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Exploring AACE Updates on the Management of NAFLD & NASH

Dr. Buse:
As clinical data continues to emerge, practice guidelines evolve to incorporate these findings. The American Association of Clinical Endocrinology has published 34 new evidence-based clinical practice recommendations for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. What do these new guidelines recommend?

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And with us today to share highlights from these new guidelines is Dr. Kenneth Cusi, who's Chief of the Division of Endocrinology, Diabetes & Metabolism in the Department of Medicine at the University of Florida.

Ken, welcome to the program.

Dr. Cusi:
Thank you, John, for having me.

Dr. Buse:
So, first, congratulations to you and the American Association of Clinical Endocrinologists for this wonderful and thoughtful summary of recommendations in the NASH and NAFLD space. Can you give us a brief overview of the overall recommendations?

Dr. Cusi:
Of course, John. Well, we felt that it was time that endocrinologists and primary care doctors had a set of diagnostic and management guidelines that would help them in navigating these complicated patients that overlap so much with obesity and diabetes, and to this end we identified high-risk groups, and we divided into two pathways, one related to specifically liver-related complications of NASH and the other to the comorbidities of these patients.

Dr. Buse:
So, based on the data that you present in the introduction on the prevalence of the problem in the population with diabetes, appropriately, there seems to be a large focus on screening recommendations. What are some of the top screening guidelines we should keep in mind in managing patients with diabetes?

Dr. Cusi:
Yeah. So, what we have found is that the old thinking that just looking into those with elevated liver enzymes was inadequate. Number one, a cutoff of 40 for ALT or AST is like saying, "Let's diagnose diabetes with an A1c of 7.5." There are a lot of people with fatty liver disease and with advanced fibrosis, uh, in that segment between 30 and 40, so that's where we cut off that down to 30. So, specifically thinking about those at risk, and again, we talk as NAFLD as an overall umbrella term in which some will just have fat associated within the hepatocytes which don't cause inflammation, but more importantly, we're worried about those who have inflammation and will advance to fibrosis. And there are three high-risk groups, that I would like to outline.

So, we have people with type 2 diabetes. So, when we talk about diabetes, we're going to focus on type 2 diabetes. We think in type 1 diabetes the evidence is still not there, but we do know that if they have obesity or metabolic syndrome, they may also be at risk, but people with diabetes, type 2 diabetes and prediabetes are at the highest risk of advanced fibrosis. Then it's anyone with obesity and associated comorbidities of obesity, and third, those with obviously fat in the liver on any imaging technique and ALT or AST above 30. And again, the confusion arises because what we're trying to identify is not fat but use it as a surrogate to identify those who are at high risk of cirrhosis—in other words, that have significant degrees of fibrosis at the time of screening.

Dr. Buse:
That was great. So the screening test that you are recommending is basically free. How is that possible?

Dr. Cusi:
Well, not completely free, but we derive it from typically tests that we do in the clinic. So the screening for fibrosis is called FIB-4, and it's called that way because it has 4 components: age, plasma aminotransferases and platelets, and the—this test was developed from the liver field for, uh, other liver diseases but applies very well to NASH. And again, we have this incorporated in our electronic medical record as a calculator, or we can just have a docket FIB-4 in our notes, and it is very practical to identify individuals who are on a path towards cirrhosis.

Dr. Buse:
And then you have a follow-up test in people who have a positive screen with the FIB-4?

Dr. Cusi:
Yeah. Yeah. So, what the studies show, the numbers we have from U.S. epidemiological studies, that is from our university and others around the world, is that if you take a hundred people with type 2 diabetes, 70 percent have fat in the liver, and about half of them have steatohepatitis that leads eventually to cirrhosis, so, one in five, between 15 to 20 percent of patients have advanced fibrosis. So the FIB-4 will be the first test to identify those at risk. The second test will be transient elastography. And there are fairly specific cutoffs that are well validated in the literature as having prognostic significance towards developing cirrhosis.

Dr. Buse:
Great. So now we've identified people at high risk for developing cirrhosis. Let's move on to treatment. How do the updated guidelines now approach the management of people at high risk for cirrhosis?

Dr. Cusi:
That's a great question, John, because the guidelines that we had until now were readily not very specific and were not very helpful for endocrinologists and primary care doctors seeing people day in and day out. Now, if your FIB-4 is below 1.3, we think that that person should just be managed for usual comorbidities, if they are obese or have type 2 diabetes. If it's above 1.3, then you do the second test, the elastography.

