MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

Section Editor: Naim Alkhouri, MD

Exercise in Patients With Metabolic Dysfunction-Associated Steatohepatitis



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G&H Has exercise been shown to improve liver fibrosis and histology without body weight loss in patients with metabolic dysfunctionassociated steatohepatitis?

JS At this point in time, direct scientific evidence is not available, at least with paired liver biopsies, to support the ability of exercise by itself to improve liver fibrosis without body weight loss in metabolic dysfunction-associated steatohepatitis (MASH). Several studies have been published to date looking at this issue, including a study recently published in the *Journal of Hepatology* by Mucinski and colleagues and earlier studies by Dr Ingrid Hickman's group in Australia, but the results have been conflicting.

In lieu of direct evidence, there is some indirect evidence that exercise by itself can achieve improvements using different noninvasive tests. Importantly, this can occur at clinically significant thresholds of response, which serve as surrogates for histologic improvement, whether MASH resolution or even liver fibrosis reversal. In support of this, my colleagues and I published a systematic review and meta-analysis in the American Journal of Gastroenterology in 2023. We analyzed over 550 adults with nonalcoholic fatty liver disease, now known as metabolic dysfunction-associated steatotic liver disease (MASLD), encompassing 14 studies. Independent of body weight loss, aerobic exercise training was able to achieve clinically significant reductions in magnetic resonance imaging (MRI)-measured liver fat 3.5 times more often than if patients only received standard clinical care and counseling. Additionally, we performed a post hoc analysis of our NASHFit trial that was published in *Liver International* last year. Fifty-three percent of adults who had histologically confirmed MASH were able to achieve at least a 17 IU/L reduction in alanine aminotransferase (ALT) following 20 weeks of aerobic training, in comparison with only 13% of those who received standard of care.

G&H Could you expand on the effects of exercise specifically on MASH resolution?

JS Continuing the theme of the impact of exercise training using noninvasive tests for indirect evidence, my colleagues and I presented another post hoc analysis from the NASHFit study at the American Association for the Study of Liver Diseases (AASLD) meeting last year. We showed that aerobic exercise training at guideline-based amounts over 20 weeks was able to achieve MASH resolution using the composite MASH Resolution Index. This index combines changes in ALT and MRI-proton density fat fraction, as well as the baseline aspartate aminotransferase value, and is gaining momentum as a combined biomarker of therapeutic response even beyond lifestyle trials. In fact, this noninvasive composite biomarker was achieved nearly 3 times more often with exercise training than with standard of care. Since last year's AASLD meeting, METCon (an exercise consortium that I am part of with colleagues in Australia and the United Kingdom) published a pooled analysis this past April in Hepatology Communications, which included not only data from the NASHFit study but from several studies in the United Kingdom and Australia. This multisite international

study confirmed our single-center findings and showed that aerobic exercise training achieved MASH resolution nearly 2.5 times more often than standard of care.

G&H What other effects have been found with exercise in MASH patients?

JS Exercise impacts so many different mechanistic pathways at the same time, which is why many benefits can be seen, even beyond the liver. Exercising regularly will improve insulin resistance and sensitivity, reduce adipose tissue, improve physical fitness, lessen cardiovascular risk, and increase health-related quality of life, where every domain of health, including mental, physical, and social aspects, will be improved.

G&H What is the current guidance for exercise in the management of patients who have MASH?

JS The AASLD, American Gastroenterological Association, European Association for the Study of the Liver, American College of Sports Medicine (ACSM), and Australian Exercise Association all have very helpful guidance, but I would say that the ACSM guidance, which came out in 2023, provides the most comprehensive review and recommendations. The ACSM recommends at least 150 minutes per week of moderate-intensity aerobic exercise (such as walking or light cycling) or 75 minutes per week of vigorous-intensity aerobic exercise (such as running). The ACSM recommends this aerobic activity plus 2 nonconsecutive days a week of resistance training, which can consist of body weight exercises or any other form of resistance training.

G&H How do the frequency, intensity, time, and type of exercise impact MASH?

JS The ACSM developed the frequency, intensity, time, and type (FITT) principle in exercise prescription for the key aspects of a well-designed exercise program. For example, I could ask a MASH patient to walk at a frequency of 5 days a week for 30 minutes in duration at a moderate intensity of around 5 metabolic equivalents of task (MET) in which they should be able to talk to the person next to them, but not sing, for a total exercise dose of 750 MET min/week. This is important because this dose of exercise is required to reduce liver fat at the clinically significant thresholds previously discussed. Once a patient already has MASLD, low-intensity exercise is not going to be sufficient to reduce liver fat. However, looking at preventative studies at least on an epidemiologic scale, even low-intensity activity is better than being sedentary.

Other things to consider include questions that have been raised about the modality of exercise. For example, is aerobic better? Should patients do resistance training? Should they do high-intensity interval training? Right

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now, there are very few head-to-head studies looking at different exercise modalities. Guidance from the ACSM suggests that aerobic plus resistance training is preferred, although this is largely based on expert opinion.

G&H What is the role of exercise in MASH patients receiving pharmacotherapy?

JS Exercise should be viewed as a complementary treatment to any drug that is approved or soon to be approved by the US Food and Drug Administration for MASH. Enrolling in lifestyle intervention, including exercise, is required for patients who are trying to receive payer coverage for resmetirom (Rezdiffra, Madrigal), which was recently approved for fibrotic MASH.

G&H How can clinicians best assess, counsel, and prescribe regular exercise to patients who have MASH?

