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The NASH Epidemic: Highlights from the AMCP 2023 Symposium

Announcer:
Welcome to CME on ReachMD. This activity, titled “The NASH Epidemic: Highlights from the AMCP 2023 Symposium” is provided by Prova Education.

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Dr. Noureddin:
This is CME on ReachMD, and I'm Dr. Mazen Noureddin. Today I'll be highlighting the key messages and clinical data presented at a satellite symposium by Prova Education in conjunction with the Academy of Managed Care Pharmacy’s 2023 annual meeting. This presentation focused on nonalcoholic steatohepatitis or what you heard before, NASH, and was titled “NASH: an Epidemic with Enormous Health and Economic Implications.” I presented at this symposium along with my esteemed colleagues, Dr. Steve Flamm from Chicago and Dr. Tiffany Kaiser.

So what are the main risk factors for NASH, and who should be identifying them? Let's talk about the disease in general, the epidemiology and the multidisciplinary challenges. Nonalcoholic fatty liver disease is a spectrum. Start with NAFLD, and then you take out the D, you end up with NAFL. And NAFL, this is what we used to call simple steatosis. And luckily, and although they are about 30% of the US population in that pocket, they are not as affected as those that progress. So those that progress are those people that get NASH. And what is NASH? What I tell my patients, on top of the fat, they get inflammation, so it's steatohepatitis, the inflammation part. And that is about 20% of the initial 30% I told you about. Still a lot of people, but not everyone. And why is NASH a problem? Because over time, it progresses into later stages when you start getting fibrosis scarring, so F0, F1 – fibrosis stage 1 – all the way to cirrhosis, which is F4. And then you know what happens once you get cirrhosis: It's initially compensated, and then decompensated, and then you eventually get complications, such as varices, ascites, hepatic encephalopathy, and you may require liver transplantation. Some people die, unfortunately.

So let's ask ourselves, before we get to that point that I just talked about, how does one have an initial suspicion for NAFLD and NASH? What are the risk factors? I always say keep an eye on the elephant in the room, which is the type 2 diabetics. The type 2 diabetics have been shown that it's not 30% that have NAFLD, it's actually 60%, which is double, which is the majority of type 2 diabetes. They also have more advanced fibrosis and cirrhosis. So the F3 and F4 prevalence of about 15% to 20% in this population.

Other risk factors that you need to suspect: metabolic syndrome, especially 2 risk factors, other diseases, psoriasis, hyperthyroidism, hypogonadism. But the 2 metabolic risk factors have been implemented in the guidance to be a base for screening; of course, the type 2 diabetics, you screen.

And how do we see these patients initially, how do they come? They're actually embedded in primary care and endocrine practices. I mentioned to you that type 2 diabetes, many of them, they have nonalcoholic fatty liver disease, and unfortunately, mostly are not discovered.

And nonalcoholic fatty liver disease patients, they have a huge burden on our system. And forget about for our system for a second; it's our patients, our care. We need to make sure they don't get complications. And those complications are the burden of our health system. So for instance, nonalcoholic fatty liver disease patients, NAFLD patients, they have higher mortality of cardiovascular disease.

And NAFLD is a risk factor for cardiovascular disease in these patients. They get cirrhosis, they get liver cancer, they require liver transplantation, and many die. And they cost our health system billions of dollars every year. Again, patients come first. And in addition to the burden on the health system and the doctors, we need to help these patients. And we need to identify them early.

So how do we mitigate this risk? If there's anything you want to take away from our presentation, it's earlier diagnosis. So here's what the guidelines by many societies – American Gastroenterology Association; American Association for Study of Liver Disease; American Association for Clinical Endocrinology; EASL, the European Society for Liver Disease; as well as South America recommendations, Asian recommendations – they all talk about screening the type 2 diabetics and people with 2 metabolic risk factors.

How do you screen? This is how you should do it. If you're a primary care or endocrine, you need to be familiarized with a test called the FIB-4. The FIB-4 is a formula. We use Google to calculate it. There are a lot of smartphone apps that they can calculate it for you. And it's a score that comes by entering data on ALT, AST, platelet, and age. And it gives you the score. And what you need to remember is the number less than 1.3. Because if it's less, that means your patient is safe and he can follow up with you. It's not the end of it; you have to help them losing weight and exercise and monitor their heart and all these things. But if it's more than 1.3, you should start thinking about more complex liver disease. If you just remember that number, you should be fine. But if you want to go a little bit into more details, numbers between 1.3 and 2.67 trigger another test, such as FibroScan, which is an ultrasound-like imaging that measures the fat and stiffness representing fibrosis of the liver. Again, between 1.3 and 2.67, it triggers another test, which is FibroScan. If you don't have it, just send the patient for gastroenterologist or hepatologist after the 1.3. After 2.67, that's absolutely referral, and we will take care of this patient in our clinic and do further testing such as FibroScan or MRI techniques such as MR elastography.

