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Recognizing & Addressing the Burden of Nonalcoholic Steatohepatitis

Announcer:
You're listening to *GI Insights* on ReachMD, and this episode is brought to you by Siemens Healthineers. Here's your host, Dr. Turck.

Dr. Turck:
Welcome to *GI Insights* on ReachMD. I'm Dr. Charles Turck and joining me to discuss how we can better recognize nonalcoholic steatohepatitis is Dr. Kenneth Cusi, who's the Chief of the Division of Endocrinology, Diabetes, and Metabolism in the Department of Medicine at the University of Florida. Dr. Cusi, welcome to the program.

Dr. Cusi:
Oh, thank you for having me today.

Dr. Turck:
So, let's just dive right in, Dr. Cusi. Would you tell us about the prevalence and burden of nonalcoholic steatohepatitis?

Dr. Cusi:
Sure. And this is a really hot topic as they say because it's affecting every healthcare provider out there. It is the most common chronic liver condition worldwide, very closely associated with increasing rates of obesity and type 2 diabetes, and we need to do something today because it's becoming the number one cause of liver transplantation beyond hepatitis C. And there's no end in sight. So, in general, the numbers vary because the only way to be completely sure is doing a liver biopsy, and we can't do a liver biopsy in millions of people. But people think that about between 14% or more of the population might have this. But more importantly for clinicians, there are very high-risk groups that they should be aware of that need to be screened in the clinic and need to be treated before they develop cirrhosis.

Dr. Turck:
So, you mentioned some high-risk groups of patients. What are those groups?

Dr. Cusi:
Well, there are three groups that have been identified. And in the last year and a half, we've had two major efforts. One was led by the American Gastroenterological Association with support from the American Diabetes Association, the Endocrine Society, the American Association of Clinical Endocrinologists, primary care groups, and others where we identified three groups: people with diabetes, people with obesity, and those with elevated liver enzymes or steatosis. Just a month ago, I also spearheaded another effort with the American Association of Clinical Endocrinologists where we fine-tuned these groups.

Again, those are prediabetes or diabetes, and when we talk about diabetes, we're talking about type 2 diabetes. Obesity, but not just obesity. You have to have obesity and metabolic syndrome. And number three, if you have steatosis, it means fat in the liver on any imaging or elevated liver enzymes. Now traditionally, elevated liver enzymes are those with a level of 40 and above in your alanine aminotransferase - ALT. But now, we know that above 30 is associated with increased mortality. So, for everybody, above 30 is a risk factor for fatty liver disease.

Dr. Turck:
I'd like to ask a little bit more about some of those groups you mentioned. Why are patients with type 2 diabetes at risk of nonalcoholic steatohepatitis?

Dr. Cusi:

Well, that's a great question. We think that this is the group with the highest risk. So again, the American Association of Clinical Endocrinologists, or AACE, and I think ADA next year and also the Liver Society, the American Association of Study of Liver Disease, are going to propose if you have diabetes, you should be screened for NASH. Why? That's your very important question. Because in most studies, they have shown to have the highest risk of fatty liver disease – about 70%. Studies by us and by others have shown that if you take ten people with type 2 diabetes, just going for their regular visit to their doctor, seven have fatty liver, and as many as one in five have advanced fibrosis. So, this is a very shocking number that we found, and in the same way that we screen with a urine test for kidney complications in diabetes, we are going to be screening with the FIB-4 all patients with type 2 diabetes to risk stratify for the chance of developing cirrhosis down the line. So, this is going to be a big change, but I think it's going to be very important to prevent cirrhosis in the group with the highest risk, as all studies show that people with type 2 diabetes have more NASH, more of that steatohepatitis theme summation, and more of this scarring of the liver – the fibrosis that leads to cirrhosis.

Dr. Turck:
And what about obesity? How are patients with obesity at higher risk of developing nonalcoholic steatohepatitis?

Dr. Cusi:
Another important question. Obesity promotes the development of fatty liver and of NASH by a number of mechanisms, but the most important to consider is that when we gain weight, that fat is very harmful because in the end, this is a sick fat that we accumulate in obesity and it releases fatty acids that break down that fat in the cell, that attack the liver, and are toxic. Same as alcohol. They are both very toxic. So, the best treatment that we have do one of two things. Number one: you lose weight, and this reduces the amount of fat that the liver is offered and improves the liver.

Or you change the biology of fat with medications like pioglitazone that converts your sick fat into a healthier fat. But obesity is the background that leads to NASH, and that's why any successful treatment needs to change that problem, or you reduce fat with some medications, like GLP-1 receptor agonists, most recently tirzepatide, or you change the biology of that fat with pioglitazone. Both are diabetes medication, and that's why coming back to the prior question, where most of our people are obese and have diabetes, you need to choose diabetes medications that also treat NASH.

