MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

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Sarcopenia in Patients With MASLD/MASH

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G&H How can metabolic dysfunction-associated steatotic liver disease, including metabolic dysfunction-associated steatohepatitis, lead to sarcopenia, or the depletion of muscle mass?

JL Patients with metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH) are particularly vulnerable to sarcopenia because the factors associated with metabolic syndrome (eg, obesity, diabetes, hyperlipidemia, and hypertension) create a systemic environment that is harmful to the muscle. These factors lead to chronic low-grade inflammation in the body that leads to inflammation in the muscle itself. They also contribute to low-grade vasculopathy that impairs blood flow to the muscle and to neurotoxicity that reduces the sensory inputs required for healthy muscle function. In addition, many patients with metabolic syndrome are less physically active, resulting in decreased mechanical loading—one of the key stimuli for maintaining and building healthy muscle tissue. With fewer signals and more inflammatory and vascular stressors, muscle in patients with MASLD receives fewer inputs to repair and regenerate. The result is metabolic syndrome myopathy, which is characterized by myoinflammation, myosteatosis, myofibrosis, and myodysfunction.

G&H On the other hand, how can sarcopenia lead to MASLD or MASH?

JL Muscle is a major metabolic organ. It takes up glucose from the bloodstream, so when individuals have less muscle mass, the body loses a key pathway for clearing glucose from the bloodstream. With less muscle available to clear glucose after eating, peak and average glucose levels rise, driving higher insulin levels, ultimately leading to insulin resistance, which is a key risk factor for MASLD.

G&H What are the challenges of diagnosing sarcopenia in patients with MASLD or MASH?

JL A major challenge is that most patients who have MASLD or MASH also have obesity. Excess subcutaneous and visceral fat can mask the physical appearance of sarcopenia. In an individual without obesity, it is often easier to identify low muscle mass on physical examination. In individuals with obesity, that visual assessment becomes unreliable because fat can obscure the underlying loss of muscle. Currently, it is not standard of care to measure body composition. The tools to do so are not commonly available in standard practice. Without direct body composition measurements in routine practice, clinicians rarely assess muscle mass systematically in

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patients with MASLD/MASH, limiting the ability to identify and address progressive muscle loss before it is too late.

G&H If muscle mass is measured in these patients, what are the best tools currently available?

JL Dual-energy x-ray absorptiometry is a gold-standard method for assessing body composition, providing information about lean soft tissue, fat mass, and bone mineral density. Other imaging-based modalities such as computed tomography scan or magnetic resonance imaging are also excellent tools to assess the psoas muscle or total abdominal skeletal muscle health and may be even more useful in patients with MASLD/MASH because these imaging studies are already used to assess the liver. Bioelectric impedance analysis offers an accessible option in the ambulatory setting. Finally, the most widely available bedside assessment is grip strength measured with a hand dynamometer. This should ideally be paired with a survey- or performance-based measure of physical function—for example, the Duke Activity Status Index or the Liver Frailty Index.

G&H Why is early identification of sarcopenia important in this patient population?

JL Early identification is essential because the liver-muscle axis has a measurable impact on health outcomes in patients with MASLD. Patients with MASLD are at high risk for losing muscle mass and developing metabolic syndrome myopathy. Metabolically unhealthy muscle increases the risk of developing MASLD and accelerates MASLD disease progression. In fact, low muscle mass makes it much more likely for a patient to progress from simple steatosis to MASH, the most advanced form of MASLD. As MASLD and fibrosis progress and muscle mass worsens, so do mortality, infection risk, hospitalization, and quality of life. Therefore, preserving muscle mass is a key lever for improving health outcomes in this patient population.

G&H What are the challenges of treating patients who have both sarcopenia and MASLD/MASH?

JL A key challenge is that the foundational management recommendation for MASH is weight loss. However, any time a patient loses weight, whether through lifestyle changes or pharmacotherapy, they do not selectively lose fat mass; they will also lose muscle mass. Studies demonstrate that loss of muscle mass can account for anywhere between 20% and 45% of the total body weight lost with any strategy to lose weight. In patients who already have low muscle mass related to metabolic syndrome—or even worse, sarcopenia—this leads to a narrow therapeutic window. Losing fat mass will improve steatosis, inflammation, and fibrosis risk (for both the liver and the muscle), but further loss of muscle mass may worsen and compromise overall health outcomes. The dilemma then is how to implement the recommendation to lose weight in order to improve liver health while simultaneously preserving muscle mass.

G&H What type of exercise is recommended for a MASLD or MASH patient who is experiencing muscle loss?

JL Current evidence supports a recommendation for resistance training at a minimum of 2 times per week, with 3 or more times per week likely optimal. Resistance training should involve both upper body and lower body muscle groups. To stimulate muscle growth, individuals should aim for engaging in 3 sets of 8 to 10 repetitions per muscle to achieve muscle fatigue, which is when an individual knows that the muscle was stressed enough to provide the stimulus to repair and regenerate.

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This, of course, needs to be paired with sufficient protein intake, which can be difficult for individuals who are engaging in programs that lead to caloric restriction. If an individual is not eating a sufficient number of calories intentionally because they are trying to lose weight, they need to make sure that they are maintaining protein targets for their muscle health. For those individuals aiming to preserve or increase muscle mass, a daily protein intake of at least 1.2 g/kg (probably closer to 1.5-2 g/kg) of body weight is recommended.

G&H What other nutritional strategies or lifestyle interventions might be beneficial in this patient population?

JL When individuals begin weight loss programs, overall calorie intake will naturally decline, but they have to maintain the protein recommendation of a minimum of 1.2 g/kg of body weight per day. Protein diversity is also important, which means making sure that the protein does not come purely from land animal meat, but from other sources, including seafood and, ideally, plants such as legumes, tofu, and soy-based products. A more diverse protein pattern supports both muscle and metabolic health, whereas excessive intake of land animal meat can increase total body systemic inflammation, which contributes to metabolic syndrome myopathy.

It is also critical to educate patients starting any weight loss program that with the loss of weight inevitably comes loss of muscle mass and that, at the current time, the only way known to mitigate that loss of muscle mass is through resistance training paired with adequate protein intake. Every patient about to embark on a weight loss program needs to be informed of this and provided with very specific strategies to preserve their muscle mass.

This includes individuals starting weight loss programs with pharmacotherapeutics such as glucagon-like peptide-1 (GLP-1) receptor agonists. Any pharmacotherapeutic that results in an individual losing body weight will lead to the individual inevitably losing some lean mass, which includes muscle and bone together.

G&H What are the priorities of research?

JL One priority of research is to fully characterize how MASH-directed pharmacotherapies affect muscle health. Although this discussion has focused on the detrimental effects of weight loss in the form of loss of muscle mass, there is reason to believe that therapies that improve metabolic syndrome may also improve muscle health through reductions in muscle fat and systemic inflammation. Given this trade-off, it is imperative to identify the patient phenotypes that are most vulnerable to treatment-related muscle loss and determine which clinical, biochemical, genetic, or imaging markers predict more severe decline in lean mass with weight loss drugs.

Another priority for the field is determining how to best preserve healthy muscle while a patient is losing weight on a GLP-1 receptor agonist–based therapy, whether through lifestyle-based interventions such as exercise and high-protein diets or through other therapeutics that might help preserve muscle mass or stimulate muscle growth simultaneously.

Disclosures

Dr Lai has served as a consultant for Novo Nordisk, Genfit, Boehringer Ingelheim, Cosmo, and Stately Bio.

Suggested Reading

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