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Commentary
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The Lean NASH Conundrum

Shivaram Prasad Singh* and Sanjib Kumar Kar

Department of Gastroenterology, S.C.B. Medical College, Cuttack 753007, Odisha, India

Introduction

The innovative and fertile minds of the researchers and physician scientists while offering new directions regarding the different aspects of life and diseases may sometimes conjure up vacuous concepts regarding diseases without robust supportive basis. Although the term Nonalcoholic Steatohepatitis [NASH], was coined by Ludwig et al from the Mayo Clinic after studying the histological findings of fatty liver in 1980 [1], the entity remained in oblivion for over a decade until it arrested the attention of gastroenterologists, hepatologists, and endocrinologists all over the world due to its varied spectrum of manifestations like benign steatosis, NASH, cirrhosis, liver failure, and hepatocellular carcinoma [2-5], and what followed was an avalanche of literature on various aspects of this entity. However, lack of definite unequivocal criteria for screening and diagnosis of NAFLD and NASH, imprecise and contradictory reports on the outcome of NASH, declaration of an epidemic of NASH and its sequelae and eagerness to publish data on different aspects of NASH created an atmosphere conducive for the concoction and fabrication of sensational and bizarre research publications and hypothesis vis-à-vis NASH.

In defining NAFLD, while all experts have unequivocally excluded the presence of alcohol intake ≥ 20 gm/day in female and ≥ 30 g/day in male, viral infection like HBV and HCV, metabolic diseases like Wilson's disease and past history of intake of steatogenic drugs like tamoxiphen and amiodarone [6-9], the modality for diagnosis of fatty liver has differed from centre to centre. Despite limitations like subjective variations and the difficulties encountered in obese patients, ultrasonographic findings of bright echogenicity is used for diagnosis of fatty liver by most researchers especially for screening and population studies. Besides, liver transaminase elevations and histological findings of steatosis and steatohepatitis have been used for diagnosis of NAFL and NASH respectively by others [9,10]. In the oft quoted study from West Bengal in India, while subjects with fatty liver diagnosed by ultrasonography alone were designated as having probable NAFL, subjects with fatty liver diagnosed by dual imaging using initially ultrasonography followed by computed tomography [liver attenuation index of ≤ -14 HU] were designated as having definite NAFL, and those subjects with raised transaminases were termed 'potentially significant NAFL'. Of these subjects, those subjects with increased liver stiffness measure [>8 kPa] were artbitrarily biopsied, and those with histological NAFLD activity score ≥ 5 were termed as NASH [9]. Surprisingly, some investigators have made a diagnosis of NAFLD on the basis of ultrasonographic evidence of fatty liver and persistent elevation of serum alanine aminotransferase (ALT)>1.5 times the upper limit, but have excluded patients who were known diabetic or had impaired glucose tolerance [10]. Thus there exists widespread inconsistency in the diagnostic criteria used for identification of NAFL or NASH by hepatologists.

Definition of Lean Nash and Justification

To complicate the already muddled scenario further, some researchers have hoisted or imposed the 'new kid on the block': lean NASH without adequate basis or justification. To create a new entity, there have to be definite specific differences in the phenotype of these subjects and also a pathogenic basis why these subjects need a different identity or sub-identity. Mere lower BMI along with the obvious accompaniments like lower values of metabolic variables cannot arbitrarily be the basis of imposing a new 'caste' among these patients. By this analogy, all duodenal ulcers from a resource constrained region may be categorized as "lean duodenal ulcer"! What does lean NASH mean? By lean NASH one probably means thin patients having steatohepatitis. Lean means thin or containing little or no fat. Different usage of the adjective lean in medical science makes for interesting reading. A lean diet means lacking in richness, fullness and quantity in diet. The term "Lean type 2 DM" means type 2 DM patients with a body mass index <19 kg/m^2 and probably results from under nutrition and its adverse effects on B-cell function. It has a typical clinical, biochemical and hormonal profile. These type of diabetics constitute about 10-25% of the diabetic population in India [11,12]. Surprisingly the cut-off for BMI in defining "lean" NASH is nowhere near the cut-off used for Diabetes mellitus. How can definition of lean be different for Diabetics and NASH patients?

Thus a major hitch in any discussion on lean NASH is the arbitrary use of BMI cut off for labeling lean NASH. With such blurred definition of the subject of research, there has been significant heterogeneity in the subjects being labeled as lean NAFLD resulting in difficulties in comparing the results or observations of different studies and extrapolating the conclusions of one study to another cohort of differently defined cohorts. Bhat et al in their study defined lean body weight according to the Asia-Pacific criteria: BMI 18.6-22.9 kg/m^2 and [waist circumference] WC<90 cm in men,<80 cm in women [10]. In their study, twenty-three (15.3%) patients were categorized as lean NAFLD. These subjects had a BMI 21.6 ± 1.5 kg/m^2, waist circumference 82.9 ± 4.7 cm (BMI<23 kg/m^2, WC< 90 cm in men and<80 cm in women). 80% of these lean NAFLD patients had insulin resistance with mean HOMA-IR of 3.4 ± 1.9, and only 4 (17%) did not have any component of metabolic syndrome. [10] The study by Singh et al had earlier shown that persons with ultrasonographic fatty liver had a higher BMI (Mean 25.9+4.17 kg/m^2) than persons without fatty liver (mean 22.1+3.27 kg/m^2) (t=5.9511; p<0.001) [6]. This study had also reported that 7 of 39 patients had BMI<23 kg/m^2 and constituted 17.9% of NAFLD population. However, if lean was defined as BMI<19 kg/m^2, then only one out of 39 kg/m^2 (2.5%) fatty liver patients had lean body weight. On the contrary, if lean NAFLD was defined as NAFLD with BMI<25 kg/m^2, then 54% [21/39] individuals were not