Dr. Turck:
So, with those high-risk groups in mind, would you share some common diagnostic and prognostic challenges that clinicians face?

Dr. Cusi:
Yeah, so clinicians' number one homework is to think about the possibility of fatty liver. But we're not interested in diagnosing fatty liver. We're interested in using fatty liver as the tip of the iceberg to stratify them for fibrosis. So, there are two things to consider: the risk of cardiovascular disease, which is increased, and we can talk about that later, but more importantly, stratify for the risk of developing cirrhosis in these high-risk groups, particularly those with obesity and diabetes. The first test is called FIB-4. It's really a diagnostic panel. This diagnostic panel is composed of the age of the patient, plasma ALT and AST, and platelets. And platelets come into the picture because if you have portal hypertension or cirrhosis, dose will go down. Remember two numbers; if it's below 1.3, you probably won't have a high risk of advanced liver disease; and again, the other number is 2.67, which I remember by multiplying 1.3 times 2. If it's above 2.67, you have advanced fibrosis, and the test has very high specificity. So, it's not wrong very often, except if you have an advanced age, above age 70.

Now with that in mind, you can risk stratify to three groups. Low risk – below 1.3, high risk – above 2.67, and for example, people with obesity and diabetes, about a third are going to fall in the gray zone between these two values, called the indeterminate zone. So, what to do next? Well, transient elastography is a test that your hepatologist does on a daily basis in his clinic. That's an imaging study, done with a device called Fibroscan that helps quite a bit. But if it's not available, you can order it for the next visit. Your hepatologists have it. Or you can do a blood test, which the American Association of Clinical Endocrinologists wanted to be the ELF test, which is proven to be quite significantly valuable in many, many studies.

Dr. Turck:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Kenneth Cusi about nonalcoholic steatohepatitis.

Dr. Turck:
So, once we identify a high-risk patient, Dr. Cusi, what are the parameters for referring them to an appropriate specialist?

Dr. Cusi:
That's great. So, FIB-4, remember below 1.3, it's not 100% safe. We do have some people, but it's a minority of patients. Most people will be positive, meaning they have a number greater than 1.3. Then you have to do the second test. You do the imaging; if you don't

have the imaging, order it. If you cannot, you just order another blood test; it's called ELF, which has three components that kind of track fibrosis. The numbers to remember are for fibroscan is if it's above 8, you probably have moderate to advanced fibrosis; above 14, there's a risk of cirrhosis. Now don't tell them they have cirrhosis because that test is not perfect. Just tell them that you need more testing. For the ELF, to make it simple, say a number above 9.8 is very worrisome for advanced fibrosis. Now your liver doctor will have additional tests. For example, there is a magnetic resonant elastography test, which is the gold standard to diagnose fibrosis. There are other commercial tests, and there's always the indication that your hepatologist will do in terms of a liver biopsy. But the greatest mission for non-specialists is to get these high-risk patients to be seen by them and further stratified.

Dr. Turck:
And just to bring this all together before we close, what kind of impact might early detection and intervention have on long-term outcomes?

Dr. Cusi:
Oh, it's very important because currently most people are diagnosed very late when they have advanced cirrhosis or decompensated cirrhosis. Little can be done in those settings, but if you identify individuals with moderate or even advanced fibrosis, weight loss by any means works, whether lifestyle changes and exercise, weight loss medications like recently approved semaglutide, liraglutide, or tirzepatide, or bariatric surgery. And their diabetes medications – because many people with NASH and fibrosis have diabetes are very inexpensive and generic drugs like pioglitazone has shown in five trials to reduce stat hepatitis, and in some cases, fibrosis in the majority of patients. And there are many drugs in the pipeline. So, we have to develop the habit of doing this and remember: your patients with NASH also have increased cardiovascular disease, so don't stop the statins. They can be used quite safely. Work on lifestyle changes. Treat their diabetes with medications that treat type 2 diabetes and NASH, like pioglitazone or GLP-1 receptor agonists, and control other risk factors for cardiovascular disease. We are at the dawn of a new age here, and I think we have to be promoting the change that we want to see in the world.

Dr. Turck:
Well with those considerations in mind, I want to thank my guest, Dr. Kenneth Cusi, for joining me to share these top strategies for recognizing nonalcoholic steatohepatitis. Dr. Cusi, it was great having you on the program.

Dr. Cusi:
It's been my pleasure. Thank you.

Announcer:
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