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## The Changing Paradigm of Treating MASLD/MASH: At the Crossroads of Hepato-Cardiometabolic Care – Chair’s Perspective

### Announcer:

Welcome to CME on ReachMD. This activity, titled “The Changing Paradigm of Treating MASLD/MASH: At the Crossroads of Hepato-Cardiometabolic Care – Chair’s Perspective” is provided by Medtelligence.

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### Dr. Alkhouri:

Hi. This is CME on ReachMD, and I'm Dr. Naim Alkhouri, the chief medical officer at Arizona Liver Health in Phoenix, Arizona. Today, I will be highlighting the key messages presented at a satellite symposium by Medtelligence at a recent meeting in San Diego, California.

We know that at least 2 million adults have a high-risk MASH in the United States. This is based on data from the NHANES database. And actually, other studies estimated that up to 15 to 16 million people in the United States may have MASH with F2 fibrosis or higher. And we are expecting that the combined burden of MASLD and MASH in the United States and North America will increase by 82% in the next 15 years or so. So what we are seeing today is really the tip of the iceberg, and we need to do a better job at screening patients at risk for MASLD. And then once we identify MASLD, we need to determine the severity of their disease.

So I'm going to share with you a case here of a 44-year-old white woman with class 2 obesity, type 2 diabetes, hypertension, dyslipidemia, so basically she has the metabolic syndrome. She had an abdominal ultrasound that showed steatosis in the liver, making a diagnosis of steatotic liver disease. She has family history of obesity and cardiovascular disease, and she is currently on several diabetes medications, including glyburide, sitagliptin, and metformin. She also takes metoprolol for hypertension, lisinopril, and atorvastatin for dyslipidemia. She has a very sedentary lifestyle. She admits to smoking and she drinks occasionally. On physical exam, her BMI is at 37.6, consistent with class 2 obesity, and her blood pressure was borderline elevated at 137/86. She has also central adiposity and mild hepatomegaly.

So what do we do when we see these patients in our clinics with steatotic liver disease and metabolic syndrome? First, we have to look at their medications and rule out other causes of steatosis in the liver, such as steroids or tamoxifen, amiodarone. I also like to rule out other chronic liver diseases, including excessive alcohol consumption, viral hepatitis, and some metabolic and genetic liver diseases. HIV has been associated with steatotic liver disease, and there are several acquired metabolic diseases that we need to think of, including lipodystrophy.

After we rule out other causes of steatotic liver disease and we are left with the diagnosis of MASLD, the next step is to risk stratify these patients and identify the severity of fibrosis. And we have two algorithms. The first one is meant for primary care physicians and endocrinologists, and this one starts with the FIB-4 index, which is a simple score that includes the patient's age, AST, ALT, and platelet count. And having a low FIB-4, less than 1.3, can exclude the presence of advanced disease. When you have a FIB-4 more than 2.67, this indicates the need for specialty referral. And then in cases where the FIB-4 is between 1.3 to 2.67, this is when you need to do a secondary risk assessment. And what is recommended by the AASLD guidelines is that you move on to a FibroScan or vibration-

controlled transient elastography, or you can do the enhanced liver fibrosis test, or ELF. And then if these are high, then you need to send to a specialist. With all of these, you need to do a detailed cardiometabolic risk assessment and try to actually treat the metabolic syndrome. Once the patients go to specialty care, then we do MR elastography and other tests to try to risk stratify them. And if the noninvasive tests are discordant, this is when sometimes we have to do a liver biopsy.

In terms of the effects of alcohol use and cigarette smoking, they're both not good for our patients. We have data showing that around 17% of patients with the diagnosis of MASLD will eventually receive a diagnosis of alcohol-associated liver disease. In fact, in my clinic, I recommend no alcohol for all patients with advanced fibrosis, and especially in patients with cirrhosis. Drinking alcohol can also increase the risk of progression to cirrhosis, decompensation, and liver cancer. Smoking is also harmful for several reasons, but including more fibrosis in the liver in patients with type 2 diabetes that also smoke.

So going back to our case, we did some preliminary labs showing a complete blood count that's within the normal limit with a platelet count of 241,000, blood sugar was slightly elevated, and the A1c is at 8.3, indicating poor diabetes control. The lipid panel showed elevated triglycerides at 270 and then we had elevated ALT and AST. Kidney function was within normal limits. This patient, in a specialty clinic, received a FibroScan that showed liver stiffness at 8.6 kPa, indicating potentially significant fibrosis, and a CAP score of 371, indicating significant steatosis.

So we talked to our patient about her diet, and she gave us a 24-hour dietary history that indicated very poor diet, which is high in processed foods and carbohydrates and what I call unhealthy fats.

So how would we treat this patient? Well, number one is always the lifestyle intervention that will focus on a healthy diet and increase exercise, but it is so important to keep in mind that you cannot out-exercise the fork. So there's no amount of exercise that will overcome a meal that's enriched in processed foods and carbohydrates. So we need to be very up front with our patients that exercise alone is not going to be the answer. It has to be the combination of healthy eating plus exercise.

