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Harnessing the NAFLD/NASH Epidemic: Preparing for a New Treatment Paradigm

Announcer:
Welcome to CME on ReachMD. This activity, titled “Harnessing the NAFLD/NASH Epidemic: Preparing for a New Treatment Paradigm” is provided by Prova Education.

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Dr. Younossi:
Hello, this is CME on ReachMD, and I'm Dr. Zobair Younossi. I'm the Chairman of the Global NASH [nonalcoholic steatohepatitis] Council. Today, I'll be highlighting the key messages in clinical data presented at a satellite symposium by Prova Education in conjunction with the Academy of Managed Care Pharmacy’s 2023 Nexus meeting in Orlando, Florida. This presentation focused on nonalcoholic steatohepatitis, or NASH, and was titled NASH: An Epidemic With Significant Implications for Managed Care Professionals. I presented at this symposium along with my esteemed colleague, Dr. Naim Alkhouri.

So let's start by looking at the global prevalence of nonalcoholic fatty liver disease [NAFLD]. This data comes from a recent meta-analysis that we published in *Hepatology*. This meta-analysis suggested that the global pooled prevalence of nonalcoholic fatty liver disease is about 30%. And when you look at different regions of the world, the highest prevalence is the Middle East and North Africa, as well as Latin America. But looking at the rest of the regions of the world, the prevalence is, almost in every region, is more than 25%. If you look at the most recent period, which would be in the past, you know, 2 or 3 years, the prevalence actually has risen to 38%. So at the moment, we think that the prevalence of NAFLD globally is about 38%.

Now when you look at the prevalence of NASH or MASH [metabolic dysfunction-associated steatohepatitis], which is the progressive form of fatty liver disease, that prevalence is about 5.27%. Again, very high prevalence in all regions of the world, but the highest prevalence of NASH is being reported in Latin America. Remember, NASH is a part of the spectrum of NAFLD, and it's a subtype of NAFLD that would predominantly progress over time. This is sort of the natural history of NAFLD, that when you look at patients with NAFLD, only about maybe 20% of them will have NASH, and these patients with NASH are those that can progress to cirrhosis and liver cancer or otherwise called by hepatocellular carcinoma.

It still is important to remember that the number one cause of death among patients with nonalcoholic fatty liver disease is cardiovascular, but liver is the third most common cause of death amongst these patients. In fact, in this context, at the moment, NAFLD and NASH have become one of the most common causes of cirrhosis and probably one of the leading cause of liver cancer in the United States. When you look at those patients who have been listed for liver transplantation, NASH, in general, is the second indication for liver transplantation. But for those patients who are over age 45, or those who are listed for liver cancer, it’s the number one indication for liver transplantation.

There are a number of extrahepatic diseases that are associated with nonalcoholic fatty liver disease. Cardiovascular, I’ve already mentioned. Extrahepatic cancers are common in these patients. And then, of course, a muscle disease called sarcopenia. When you look at fatty liver disease and cardiac sort of complication, it’s not only cardiac or coronary artery disease, there is also a number of other cardiomyopathies that are associated with this disease. So in fact, when you look at the liver and infiltration of fat in the liver, you have a milieu that is proinflammatory and also lead to deposition of fat in other organs. So if you have epicardial fat tissue deposition, that leads to left ventricular diastolic dysfunction, but also other things that's related to arrhythmias. Now on the cardiac side, there is also evidence of endothelial dysfunction. And that leads to, of course, arterial hypertension, and also atherosclerosis and coronary artery disease. So

this is why coronary artery disease or cardiovascular diseases is the most common cause of death among these patients.

Another common extrahepatic manifestation is sarcopenia. That, of course, sarcopenia is more common in patients with nonalcoholic fatty liver disease is from a study we published and, from NHANES dataset, patients who have sarcopenia and fatty liver disease together, they tend to have higher, not only risk of scarring of the liver, but also higher risk of mortality, all-cause mortality, cardiac mortality, and cancer mortality.

And finally, the disease that is also associated with NAFLD is extrahepatic cancer, especially colorectal cancer, gastric cancer, and others. So then this is actually independent of obesity, this increased risk of cancer.

Now, in addition to the clinical outcomes, nonalcoholic fatty liver disease and NASH is associated with economic burden. We published a study a few years ago showing that over a 20-year period of time that the cost in the United States for patients with NASH is about $100 billion. This is a recent study looking at estimated lifetime direct medical costs, and that's about $223 billion. In fact, when you go with different stages of fibrosis, this is estimated here by a score called FIB-4. The higher the stage, the higher the cost of care associated with fatty liver disease.

Now, how do you actually assess these patients? First of all, you have to look at initial suspicion for presence of cardiometabolic risks. Here, the most important one being type 2 diabetes. But of course, the more components of metabolic syndrome you have, the higher the chance of having significant liver disease. Those patients who come in with elevated liver enzyme, they should also be evaluated for fatty liver disease, as well as those who have fatty liver by imaging.

So who should we screen? Of course, anybody that you have suspicion for NASH. It's important to remember that those patients who have stage 2 or higher are the main concern in terms of progression to more advanced liver disease and adverse outcome. This has been shown in multiple meta-analyses. And those patients who have type 2 diabetes, as I mentioned, these are the patients who are at risk for more adverse outcome.

