MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

Section Editor: Naim Alkhouri, MD

Overview of Lean MASH and MASLD

Vincent Wong, MD
Mok Hing Yiu Professor of Medicine
Department of Medicine and Therapeutics
Faculty of Medicine
The Chinese University of Hong Kong
Hong Kong, China

G&H How should lean metabolic dysfunction-associated steatohepatitis be defined?

VW By definition, if someone is labeled as having lean metabolic dysfunction-associated steatohepatitis (MASH), 2 criteria should be met. First of all, the patient should be lean. According to the World Health Organization (WHO), a patient with a body mass index (BMI) over 25 is overweight and a patient with a BMI over 30 is obese. If someone is neither overweight nor obese, they are considered lean, which means that a BMI below 25 is typically considered lean. However, these cutoffs differ based on ethnicity; for example, different BMI cutoffs are used to define overweight and obesity in Asia. Second of all, in addition to being lean, the patient would need to have MASH at the same time, meaning that they not only have fat in the liver, but also inflammation and tissue injury. In pathologic terms, that means the patient would have steatosis, lobular inflammation, and hepatocyte ballooning, which are the defining features of MASH.

Some experts say that the term lean MASH can be misleading because the word lean makes people think that these patients do not suffer from problems of excessive adiposity. If someone has MASH, by definition, they must have at least 1 cardiometabolic risk factor. Quite often in clinical studies, these individuals tend to have central obesity. That means their waist circumference is high, or visceral obesity can be detected if imaging is used. Therefore, although the patient's BMI is low and considered to be lean according to the WHO's definition, there are other indicators based on adiposity that the patient is not metabolically healthy.

It should be noted that lean MASH is part and parcel of the spectrum of metabolic dysfunction-associated steatotic liver disease (MASLD) and not a separate entity. According to the latest definition, MASLD is a spectrum of disease from simple steatosis to MASH, and patients can have different combinations of cardiometabolic risk factors. On the whole, histologic series have shown that roughly 30% to 40% of individuals with lean MASLD have MASH.

G&H What proportion of patients with MASH or MASLD is lean as opposed to obese or overweight?

VW The proportion differs according to geographical region and also by the type of study and how the diagnosis of MASH or MASLD was made. However, overall around 10% to 20% of patients with MASLD worldwide would be classified as having normal BMI or being lean. Although lean MASH and MASLD have been discussed more often in recent years, I do not think their proportion has changed much recently when looking at findings from systematic reviews and meta-analyses.

G&H How does the pathogenesis of MASH compare in lean vs nonlean patients?

VW The pathogenesis is largely similar in both groups. It is still based on overnutrition, accumulation of liver fat through dietary fat intake, fatty acid from adipose tissue, and also de novo lipogenesis in the liver. With the accumulation of toxic lipid species, people start to develop steatohepatitis, then fibrosis progression, and finally the development of cirrhosis and complications.

In terms of risk factors, central obesity is quite important in lean patients. Our group, as well as others, has illustrated that among patients who have MASH, the proportion with MASH-related gene polymorphisms such

as the *PNPLA3* gene polymorphism is higher in patients who are lean. This is quite intuitive because the development of MASLD and MASH is often a combination of genetic, environmental, and lifestyle factors. If someone is not overweight or obese and still develops MASH, it usually means that other risk factors, such as diabetes, central obesity, or genetic predisposition, are more prominent.

G&H Other than BMI, how does MASH in lean patients differ from MASH in obese or overweight patients?

VW On the whole, our group and others have found that lean patients with MASH tend to have less severe liver disease. The degree of liver fibrosis tends to be lower, and the degree of inflammation tends to be lower. Otherwise, MASH in lean individuals is quite similar to MASH in overweight/obese individuals, and the degree of insulin resistance is similar as well. However, some patients who are lean and develop MASH may have endocrine pathologies, such as lipodystrophy, hypothyroidism, pituitary disorders, or even some monogenic disorders.

