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Managing Liver Disease in Diabetic Patients: A Comprehensive Approach to Care

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and today we'll be discussing liver disease in diabetic care with Dr. Michael Charlton. Dr. Charlton is a Professor of Medicine and Co-Director of the Transplant Institute at the University of Chicago.

Dr. Charlton, welcome to the program.

Dr. Charlton:
Thank you for having me. I'm pleased to be speaking on this important topic here today.

Dr. Buch:
Thank you so much. So, Dr. Charlton, let's start with some definitions. Please define nonalcoholic fatty liver disease, NAFLD; nonalcoholic fatty liver, NAFL; and nonalcoholic steatohepatitis, also known as NASH.

Dr. Charlton:
That's a great starting point because nomenclature is one of the things that have changed recently. The terms that you referenced, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, they really emerged in 1980 from Mayo Clinic from a pathologist and a liver specialist, a hepatologist, who was seeing an increasing number of patients whose liver biopsies looked like they were drinking too much—it was indistinguishable based on the biopsy finding—but they, incredibly, weren't. And patients who had this tended to have more weight than was healthy, so they had obesity and some of the metabolic complications that go along with that, so hypertension, dyslipidemia, type 2 diabetes, and so they called it nonalcoholic steatohepatitis.

So the term NAFLD, nonalcoholic fatty liver disease, is an umbrella term for anyone with extra fat in the liver, and that could be based on ultrasound, any imaging study that sees it, or biopsy. And nonalcoholic steatohepatitis, or NASH, refers to the presence of the extra fat in the liver, or steatosis, but in addition, some amount of inflammation, perhaps ballooning with or without any degree of fibrosis or scarring of the liver.

Now about a month ago that nomenclature changed. It was problematic from the beginning because it's a negative definition. There are very few terms in the whole of medicine where you refer to a disease based on what it isn't. There are few examples. Like non-A and non-B hepatitis was around until we knew it was hepatitis C, and then we very quickly changed the nomenclature to hepatitis C. In this instance, referring to it as nonalcoholic had other problems because it's somewhat stigmatizing. Patients don't like to have their illness have the term, *alcohol,* even in a negative sense. And then the term, *fatty,* was also disliked or found to be stigmatizing by a notable proportion of patients. So between the negative-term definition and the use of the term, *fatty,* and the stigmatization that goes along with it, it's a general dislike by some patients.

Those problems needed to be addressed, and so the major medical societies, 60 of them, representing many countries around the world, agreed through a longstanding nearly two-year Delphi process to change the nomenclature to metabolic dysfunction-associated steatotic liver disease, so NAFLD is now MASLD, and NASH, nonalcoholic steatohepatitis, is now metabolic dysfunction-associated steatohepatitis. So NAFLD is now MASLD, and NASH is now MASH.

Dr. Buch:
And again, that leads into what we were going to be talking about because diabetes is related. So can you talk a little bit about why we've now included diabetes type 2 in this metabolic-associated fatty liver?

Dr. Charlton:
It's true. From the very beginning, the association with type 2 diabetes was there. This is highly prevalent. It's the most prevalent liver disease. One-quarter of people in the United States, over 80 million people, have at least steatotic liver disease or extra fat in the liver, and the proportion with the steatohepatitis or the inflammation, as well as the fat in the liver, that's probably 16 percent of those patients, and a smaller proportion have advanced fibrosis, but there's up to five million people with bridging fibrosis or cirrhosis, which are the most advanced amounts of scarring in the liver. That's where all the complications occur. When you look at patients with type 2 diabetes, it's about 50 percent. At least the patient with type 2 diabetes will have metabolic dysfunction-associated steatotic liver disease and MASH. The proportion of patients with diabetes who have advanced or significant scarring of the liver or fibrosis, it's as high as one-fifth and one-tenth of patients. The estimates vary depending on the study, but it's a very high proportion. This is a really at-risk group and an important group to consider liver disease in.

Dr. Buch:
Thank you. And here is a really important question. What should we know about the progression of NAFL to NASH, cirrhosis, and hepatoma?

Dr. Charlton:
It's highly variable. If you take everyone, the whole 80 million people in the country, based on longitudinal studies conducted by the National Institutes of Health and in clinical trials as well in placebo arms, we know that the change in fibrosis stage—and there are four fibrosis stages zero, one, two, three and four—the change rate is about one fibrosis stage increase per seven years. It can be more than that depending on risk factors, such as diet, use of alcohol, presence of type 2 diabetes, and it can be less than that. Of course, if you eat well and you have some genetic protective factors versus susceptibility factors, the rate can change, and the rate can increase substantially if you increase the number of cardiometabolic risk factors and alcohol use.

Dr. Buch:
And that's a wonderful segue to the next question. There are many of our primary care providers listening out there. How should clinicians be utilizing fibrosis 4, also known as FIB-4, to assess the state of fibrosis?

