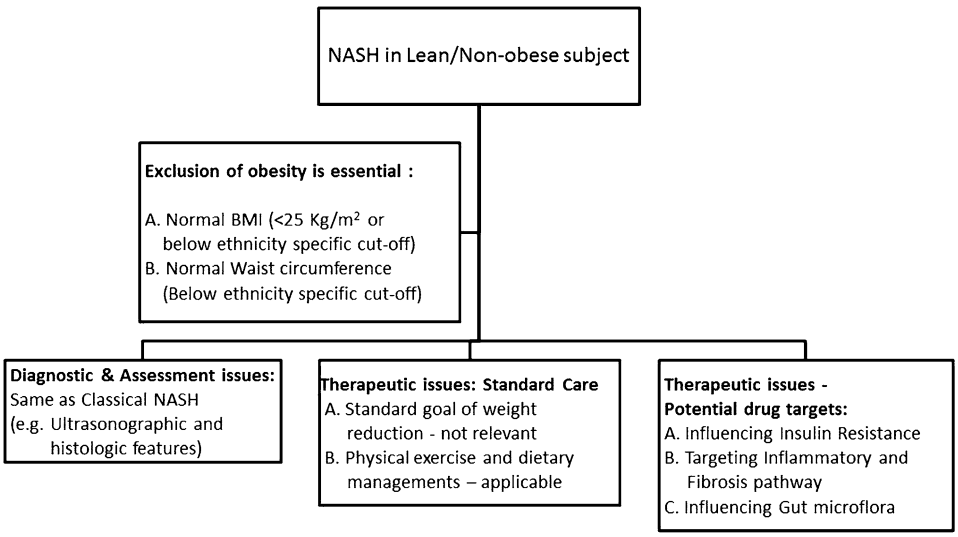

Fig. 3 Issues for diagnostic consideration of 'lean NASH'

Ethnicity specific cut-off values for anthropometric parameters are proposed by World Health Organisation as well as International Diabetes Federation [Ref No. 18]

WC in NAFLD/NASH). Such attempts are, however, commonplace in the evolution of nomenclature of defined entities in clinical sciences. Non-A-non-B hepatitis was the transitional coinage for a long time until the hepatitis C virus was cloned and demonstrated to be the elusive non-A-non-B agent. While IR unites the MS cluster and tries to provide uniformity concerning the genesis, significant divergence exists among the constituent phenotypes in terms of the strength of the association and biological principles. NAFLD and most importantly NASH already have an exclusionary component and a fair amount of arbitrariness (amount of alcohol intake) in its current name. It may be argued that adding another prefix that again relies on a probabilistic rather than putative or demonstrated mechanistic association would be adding further confusion and inaccuracy in understanding the disease. Until a uniformly acceptable pathophysiological and/or etiology-based classification emerges, the term "lean NASH" would continue to provide us an opportunity to ponder and refine this subset of fatty liver in non-obese people with potentially significant liver disease.

Conflict of interest Abhijit Chowdhury and Kausik Das declare that they have no conflict of interest.

Ethical standards This article does not contain any studies with human or animal subjects.

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