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# Chairperson's Perspective: Treating At-Risk MASH: What Are You Waiting For?

**Announcer:**
Welcome to CME on ReachMD. This activity, titled "Chairperson's Perspective: Treating At-Risk MASH: What Are You Waiting For?" is provided by Prova Education. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

**Dr. Noureddin:**
This is CME on ReachMD, and I'm Dr. Mazen Noureddin. Today I'll be highlighting the key messages presented at a satellite symposium by Prova Education at the recent meeting in Park City, Utah.

Let me tell you about this study, which reflects the prevalence of MASLD and MASH in the US cohort. Our beloved friend, Stephen Harrison, did this study in Texas where he studied the prevalence of MASLD and MASH in the state. Interestingly, the prevalence of MASLD was up to 40% in this population, with 14% of MASH prevalence. That's a high prevalence of such a disease. And you see here the breakdown by males, females, Latinos, BMI, type 2 diabetes, and other metabolic risk factors. And what you see here, if you have metabolic risk factors, especially if you start combining them, such as the last part, type 2 diabetes, BMI, and hypertension, it's up to 74% of the population that have MASLD, and up to 46% of them have MASH, emphasizing the importance of metabolic features in such a population.

Let's look at the disease in general. So this is MASLD as the umbrella. You have  normal liver. And some people, they develop fatty liver. This is about 40% of the population in that study. And those MASLD patients, they progress to another population, which is MASH, which is the advanced form. Not everyone progressed, just 20% of those. And MASH is technically fat plus inflammation plus cell injury. So MASLD is just fat or steatosis, and MASH is steatosis plus inflammation plus cell injury, such as ballooning. And then, over time, you start having this progression of fibrosis, stage 1, 2, and 3, and eventually cirrhosis, which is a devastating outcome, and, of course, hepatocellular carcinoma, in addition to decompensations from cirrhosis, which is the outcome that we don't need for our patients.

So what is important also to know is that type 2 diabetes, I call it, is one of the elephants in the room. Type 2 diabetes patients have a higher risk of MASLD and a higher risk of MASH, as well as a high risk of advanced fibrosis. This is a study that was done in France recently from 713 patients screened in hepatology practices. The prevalence of MASH in this population was up to 58%. And look at the prevalence of F3 and F4 population. It was up to 38%, emphasizing that type 2 diabetics have one of the highest risks to develop NASH or MASH, as well as advanced fibrosis, including F3 and F4s.

But it is also important to remember that the leading cause of mortality in MASLD is cardiovascular disease, followed by non-liver malignancy and then followed by liver disease. So here it shows you the breakdown of the risk factors and the association between morbidities, mortalities, and fibrosis, including those mortalities from cardiovascular disease and non-liver malignancies.

What is also important to know is that, in the last 2 years, we had a lot of guidelines streamlining the process. And this is the American Association for the Study of Liver Diseases, highlighting who should be screened. And those are the high-risk population. Again, high-risk population. So who are those? If you're prediabetic or a type 2 diabetic, or you have 2 metabolic risk features, you have to screen with the test called the FIB-4 test. And this is done in primary care. And the FIB-4 is a combination between ALT, AST, age, and platelets. You can just go on a formula, and it will calculate it for you. If the FIB-4 is more than 1.3, this is when you refer to a GI and hepatology, or you do a test such as transient elastography, or a lot of people know it as FibroScan, or an ELF test, which is a blood

test. Values above 8 for a transient elastography trigger GI and hep referral, and ELF more than 7.7 also trigger GI and hepatology referral.

It's important also to know that the concept of stiffness is key. We used to do liver biopsy back in the days to show the fibrosis F1, F2. But we learned from imaging that this fibrosis can be presented by stiffness. With a soft liver, you don't have complications. When the liver gets stiff or firm, you start having complications. And that can be detected by different methods. The most common one is called vibration-controlled transient elastography. You have ultrasound shear wave also studying that, and eventually MR elastography that study this population.

Let's look at other tests out there. If you don't have access to those, there's a blood test that the guidelines mention called the ELF. And the ELF is a blood test that has 3 components that represent fibrosis biomarkers. Levels more than 9.8, in particular, indicate this patient likely has advanced fibrosis and eventually can go to cirrhosis. And levels more than 11.3 point toward that this patient might have complications in the near future.

Liver biopsy, we don't use it as often as before. However, it still has value. For instance, when you have another etiology that you're suspecting, such as, for instance, autoimmune hepatitis, if you have doubt, you go for biopsy. In addition, if you have discordance between noninvasive testing, or you really want to confirm cirrhosis and the others NIT did not, you still can consider liver biopsy.