Now, well, you identify the patients. Let me tell you the update on managing and treating these patients. So we all start from the holistic approach, the most common sense approach that every patient should do, indeed all of us should do, which is exercise and weight management. You have to be at your ideal weight goal, and if you're overweight, you need to lose weight. Of course, there is a question about the kind of diet, and I always say tailor it toward your patient. There is intermittent fasting, there's low-carb diet. The most proven one is actually the Mediterranean diet. You have to ask them about limiting alcohol consumption, especially on those with fibrosis.

There are some medications suggested by some guidance, but they are not FDA-approved, such as vitamin E or pioglitazone, but they have their own complications, such as cardiovascular effects with vitamin E and prostate cancer and weight gain with pioglitazone.

The NASH treatment is not approved yet. We do anticipate that we're going to have FDA-approved treatment this year or the next year, for sure by 2024. But let me tell you about them for a second. I guess, let's talk about the emerging pharmacological therapy for NASH. Before I go to that, I want to tell you the endpoints of clinical trials. So there are now multiple *New England Journal* papers on treatments for NASH. And this is what you need to know about them. In early-phase trials, we use MR, fat fraction, and look at changes in the fat. Most of you read *The New England Journal*, so what you see usually in this journal, the phase 2b or phase 3, the registry trial, and the focus on histology. And what we look for, histology – again, this is only in clinical trials; we don't do that in practice. And I think it will go away in clinical trials in the future. But for now, the regulator asks for liver biopsy, asking for 1 of 2 things. The first thing is fibrosis improvement. So if you go from stage 3 to stage 2, that's an improvement on that patient. Of course, they should not worsen the NASH. So you look at that for fibrosis improvement. The other outcome, we call it NASH resolution. And in lay term, it's pulling the inflammation steatosis and ballooning, which is the cellular injury, down, and you see that difference on liver biopsy.

Now let's talk about the pipeline. Well, we have multiple phase 3 studies. The 3 major ones are the following: There is resmetirom, obeticholic acid, lanifibranor. Resmetirom is a thyroid hormone beta receptor in the liver. And why thyroid hormone beta receptors? It turns out the liver actually has thyroid hormone beta receptors that are specific for the liver. And in a way, in NASH patients, if you want to simplify it, your liver is kind of hypothyroid when you have NASH or liver diseases. So regulating the TH beta pathway regulates glucose and lipid metabolism. Indeed, endocrinologists knew about that many years ago and used it to manage dyslipidemia. But it turned out it has an effect on the liver as well. So you, here, get multiple effects. You reduce fat inflammation and fibrosis in the liver, and you improve their lipid panel.

Well, it turned out this is true in multiple clinical trials. That led to the recent announcement of the MAESTRO trial. The MAESTRO trial of resmetirom is a phase 3 study. And what happened here is they treated NASH patients, they did liver biopsies, and the treatment was resmetirom. And the trial in its phase 3 has achieved the primary endpoint. Indeed, it achieved NASH resolution and it achieved fibrosis improvement. And there was a favorable effect on lipid panel. We do anticipate that this drug will be approved in 2023 or 2024. Exciting news for the field of NASH. There are options in the near future.

Obeticholic acid, another drug. It's an FXR receptor regulator. The FXRs regulate bile acid, but they also regulate glucose and lipid metabolism. And this is what happened, in the phase 3 study, they improved fibrosis. The FDA has asked for additional safety data, and the sponsor has shown them these data, that it's still safe, and they showed them the fibrosis improvement is still there. There was no NASH resolution. And the side effects of this drug is worsening the lipid panel and itching. However, it is still exciting to see this drug getting closer to the finish line and hopefully with an approval soon.

Lanifibranor is another drug that in a phase 2b study published in *The New England Journal of Medicine*, the study then showed that Lanifibranor, which is pan-PPAR receptors, it showed that improved histology including NASH resolution, fibrosis improvement, and both met at the same time: NASH resolution and fibrosis improvement. It is now in phase 3 studies.

Take-home message: The field has evolved. It's an exciting time in 2023, that we're going to see drugs that hopefully will be approved and offer more options for our patients. If you do have type 2 diabetic patients or patients with 2 metabolic risk factors, it is a must as of today to screen these patients for nonalcoholic fatty liver disease and fibrosis.

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

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