Dr. Charlton:
With 80 million people with any condition, whatever it would be, you have to have a test that's widely accessible, and it really can't be too expensive or difficult to perform, so it's a test that incorporates four things. The FIB-4 is fibrosis 4, and those four things are really simple; they're age, AST, or aspartate aminotransferase, ALT, or alanine aminotransferase, and platelet count. Almost anyone who's been to any provider's office will probably have those four things or could easily get those four. A lot of electronic medical records now have a dot phrase or smart phrase where you can calculate it by just entering FIB-4. And there's three ranges. You'll have low-risk range, intermediate risk, and high risk. If a patient has intermediate or high-risk FIB-4, they should go on to further assessment with transient elastography, which it measures liver stiffness, or some other blood test—for example, the enhanced liver fibrosis test, which measures likelihood of having more advanced liver disease now and complications in the future. So it's a pretty simple algorithm that's been adopted by the American Association for Clinical Endocrinology, and also the American Association for the Study of Liver Diseases.

Dr. Buch:
So a follow-up question with regard to that, and it's been in literature a lot these days, is the accuracy of FIB-4 in making that initial diagnosis. How would you comment about that?

Dr. Charlton:
It's a test, which is very good at excluding people without disease, so the specificity is good, but it's not that sensitive. So if you have somebody with an intermediate or higher risk, their likelihood of having disease is variable, but people who have a low-risk FIB-4 score, they're 95 percent likely to not have advanced disease, so you've excluded it in 95 percent of patients. That's pretty good. And there aren't any tests that meaningfully perform better than that. So it's really good at excluding people without advanced disease, and that's how it really needs to be used in a large practice setting.

Dr. Buch:
Thank you. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Michael Charlton about liver disease in diabetes care.

Now, Dr. Charlton, if FIB-4 is high, why are confirmatory tests necessary?

Dr. Charlton:
A great and important question, and the reason is that although FIB-4 is good at excluding people without advanced liver disease, the

sensitivity is not that good, so most patients in the high-risk FIB-4 range don't have advanced disease, so you have to then do some confirmatory tests so you don't commit a patient to management changes for something that they may not have, which would be at risk or more advanced inflammation and fibrosis in somebody with metabolic dysfunction-associated steatotic liver disease, or MASLD.

Dr. Buch:
So let's continue with that thought. Can you explain a little bit more to our primary care colleagues about elastography and other tests that are appropriate for follow-up of intermediate or high FIB-4?

Dr. Charlton:
Yeah. So there's a group of tests that measure liver stiffness, and they perform elastography either through the generation of high-frequency ultrasound waves—that's the most common form—so that's vibration-controlled transient elastography often obtained with a device called a FibroScanner. That's reasonably inexpensive. It gives you points of care results. And the importance of liver stiffness is that a liver with scarring stiffens, so the speed with which those waves move through the liver is proportional to the fibrosis or scarring of the liver, so increased liver stiffness can be detected by the elastography measurement. You can also do this with magnetic resonance elastography where you hold a frisbee-sized device over the liver, and it beats at 60 beats per second, and it develops a heat map of liver stiffness by measuring the speed with which those waves move through the liver as well. There's another type called shear wave elastography, much less common, at least up to this point. So it's mostly high-frequency ultrasound device or transient elastography or MR elastography, and the most common by far of those two is the vibration-controlled transient elastography.

Dr. Buch:
Thank you for that. And what should we know about SGLT inhibitors in nonalcoholic fatty liver disease?

Dr. Charlton:
Well, these have been really exciting therapeutic agents for the management of diabetes now and expanding a group of indications, and because of their mechanism inhibiting glucose absorption in the small intestine for SGLT1 and in the kidney for SGLT2, you're going to decrease the net energy absorption and retention in people, and this is important because the net retention of lipids or fat within the liver is proportional to the amount of energy that's delivered to the liver and glucose is an important part of that. They have other things that are appealing in that they decrease the risk of cardiovascular events as well, and by far the most common cause of death in patients with MASLD or MASH are cardiovascular events. The second most common is cancer, so there's an inherent appeal from several regards to these two types of medications. In addition, SGLT1 seems to increase the production of glucagon-like peptide receptor agonists endogenously as well, so between the weight loss, the decreased glucose excursions, and the decreased cardiovascular risk, these are very appealing drugs, but they're very nascent in terms of the clinical trial results that are available in MASLD and MASH.

Dr. Buch:
In the last few moments of our discussion, Dr. Charlton, what else should we know about liver disease and diabetes?

Dr. Charlton:
I think if there's one thing that anyone who's listening today would take away, I would love for it to be that when they think of somebody or they're seeing a patient with established or new diagnosis of type 2 diabetes mellitus, they think of, say, a bell, and you look at blood pressure, eyes, lipids, and you add that fourth thing, which is liver. Liver disease is highly prevalent in patients with type 2 diabetes, and it's much more likely to be a clinically significant issue in patients with type 2 diabetes. So add it to the list of things that are routinely evaluated for, and you're just starting with that simple FIB-4 in patients with type 2 diabetes. So think type 2 diabetes, think liver.

Dr. Buch:
Well, we've certainly covered a lot of ground today. I want to thank my guest, Dr. Michael Charlton, for joining me in this important discussion. Dr. Charlton, it was great speaking with you today.

Dr. Charlton:
Likewise. And again, thank you very much for having me.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can Be Part of the Knowledge. Thanks for listening.