G&H Being that MASH is most common in patients who are obese or overweight, when should it be suspected in lean individuals and how should it be diagnosed?

VW Awareness of lean MASH is important. I am not advocating for population screening in the absence of cardiometabolic risk factors; that is not in line with the current recommendations from international guidelines. That being said, it needs to be understood that BMI is, after all, just 1 of the cardiometabolic risk factors for MASH. Clinicians should take note of other cardiometabolic risk factors, including waist circumference, blood pressure, glucose level, and lipids. If a patient has these other cardiometabolic risk factors, even though their BMI may be considered to be lean, clinicians should still go through the same diagnostic workup for MASH that is done for overweight or obese individuals. For diagnosis, the same tests are used. In most settings, abdominal ultrasonography is used to detect fat first. Likewise, the same noninvasive tests of liver fibrosis (such as simple fibrosis scores, specific fibrosis biomarkers, and ultrasound or magnetic resonance elastography) can be used in lean patients. Our group has found that the performance of noninvasive testing in lean patients is similar to or even better than when used in obese patients.

G&H What are the current treatment recommendations for lean patients with MASH or MASLD?

VW The first question that needs to be asked is whether clinicians should advocate for weight reduction and lifestyle changes when a MASH patient's BMI is relatively normal. My answer is yes. In the *Journal of Hepatology* in 2018, my colleagues and I published the results of a randomized controlled trial for a lifestyle intervention program vs usual care in patients with MASLD. The primary endpoint was resolution of MASLD, as measured by proton magnetic resonance spectroscopy. Half of the patients had a BMI less than 25 at baseline, and half had a BMI over 25 at baseline. We found that lifestyle intervention was more effective in inducing resolution of MASLD in both groups. There was also a dose-response relationship between the degree of weight reduction and the proportion of patients who had remission of MASLD. More importantly, lean patients with MASLD could achieve the same degree of liver fat reduction at a lower degree of weight reduction. The take-home messages from our study were 2-fold. First, clinicians should still advocate for a healthy lifestyle in patients who are lean. Second, lean patients do not need to lose as much weight to achieve a similar degree of improvement in the liver.

However, not every patient can follow lifestyle advice and even fewer can maintain it. On top of that, some patients will still have active liver disease despite making lifestyle changes. Therefore, pharmacologic treatments need to be considered. Unfortunately, in essentially all of the phase 2 and 3 studies in the field of MASLD and MASH, BMI is one of the inclusion criteria. Lean patients are simply excluded from those programs, and there is a lack of good data on how these drugs would perform in the lean population. This is a knowledge gap that must be filled in the next few years.

G&H If lifestyle modifications are not sufficient, how are lean MASH patients usually treated?

VW Pharmacologic treatments are often used even if they have not been studied in lean patients, but clinicians have to inform patients that such use is off-label. We must make that point very clear. In the United States, the first drug approved for the treatment of MASH is resmetirom (Rezdiffra, Madrigal). No data are available on its performance in the lean population, so I am not sure how colleagues from the United States would use the drug in these patients. Elsewhere, treatment choices would include vitamin E, pioglitazone, and glucagon-like peptide-1 (GLP-1) receptor agonists. Vitamin E and pioglitazone have limited data in the lean population, but there have already been several randomized controlled trials on histologic outcomes. There are also retrospective data on clinical outcomes for vitamin E use. These data

can be discussed with lean patients.

One side effect of pioglitazone is weight gain, which theoretically may be less concerning if the patient is lean. However, this should be discussed with the patient as well. On the other hand, GLP-1 receptor agonists can be tricky to use in the lean population because they lead to profound weight reduction, particularly if clinicians choose drugs that have a stronger weight loss component, such as semaglutide, liraglutide, or the dual agonist tirzepatide. Although data are not available on the use of GLP-1 receptor agonists in lean MASH patients because all MASH patients were either overweight or obese in the clinical trials, there have been studies in the type 2 diabetes field that included lean patients. In that population, the reduction in hemoglobin A1c was similar in lean vs obese patients. Whether lean and obese patients would also have similar results with these drugs in the MASH field is not known yet.