Would I treat this patient with the GLP-1 receptor agonist? And the answer is absolutely yes because this patient has metabolic syndrome with class 2 obesity and type 2 diabetes that is poorly controlled, so I think this would be a good option for this patient. We know that GLP-1s have pleiotropic effects, so they work on the brain and decrease your appetite. They work on the stomach and delay gastric emptying through weight loss. They can also decrease the amount of fat in the liver and indirectly help with decreasing fibrosis. They also have beneficial effects on the kidneys in terms of improving chronic kidney disease, and they have multiple cardiovascular benefits.

And more recently, we are learning that GLP-1s have, actually, beneficial effects in patients with MASLD that go beyond just weight loss and improving insulin sensitivity, and they actually improve outcomes in every fibrosis stage. The only cases where I would probably avoid using GLP-1 receptor agonists is patients with decompensated cirrhosis.

We have several emerging, what we call, incretin targets. So these are the hormones produced in the intestines, similar to GLP-1. I think everyone is familiar with the GLP-1 receptor agonist semaglutide, and we have phase 3 data that I will share with you. But we have several dual and triple agonists, including GLP-1 plus GIP, such as tirzepatide, and we had promising data from a phase 2 trial that presented recently. We also have a dual agonist that includes a GLP-1 plus glucagon. And glucagon is known to have direct effects in the liver and enhances the utilization of fatty acids in the liver. So we have a few promising compounds in that category, including efinopegdutide, and more recently, we saw very promising data with survodutide. This was a phase 2b with biopsy at baseline, biopsy at the end of treatment, showing very high rates of MASH resolution and also significant improvement in fibrosis.

We also have triple agonists that include GLP-1, GIP, and glucagon. And an example is retatrutide that showed promising data in a phase 2a trial.

So semaglutide, the ESSENCE trial, is a phase 3 study that did liver biopsies at baseline and then biopsies after 72 weeks of treatment, and they hit both primary endpoints in terms of MASH resolution on the repeat biopsy and also fibrosis regression by one stage without worsening in MASH. So this is a major development in the field that will help our patients.

We have, as I mentioned earlier, emerging data with other incretins. So survodutide showed very promising data in the phase 2b trial, heading statistically significant improvement on MASH resolution and fibrosis regression. Tirzepatide also showed very high rate of resolution of MASH with a signal on fibrosis. And then we have more preliminary data with retatrutide in terms of reduction in liver fat on MRI-PDFF, but very marked reduction, and many patients normalizing the amount of liver fat. And then we have efinopegdutide that showed improvement in liver fat. And actually, this was compared to semaglutide alone and showed higher rates of defatting of the liver. Cotadutide is another GLP-1 glucagon but had lower potency, and I don't think it's being developed further to treat patients with at-risk MASH.

So in terms of following up and management of our patients, I think adding a GLP-1 to the regimen is a good idea. Before we start a GLP-1 in our patients, it's very important to talk about the goals and what they need to expect in terms of weight loss. The fact that this will be a weekly subcutaneous injection, it will require dose escalation; every 4 weeks we typically increase the dose. And by doing this, we improve tolerability. They need to understand that they need to eat a healthy diet that's high in protein to prevent muscle loss, and they need to hydrate really well to avoid inducing acute kidney injury. And then they need to exercise when they take a GLP-1. And we talk to them about managing side effects.

And the main side effects that I see in my clinic include dyspepsia, nausea, sometimes vomiting, constipation in most patients, but some patients will develop diarrhea. For the most part, if you dose escalate properly and guide the patients, you are able to keep them on these medications. Hypoglycemia can happen when there is combination with other diabetes medications. And then some patients may have dizziness or headache. It is very important to also tell the patients that if they don't tolerate a high dose, that we can actually decrease the dose. It is important to also assess for sarcopenia, which is muscle loss at baseline, and try to prevent it by high-protein diet and making sure that they exercise while they take GLP-1.

So to conclude our case, I think we should probably continue with the statin therapy, because we see a good response in terms of LDL cholesterol. I would change the diabetes medications and potentially stop the glyburide and the sitagliptin and start the GLP-1 treatment with semaglutide or potentially a dual agonist like tirzepatide. I would also discuss smoking cessation. This is very important for several reasons, but also including potentially helping with liver fibrosis. Because alcohol is damaging to the liver and has absolutely no health benefits, we can discuss cessation of alcohol or at least decreasing the amount of weekly alcohol consumption. And then, of course, developing a healthy diet with an exercise plan is a must. And then schedule a regular follow-up with repeating the liver stiffness measurements to make sure that our patient is heading in the right direction and is not developing worsening liver fibrosis.

So this went by fast. Thank you for joining me. Unfortunately, our time is up. This has been CME on ReachMD. Thank you.

**Announcer:**

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