NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

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Lean Nonalcoholic Steatohepatitis and Nonalcoholic Fatty Liver Disease

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G&H Is lean nonalcoholic steatohepatitis on the spectrum of nonalcoholic fatty liver disease or a novel entity?

NG Lean nonalcoholic steatohepatitis (NASH) is on the spectrum of nonalcoholic fatty liver disease (NAFLD) but is often underrecognized and underreported. Although NAFLD in nonobese individuals may be caused, on rare occasions, by entities such as drug toxicity, infections, and genetic disorders, the most common cause is metabolic, which is the focus of this discussion. A common misconception is that NAFLD, which includes NASH, is exclusive to individuals who are obese or overweight. This is simply not true, as lean individuals, defined as those who have a normal body mass index (BMI) based on ethnic-specific cutoffs, may still display the classic histopathologic features of NASH, which include steatosis, lobular inflammation, and hepatocyte ballooning.

However, it is important to note that better definitions are needed to describe what is truly obese or overweight across all races and ethnicities. Definitions of ideal BMI vary across medical organizations, and we know that Asian populations tend to have increased risks of cardiovascular disease and type 2 diabetes at lower BMIs compared with other populations. Thus, tighter definitions for what lean actually represents may help further understanding of this intriguing spectrum.

G&H How common is NAFLD or NASH in individuals who are lean as opposed to those who are obese or overweight?

NG The prevalence of lean NAFLD varies across populations. One large Western population study demonstrated that approximately 7% of lean individuals have evidence of NAFLD. However, other Western studies have noted a prevalence of up to 20%. Asian population studies have noted similar ranges but generally show a higher prevalence of lean NAFLD comparatively. Nonetheless, the prevalence of lean NAFLD is lower than the prevalence of obese or overweight NAFLD, which is often reported to be over 25%.

G&H How often does lean NAFLD progress to lean NASH?

NG This is a confounding issue. The rate of progression is not exactly known, but some literature suggests that patients who have lean NAFLD seem to have a very aggressive histology, characterized as increased lobular inflammation and hepatocellular ballooning, which both increase susceptibility to fibrosis and progression thereof. However, other literature conflicts, stating that patients who have lean NAFLD are less likely to have NASH or advanced histology and may also demonstrate

less hepatic steatosis compared with overweight or obese individuals. It should be noted, however, that these findings come from different patient populations across varying ethnic groups. More needs to be learned about the geographic and ethnic influences of lean NASH and which unique factors may increase the risk of advanced histologic disease.

G&H What are the biggest risk factors for NAFLD and NASH in patients who are lean?

NG The biggest risk factors for the development of traditional (overweight/obese) NAFLD are generally related to metabolic syndrome, including impaired fasting glucose, abnormal lipids, increased waist circumference, and abnormal blood pressure. Patients with lean NAFLD and NASH still demonstrate these conditions, but much less frequently than their overweight and obese counterparts. Although patients with lean NAFLD and NASH are normal weight, they are often regarded as metabolically obese, as they seem to have some element of insulin resistance, particularly at the level of adipose tissue. It should also be noted that lean individuals are likely to have impaired fat storage mechanisms, lower muscle mass, and increased visceral adiposity. Other risk factors include genetic predispositions such as higher prevalence of *PNPLA3*, high fructose and cholesterol dietary intake, and alterations in the gut microbiome.

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It is important to keep lean individuals in mind when assessing for NAFLD. Although the risk factors for lean NAFLD may not be as apparent or align completely with those of traditional NAFLD, the outcomes of these 2 conditions are similar. I implore my colleagues to look more broadly at their patient populations for the aforementioned risk factors, as well as for abnormal liver enzyme levels or patients with diabetes who are not obese. Such patients may be evaluated for NAFLD with noninvasive serologic risk calculators, elastography, and specialized fat quantitative imaging to help best predict who has the highest risk of NAFLD and NASH.

G&H Are there any other differences in NAFLD and NASH in patients who are lean vs in patients who are obese or overweight?

NG In general, the consensus is that lean patients with NAFLD have higher visceral adiposity (ie, fat between organs or intra-abdominal fat) and relative sarcopenia, whereas obese or overweight patients with NAFLD have more peripheral adiposity (ie, fat in the buttocks, hips, and thighs) as well as truncal adiposity. Thus, there is clearly a difference between these conditions in fat distribution as well as in body mass composition. There is also some evidence to suggest that the fat cells in patients who are lean are highly dysfunctional compared with their overweight or obese NAFLD counterparts.

The literature also suggests that there may be more genetic influence in lean populations. The genetic polymorphisms most discussed are associated with the *PNPLA3* and *TM6SF2* genes, among others.

G&H How should lean patients with NAFLD and NASH be treated?

NG This is an interesting question, as these patients are not overweight or obese in the traditional sense, and weight loss via diet and physical activity is typically the first recommendation for the treatment of NAFLD and NASH. However, there is sound evidence to suggest that weight loss does help lean patients with NAFLD and NASH as well. Thus, treatment should first focus on lifestyle changes and perhaps increasing muscle mass and decreasing fat content. Changing the body composition is important.