G&H Are you aware of plans to perform research on MASH drugs specifically in lean patients?

VW For drug companies, I do not think that would be a priority right now. I would imagine they would want a population with the highest probability of having liver fibrosis and MASH, and therefore would use an overweight or obese population. Any research would be further in the future. After MASH drugs are approved, there may be investigator-initiated, phase 4 studies to test this special population.

G&H How do outcomes and mortality compare in lean MASH patients vs nonlean MASH patients?

VW This is a highly confusing area, and the data are conflicting: there are data showing that lean patients have better outcomes, whereas there are also data showing that lean and nonlean patients have the same outcomes. Some studies have even indicated that mortality may be higher in lean MASH patients. One year ago, a systematic review and meta-analysis published in *Clinical Gastroenterology and Hepatology* looked at 10 observational cohort studies. The main conclusion was that the lean MASLD population had less severe liver histology at baseline, but subsequent overall mortality was higher. Liver-related mortality was also higher, but cardiovascular mortality was lower. Additionally, liver-related events, including cirrhotic complications and liver cancer, were not increased. The disconnect between liver complications and liver-related mortality is difficult to reconcile, which might indicate a problem with the source data.

In my mind, the difficulty of studying this population is the possibility of reverse causality. I would say that overall at the population level, lean is better than obese, and lean patients are less likely to have metabolic disease, as well as cardiovascular events or liver disease, for that matter. However, there are also some people who are lean because of reverse causality. When liver disease has progressed to a certain stage, toward cirrhosis or liver decompensation, patients often have sarcopenia and lose skeletal muscle. Or, if they are sick, they may have multiple complications and may also lose weight. In fact, when my colleagues and I conducted a secondary analysis of simtuzumab and selonsertib clinical trials, weight reduction of 5% or greater during the first year was associated with a higher risk of liver decompensation and death in subsequent years. Therefore, it is important to distinguish between people who are lean because they are metabolically fit and those who are lean because they have lost weight because of advanced liver disease. If the distinction is not made clearly, there will be confusing and conflicting data.

Disclosures

Dr Wong has served as a consultant or advisory board member for AbbVie, AstraZeneca, Boehringer Ingelheim, Echosens, Eli Lilly, Gilead Sciences, Intercept, Inventiva, Merck, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, and Visirna, and has served as a speaker for Abbott, AbbVie, Echosens, Gilead Sciences, Novo Nordisk, and Unilab. He has received a research grant from Gilead Sciences and is a cofounder of Illuminatio Medical Technology.

Suggested Reading

Danpanichkul P, Suparan K, Kim D, Wijarnpreecha K. What is new in metabolic dysfunction-associated steatotic liver disease in lean individuals: from bench to bedside. *J Clin Med*. 2024;13(1):278.

Fu C, Wai JW, Nik Mustapha NR, et al. Performance of simple fibrosis scores in nonobese patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2020;18(12):2843-2845.e2.

Ha J, Yim SY, Karagozian R. Mortality and liver-related events in lean versus nonlean nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2023;21(10):2496-2507.e5.

Leung JC, Loong TC, Wei JL, et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. *Hepatology*. 2017;65(1):54-64.

Lin H, Wong GL, Whatling C, et al. Association of genetic variations with NAFLD in lean individuals. *Liver Int*. 2022;42(1):149-160.

Wijarnpreecha K, Li F, Lundin SK, et al. Higher mortality among lean patients with non-alcoholic fatty liver disease despite fewer metabolic comorbidities. *Aliment Pharmacol Ther*. 2023;57(9):1014-1027.

Wong VW, Wong GL, Chan RS, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. *J Hepatol*. 2018;69(6):1349-1356.

Younes R, Govaere O, Petta S, et al. Caucasian lean subjects with non-alcoholic fatty liver disease share long-term prognosis of non-lean: time for reappraisal of BMI-driven approach? *Gut*. 2022;71(2):382-390.