JS Clinicians should use a framework to assess, counsel, and prescribe exercise in an iterative process that is the same every time. This will allow them to be more effective when trying to help their MASH patients exercise. I use a standard framework called SBIRT, which stands for screening, brief intervention, and referral to treatment. For screening, I need to know what my patient is currently doing and try to figure out how active they are by using several tools. One is the Physical Activity Vital Sign, which comes from the ACSM and is a 2-question tool that the patient can complete in less than 15 seconds. This tool tells me how much activity the patient is completing each week. Once I know what the patient is doing, the second part of screening is figuring out what prevents them from doing more. Over 80% of adults with MASLD do not achieve the weekly amounts of guideline-based activities.

My colleagues and I developed a MASLD-specific exercise barriers questionnaire that was published in *Digestive Diseases and Sciences* in 2021. This tool allows us to understand not only barriers to activity, but also facilitators that promote achievement of the guideline-based amounts of recommended exercise. Understanding what makes each person unique and what allows them to be active will help providers design an individualized exercise program.

Additionally, it is not easy to put patients through formal exercise testing, so having a questionnaire that can assess exercise capacity is helpful. I routinely use the Duke Activity Status Index, which consists of 12 questions that patients can answer in under 2 minutes. This questionnaire tells me what their physical fitness is and if they are frail. Starting with this framework helps me formulate how I want to deliver the patient's exercise intervention.

However, before this delivery, the brief intervention component of the SBIRT framework has to be addressed. This is where the health care provider can educate their patients and get buy-in by telling them about all of the benefits of exercise. Once buy-in is obtained, it is time for the last part of the SBIRT framework, which is referral for treatment. This can be as simple as pulling out an exercise prescription pad and writing down what the patient should do in terms of each aspect of

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the aforementioned FITT principle in exercise prescription. Providers can also refer their patients to an exercise professional. Unfortunately, this does not occur often; in fact, only 10% of adults living with MASLD are referred to an exercise professional. To help increase uptake of this, the ACSM created a tool searchable by zip code and qualification to identify exercise specialists who can help deliver the exercise prescription and supervise patients to make sure they are safely and effectively completing the exercise program.

G&H Could you expand on the role of the exercise professional in the context of the multidisciplinary care team?

JS An exercise professional is a wonderful partner and companion to the health care provider. They provide not only a novel expertise, but one that is complementary, whether in the form of a clinical exercise physiologist or certified personal trainer, especially if they have training in chronic disease or additional experience. However, these professionals are underutilized resources. In my opinion, all patients living with MASLD or MASH would benefit from at least a 1-time consultation, but this is particularly important for patients who are living with obesity, are sarcopenic, or have underlying metabolic syndrome. The ACSM recommends trying to engage an exercise professional for every individual if possible.

G&H What research has been conducted on interventions to help MASH patients start and/ or maintain regular exercise programs?

JS Many different tools have been studied to help patients both start and then sustain regular exercise. My colleagues and I have studied behavioral coaching, whether by telehealth or in person, and found that if this type of coaching is rooted in motivational interviewing, there is quite a bit of evidence to support its efficacy. We have also found in our studies that supervising patients performing exercise, whether in person or with telehealth, leads to the largest exercise adherence rates at least in the short term.

Digital therapeutics are also important. There is only 1 hepatologist for every 40,000 adults living with MASLD in the United States, so it is very difficult to take care of and reach every individual who needs help. Therefore, having a scalable platform that allows providers to reach more people is very important. Our research group has studied several mobile health apps, which are delivered via smartphone. We published a study using Noom, which uses a holistic, comprehensive lifestyle approach rooted in behavioral psychology. It is not strictly an exercise intervention, but this comprehensive program increases awareness of the importance of being active in addition to making dietary changes and using behavioral motivation. In a study we published in Hepatology Communications in 2023, this program helped patients become 35% more physically active.

We have also partnered with Dr Andrés Duarte-Rojo, who is now at Northwestern, and are conducting a pilot study using his exercise prescription program called EL-FIT (Exercise and Liver FITness), which is delivered through a smartphone. It has previously been validated in liver transplant candidates who have advanced liver disease. Through this pilot study, we are trying to determine whether this program is feasible in adults with MASLD and equally efficacious in terms of improving physical function and fitness.

G&H What are the biggest questions that remain in this area?

IS There are 3 highly significant questions that need to be answered to move forward in this field. First and foremost, it is still not known whether exercise without weight loss can improve liver fibrosis based on direct evidence, meaning liver histology. Second, the optimal dose of exercise needed to obtain this histologic benefit is not known. When I see patients in the clinic, they do not ask to do more activity; rather, they want to know the minimum they can do to receive a benefit because they often do not have time to perform very high amounts of physical activity. The ceiling and floor are still not known in terms of the dose of exercise. The last question, from a policy standpoint, is how to integrate exercise into clinical care pathways and then how to deliver this intervention to the millions of people living with this condition. This is not going to happen through in-person supervised exercise. This is where I think digital interventions can be scaled across health systems. We just have not seen an effective way to do this yet.

G&H What misconceptions have you seen in the medical community about this topic?

JS It is not a surprise that there are misconceptions in this area because US medical schools do not spend time teaching future physicians how to use exercise as medicine. I think many physicians still believe that exercise is only effective if patients lose weight, or they think that patients will not engage in exercise or are not interested. I think these beliefs are untrue. Exercise has so many weight-neutral benefits. Diet changes tend to be important for trying to lose weight while exercise is more of a weight maintenance tool. As for the misconception about patients not being interested or not engaging, I think that the right tools have not been found because when patients are given what they need to succeed and have a supportive environment, adherence is achievable even in sedentary populations. Our studies have shown that patients complete more than 85% of their exercise sessions when they are in a supportive environment. More than 90% of adults living with MASLD say they want to be more active, but only 1 out of 2 say they know how to achieve that. I think the interest is there, and the onus is on us as a medical community to put resources in place to help our patients.

Disclosures

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Suggested Reading

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