The important thing is that, as incorporated in this year's ADA guidelines, under the management of NASH and now expanded in the AACE guidelines is that we have drugs approved for the treatment of diabetes that can help patients with NASH. So, again, there are no FDA-approved medications, but these medications have shown in randomized controlled trials to be effective in 50 to 60 percent of patients that are treated with them. So, GLP-1 receptor agonists, last year some of you may have seen a paper in the New England by Newsome, et al. that we—I was also coauthor showed that semaglutide had the doses that would be equivalent to the weekly dose of the 2.4 mg, at the highest dose was able to reverse steatohepatitis in about 60 percent of the patients, lower doses somewhat less. It didn't reverse the fibrosis, but it did slow down the progression, so now it is undergoing a large phase III trial to achieve FDA approval.

The other drug is pioglitazone, which now a generic that costs probably less than $5 a month. And there are 5 studies—I participated as a PI in 3 of them—and it has been fairly consistent in studies up to three years to again reverse steatohepatitis and depending on the definition of resolution of NASH, 50 to 60 percent of patients. We believe today that lower doses are as effective as shown in some of the trials at 30 mg, and I have an NH-sponsored study testing the 15 mg dose. So, in the clinic what I do if the patient does not have heart failure or history of bladder cancer—although most studies have been negative with pioglitazone in that sense—I start 15 mg, and if they are doing well, I would eventually use 30 and rarely use more than 30 mg a day.

Dr. Buse:
Thank you. For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm speaking with Dr. Ken Cusi about the new American Association of Clinical Endocrinology guidelines on diagnosis and management of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.

So, Ken, you make a very important point in the paper about extrahepatic manifestations. What can you tell us about that?

Dr. Cusi:
Well, this is the other big thing. I mean diabetes and NASH are like I like to say like a couple who get the worst out of each other. So people who have diabetes and NASH, NASH tends to progress more, but NASH itself exacerbates apparently, many of the comorbidities of diabetes. So, if you are obese and have NAFLD, your chances of developing diabetes are double or triple. Moreover, if you have fatty liver disease, your chances of cardiovascular disease double or triple, depending on the meta-analysis, so we have to be much more aggressive in managing obesity, hypertension, atherogenic dyslipidemia and treating diabetes early on as aggressively as we can. And in the guidelines we have included specific recommendations to guide doctors in primary care or in endocrine clinics on

what is unique about the management of these patients.

Dr. Buse:
Very good. And I take it as a given that in general the treatments that you discussed before for the fatty liver disease, using GLP-1 receptor agonists, maybe semaglutide, or pioglitazone, that may improve the, the sort of extrahepatic manifestations as well?

Dr. Cusi:
Yeah. So this, this audience probably is very well tuned with the beneficial cardiovascular effects of GLP-1 receptor agonists, probably less with pioglitazone, which has not been studied as carefully as the randomized trials with SGLT2s and GLP-1s but has shown in some studies to improve that. I have to say that, again, lifestyle is the cornerstone of treatment: weight loss by any means, lifestyle changes that lead to weight loss, bariatric surgery, which is heavily underutilized and can be used safely until decompensated cirrhosis—not recommended if you have decompensated cirrhosis, but even in the early stages of cirrhosis, bariatric surgery in a tertiary center should be considered. And again, weight loss agents with GLP-1 receptor agonists are probably all tools that primary care doctors and endocrinologists should be using today. So weight loss is key in the successful management in much these people. And again, I think that what we need to target in this is the visceral fat either by reducing the mass of adipose tissue or changing the biology of fat. That is what pioglitazone does.

Dr. Buse:
Very good. So, as we come to the close of our program today, Ken, I want to give you the final word. Do you have any takeaways that you'd like to leave with our audience?

Dr. Cusi:
Well, No. 1, I think we need to give to nonalcoholic fatty liver disease and its risk of cirrhosis the same attention we do as for other diabetic complications, such as retinopathy and nephropathy. We need to be developing the mindset for screening, remember FIB-4 and eventually elastography, which is more commonly used with a device called FibroScan. And finally, lifestyle changes and use of medications approved for diabetes are going to be key in preventing cirrhosis in a lot of our patients. And stay tuned. There are a number of new drugs in development, but they are still about two or three years away from coming to the clinic, but it's a very active field.
So it is now that I think doctors have to take this into account and incorporate NASH in the daily care of your patients.

Dr. Buse:
Well, thank you so much. And with those final thoughts in mind, I want to thank my guest, Dr. Ken Cusi, for sharing insights on the American Association of Clinical Endocrinology guidelines on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Ken, it was a pleasure speaking with you today.

Dr. Cusi:
Thank you, John.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit ReachMD.com/DiabetesDiscourse, where you can be Part of the Knowledge. Thanks for listening.