Those are the stages again for MASH and MASH with fibrosis. So F0, you have inflammation, steatosis, and ballooning; then F1; then F2, which is significant fibrosis where morbidity and mortality increase; then F3s with advanced fibrosis; and F4s. And it's thought that patients with F2 and F3, that they will benefit from liver-directed therapy, and eventually we need to find treatments for the F4 patients. In the F0/F1 patients, you just need lifestyle intervention and weight loss measurements that can be done also by pharmacological therapy.

So what are some of the lifestyle recommendations for treating MASH patients?

It should be a patient-centered approach. Weight loss and exercise and managing the weight very carefully. And there are multiple things that you can do, such as exercise programs, multiple steps. And those are some of the studies that they have been done in that area. In addition, you want to consider beneficial factors. Coffee is helpful; Mediterranean diet is helpful. And avoiding fructose, smoking, and alcohol is very important. In addition, you can manage comorbidities, weight loss or GLP-1s. If you have type 2 diabetes, you need to control it with medications such as pioglitazone and GLP-1. Statins for dyslipidemia, hypertension, and sleep apnea. You need to control all these factors to help with the comanagement for MASH.

However, when you have MASH in F2 and F3, you still need liver-directed therapies. And that's what is here. Resmetirom, which is the first and only FDA-approved medication for NASH with significant advanced fibrosis. And this is a paper that is an expert panel that we put together on how to treat these patients. If you have a MASLD patient, when you rule out other causes, especially alcohol, you look for assessment of fibrosis.

And I'll simplify it in this slide. For transient elastography between 10 and 20, these patients qualify for treatment. You can use other methods, such as MR elastography and ELF, but it's common to use transient elastography, again between 10 and 20. But when you hit 15, you have to be a little bit careful because between 15 and 19, some could have cirrhosis. So we want to make sure they don't have that by looking at the platelet number, which should be more than 140, looking at the imaging, there's no nodular liver, size of spleen, collaterals. All these should not be there.

It is thought also when you have high stiffness, such as 20 on transient elastography, or high ELF, more than 11.3, this is a red line that we should not treat these patients. Again, we should not treat these patients.

So the resmetirom program, it was actually a very large phase 3 program that included multiple, multiple studies, and here in the middle is MAESTRO-NASH that led to the FDA support of its approval. And next to it, there is the MAESTRO-NASH OUTCOMES, which is a study that is ongoing on cirrhotic patients that is going to tell us if it's going to be helpful in cirrhotic patients as well. Again, to be clear, we cannot treat cirrhotics with resmetirom as yet. It's only patients with significant advanced fibrosis or F2 and F3. And these programs led it to a high safety profile in our patients.

And this is the study that was done in F2 and F3. It was a phase 3 study called the MAESTRO-NASH study that showed efficacy that was statistically significant – on the left in improving steatohepatitis, or resolution of NASH, and on the right, improvement of fibrosis by one stage, which was also statistically significant. So we only needed to hit one of them to get the FDA approval, subpart H, but in this study, we were able to hit both of them.

And finally, this is what shows you how to monitor. So for patients with significant advanced fibrosis, you start resmetirom. And then in 3 months, you do labs. And then in 6 months, this is when I do labs and transient elastography or another measure to see the first signal. The decision to decide if it's efficacious or not should not happen until 1 year, which is how long it took us to assess the paired biopsy.

You don't need biopsy here, but this is how the study was done. So at 1 year, I repeat liver enzymes as well as transient elastography to double-check my patient. Improvement or steadiness is a great sign. And if it's worsened, you want to look for other causes.

What we also showed in a study here, we showed that beyond 1 year, 2, and 3, we also continued to see improvement on transient elastography, which tells us that long treatment is also helpful in such patients.

Side effects are usually rare, but GI side effects, such as diarrhea and nausea, have been seen, and those are self-limited, usually, and well tolerated.

The effect on weight loss has been also studied. So the bottom line here, we had patients on GLP-1 that entered in the MAESTRO-NASH trial, and these GLP-1s did not affect the severity of the disease in the MAESTRO-NASH trial, neither did it add anything to the resmetirom treatment. However, in this study, what we found also is that some patients on resmetirom lost weight. And if you lose weight, you have additional efficacy. More than 50% improve their steatohepatitis, and 40% improve their fibrosis. So it's really also helpful to lose weight and exercise. Resmetirom can. We have seen patients doing that, and if you lose weight, there's even more efficacy with resmetirom. This is already I mentioned, the concomitant use did not affect the result of MAESTRO-NASH if you use the GLP-1.

So that's a summary. We have a new FDA drug approval now. We have the screening guidelines. We have guidelines on how to start, monitor therapy.

Thank you for joining me. Unfortunately, our time is up. This has been CME on ReachMD. Thank you very much.

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