There is also literature to suggest that certain types of foods, especially high-carbohydrate foods, may predispose lean patients to NAFLD. Changing a patient's diet to one with lower carbohydrate intake may also help in the treatment of lean NASH.

Therefore, at the current time, treatment of lean NASH is essentially no different from treatment of nonlean NASH. Research is needed to identify specific environmental or genetic triggers that may be the focus of therapeutics in the future.

G&H Has weight reduction been shown to have an effect specifically on histology and fibrosis in lean patients with NASH and NAFLD?

NG Weight reduction has been shown to improve the histology of lean patients with NAFLD. The reduction does not have to be very high; less than or equal to 5% can make a histologic difference in lean patients and improve their NAFLD activity score, which is used to define NASH. More data are needed to explain whether weight loss consistently improves fibrosis in lean patients with NASH. In addition to weight reduction, clinicians should also advise adequate physical activity and improved sleep quality.

G&H Are the numerous NASH drugs currently in development specifically being studied in some patients who are lean?

NG The majority of clinical trials that I am involved with do not discriminate against lean or obese NASH populations. In general, drug therapies are targeted for patients with histologic evidence of NASH or appropriate fat content on specialized liver imaging, but overall are not specific to lean patients. Most trials do not make a distinction in terms of who is eligible for the trial with regard to BMI; however, many trials will exclude underweight or nonoverweight patients. In addition, patients who have too high of a BMI may be excluded because of increased risk of having an untoward outcome with a liver biopsy or because of the inability to comfortably undergo magnetic resonance imaging. More data are needed on which drugs are most effective in the lean population, and more attention should be focused on lean patients when developing NASH protocols.

G&H Are the outcomes the same in NASH and NAFLD patients who are lean vs those who are obese or overweight?

NG There is a paucity of data on patient-reported outcomes in lean patients specifically. However, although debated, literature suggests that patients who have lean NASH may have higher all-cause mortality and that their histologic disease may be more advanced than in NASH patients who are obese or overweight. A small amount of data suggests that the composition and quality of the fat may be protective in overweight and obese patients as opposed to lean NAFLD patients, who may have dysfunctional adipose tissue. A retrospective study found that, following transplant, NASH patients who had the lowest BMI experienced worse long-term graft and patient survival; however, in patients who did not have NASH, survival was worse in those who had higher BMIs. More prospective longitudinal studies are needed to answer this important question. There is still much that is not known or understood, so it is difficult to draw any conclusions based on valid evidence.

G&H What are the priorities of research in this area?

NG I am not aware of clinical trials specifically conducting subgroup analyses of lean patients with NASH. As mentioned, the trials are fairly broad in terms of which patients can be enrolled, and use the same endpoints and outcomes (eg, improvement of fibrosis without worsening of NASH and vice versa) for NASH patients who are overweight or obese and NASH patients who may be defined as lean. More research is needed specifically in lean patients with NASH.

Disclosures

Dr Gunn has no relevant conflicts of interest to disclose.

Suggested Reading

Alam S, Jahid Hasan M, Khan MAS, Alam M, Hasan N. Effect of weight reduction on histological activity and fibrosis of lean nonalcoholic steatohepatitis patient. *J Transl Int Med*. 2019;7(3):106-114.

Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. *JHEP Rep*. 2019;1(4):329-341.

Bambha KM, Dodge JL, Gralla J, Sprague D, Biggins SW. Low, rather than high, body mass index confers increased risk for post-liver transplant death and graft loss: risk modulated by model for end-stage liver disease. *Liver Transpl*. 2015;21(10):1286-1294.

Basaranoglu M. Lean and nonobese NAFLD/NASH from a hepatologist's point of view. *J Clin Gastroenterol*. 2021;55(1):93-94.

Chrysavgis L, Ztriva E, Protopapas A, Tziomalos K, Cholongitas E. Nonalcoholic fatty liver disease in lean subjects: prognosis, outcomes and management. *World J Gastroenterol*. 2020;26(42):6514-6528.

Denkmayr L, Feldman A, Stechemesser L, et al. Lean patients with non-alcoholic fatty liver disease have a severe histological phenotype similar to obese patients. *J Clin Med*. 2018;7(12):562.

Phipps M, Wattacheril J. Non-alcoholic fatty liver disease (NAFLD) in non-obese individuals. *Frontline Gastroenterol*. 2019;11(6):478-483.

Satapathy SK, Jiang Y, Agbim U, et al; Global NAFLD Consortium. Posttransplant outcome of lean compared with obese nonalcoholic steatohepatitis in the United States: the obesity paradox. *Liver Transpl*. 2020;26(1):68-79.

Wattacheril J, Sanyal AJ. Lean NAFLD: an underrecognized outlier. *Curr Hepatol Rep*. 2016;15(2):134-139.

Younes R, Bugianesi E. NASH in lean individuals. *Semin Liver Dis*. 2019;39(1):86-95.