***Corresponding author:** Shivaram Prasad Singh, Head, Department of Gastroenterology, S.C.B. Medical College, Cuttack 753007, Odisha, India, Tel: +91 6712505466; E-mail: scb_gastro_dept@hotmail.com

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obese (BMI<25 kg/m^2) and lean NAFLD then could make up over half of the NAFLD population [6]. In this study, 20 of 93 (21.5%) subjects with BMI 19-24.9 kg/m^2 had NAFLD. However, in the study by Das et al, the authors stressed that most of the NAFLD subjects (75%) were not overweight; 103/164 (63%) had normal BMI (18.5-24.9 kg/m^2) and were considered lean NAFLD. Besides, in this study, 20 of 164 (12%) were underweight (BMI <18.5 kg/m^2). [9] However, it must be stressed here that this population which was studied by Das et al appeared to be completely different from the populations of other Indian studies. The Study population had an abnormally low BMI compared to any other study. The study by Choudhary et al. described lean NAFLD as NAFLD with BMI<23kg/m^2. In this study, 29% had lean NAFLD and 72% were overweight or obese [13]. In another study from our region, a significant proportion of NAFLD patients [16%] had normal BMI (lean body weight, BMI<23 kg/m^2) [14]. However studies from the West consistently employ BMI<25kg/m^2 as cut off for lean NAFLD [15-19].

The recent NCD Risk Factor Collaboration (NCD-RisC) publication [20] has highlighted the problem of how different definitions for diabetes can provide different estimates of population prevalence of diabetes, and differentially identify people without previous diagnosis as having diabetes, besides failing to identify a substantial proportion of previously undiagnosed people who would be considered as having diabetes using a different method. It is evident then that there is a similar problem in definition of lean NASH; lowering or hiking the cut-off BMI value would not only create confusion in identification of a lean NASH patient but would also result in influencing the burden and epidemiological statistics: the proportion of NAFLD or NASH patients who would be termed lean. It is very important that hepatologists and endocrinologists thrash out this contentious issue and evolve a consensus to arrest the burgeoning confusion.

Clinicopathogenesis

Younossi et al have reported that the lean individuals with NAFLD have a different clinical profile than overweight-obese individuals with NAFLD [21]. They reported that factors like younger age, female sex, and a decreased likelihood of having IR and hypercholesterolemia have independent association with lean NAFLD. Similarly NASH was also independently associated with being Hispanic, having a younger age, and having components of metabolic syndrome such as hypertension [21]. In comparison to lean individuals, obese/overweight NAFLD patients had higher age, greater waist circumference and higher NAFLD activity scoring indicating more severe disease. However, Choudhary et al have shown that there was no difference in adipose tissue volume or in components of metabolic syndrome [13]. It has been suggested that probably genetic predisposition for insulin resistance and metabolic syndrome and environmental factors like inflammatory diet, physical activity and gut microbiome play nearly equal role in both lean NASH and obese NASH [22].

Management Dilemma

Weight loss, lifestyle modification, and exercise form the key stone of any treatment regime for NAFLD patients especially in the overweight or obese NAFLD patients. Other forms of treatment like Insulin sensitizers including thiozolidinediones, antioxidants like vitamin E, and statins only have a role in treatment of biopsy proven NASH irrespective of lean NASH or obese NASH [23]. However, it is unclear how the lifestyle modification would impact patients of NAFLD who are as such nonobese or lean. It is also not clear how such patients would behave in the long run, and how much predisposed they would be to progression to chronic liver disease.

Conclusion

In the absence of a robust definition for lean NAFLD/NASH, and the absence of a definite pathogenetic background, the race to join the lean NAFLD bandwagon has as expected thrown up different definitions of 'lean NASH'. Creation of such arbitrary labels would in all probability lead to wasteful exercise and wasteful expenditure especially in resource constrained settings where the population is leaner. Lack of uniformity in defining NASH reminds us of the following exchanges from Alice in Wonderland: "Then you should say what you mean' said the March Hare. 'I do' Alice replied hastily, at least - at least, I mean what I say – that's the same thing, you know.' 'Not the same thing a bit' said the Mad Hatter. 'Words mean what I want them to mean!' said the Queen of Hearts disdainfully!"[24]. Such an attitude can have no place in the world of medicine, and if there is development of data to justify segregation of this class of NAFLD, then an acceptable definition for lean NASH has to be carefully evolved.

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