But when you're seeing a patient with nonalcoholic fatty liver disease in your clinic, how do you identify these patients in terms of risk? And there are a number of pathways and guidelines that's been suggested. This is the one that was recently published for the American Association for the Study of Liver Disease. There is one for the American Association for Clinical Endocrinology, and others, which is very similar. You do a test called FIB-4. Easy to do. FIB-4 can be obtained with the laboratory that's available for patients and the formula's on the internet. If you have a FIB-4 that is less than 1.3, those patients are considered to be low risk, and they can be followed by their primary care physicians and not really have anything else. If the patients have type 2 diabetes or diabetic sort of situation, you have to repeat FIB-4 every 1 to 2 years; otherwise, every 3 to 4 years would be fine. Now for those patients who have a FIB-4 more than 1.3, or 1.3 and higher, you can do a secondary test. These are the 2 common tests that's done; one is called transient elastography and another one is called enhanced liver fibrosis test, which is a blood test. And those tests can, again, tell you which patients are at high risk. And you only focus on those patients who have higher FIB, ELF test, and higher transient elastography, and those are the patients that you can send to hepatology or liver specialty for subsequent assessment. And they would be the candidates for future treatment.

How do you manage? Of course, you have to address the metabolic syndrome and improve those components, including weight loss, through diet and exercise. And of course, treat type 2 diabetes appropriately and effectively, as well as hypertension and dyslipidemia. There are a number of drugs that are being sort of developed that are liver targeted that will come into the future and a number of drugs that are also being assessed that hopefully not only improve liver outcome, but also non-liver outcomes, especially cardiac outcomes.

This is the weight loss slide that's been published a few years ago. In order to actually improve all aspects of liver histology, meaning not only fat, which is steatosis, but also fibrosis, you need to lose about 10% of the baseline weight. When you look at what was the percentage of patients in this clinical trial that actually achieved that, that was about 10% or so. So losing weight with diet and exercise is a factor that's hard to manage. You have to remember that weight loss should be considered as a prescription, not just basically telling the patient go ahead and lose weight and come back in 6 months; that's not going to work. So you have to actually take this seriously and provide patients with the tools to be successful.

For those who are just tuning in, you're listening to CME on ReachMD. I'm Dr. Zobair Younossi. Today, we're discussing NASH and the role of managed care professionals. Welcome.

A number of drugs that are not FDA-approved but have been suggested as off-label use, vitamin E was actually used in a study called PIVENS. It was better than placebo for NASH patients, but there are some potential side effects that are listed here. Pioglitazone, which is a drug used for treatment of diabetes, has also been shown to improve histology in patients with NASH, and that's been suggested for some patients with biopsy-proven NASH and diabetes. But again, there are some side effects that are listed here.

When you're looking at the new drugs that are being developed for treatment of nonalcoholic steatohepatitis, there are 2 important

endpoints. NASH resolution or fibrosis improvement, this is really what the FDA is requiring. The European [Medicines] Agency that's called EMA requires both of these 2 endpoints to be met. There are a number of drugs that have been used. This is only a partial list of studies that were primarily in phase 3. And you can see there are lots of failures here.

There are 3 drugs that I'm going to talk about here that would be important to mention because they're ongoing in terms of clinical trial. This is the first one, called lanifibranor, which is pan-PPAR agonist. It's a phase 2b study called NATiVE3 study. And as you can see, for patients with NASH, all the endpoints that we are interested in, in terms of resolution of NASH, improvement of fibrosis, and both, were higher in both doses of lanifibranor, as compared to placebo. So this is a drug that is going to phase 3 and hopefully we'll have data in the next couple of years.

The second drug that I want to talk about is semaglutide, which is the GLP-1 agonist. This drug was also evaluated in a phase 2 clinical trial. And as you can see here, the NASH resolution occurred in the 0.4-mg dose of semaglutide at a very high rate compared to placebo. Unfortunately, the fibrosis improvement did not happen.

Both lanifibranor and semaglutide are generally safe, but you know, they're expected to have their side effect profile. For GLP-1s, it's GI [gastrointestinal] side effects that are predominant, but they're, in general, safe drugs.

The third drug is a thyroid beta receptor agonist called resmetirom. This is data from phase 3 MAESTRO-NASH trial. And again, this drug met both NASH resolution and fibrosis improvement and has a favorable lipid profile. Side effects, again, some mild GI side effects. This drug is well tolerated. The cost-effectiveness of resmetirom for NASH was done by the Institute for Clinical and Economic Review and suggests that this drug is cost-effective according to the willingness to pay for the United States from a healthcare sectors perspective.

So in summary, NAFLD/NASH and complications of NAFLD are growing and causing significant clinical and economic burden. Fibrosis stage, stage 2 or higher, as determined by noninvasive tests, can help you risk stratify patients with NAFLD and one of the algorithms can be used. So like the AACE [American Association of Clinical Endocrinology] study or AACE algorithm. Lifestyle intervention should be the first approach in a systematic approach in a coordinated effort to help patients lose weight through diet and exercise. It can be effective, but it's hard to achieve the endpoint of weight loss. There are a number of drugs that are available right now to manage the risk factors, like diabetes, that should be used right now. But there are a number of drugs that are being developed specifically for NASH in the near future. Hopefully, we'll have a few of those in the near future, in the next year or 2.

That's all the time we have today. So I want to thank the audience and our viewers for listening in. It was great speaking with you today, and hopefully we'll see you again.

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