Transcript Details

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Stemming the Tide on MASLD/MASH: It Starts on the Frontlines in Endocrinology and Primary Care Clinics

Announcer:
Welcome to CME on ReachMD. This activity, titled, "Stemming the Tide on MASLD/MASH: It Starts on the Frontlines in Endocrinology and Primary Care Clinics," is provided by Medtelligence and supported by Boehringer Ingelheim Pharmaceuticals, Inc.,and Novo Nordisk, Inc.

This replay of a live broadcast discusses cardiometabolic risk factors and how to improve your care of patients with MASLD/MASH.

Dr. Bansal:
Thank you for joining us for this live broadcast on Global Fatty Liver Day. I'm your Chair, Dr. Meena Bansal. I'm the Chief of the Division of Liver Diseases at Mount Sinai, and I'm joined by my esteemed friends and colleagues.

Dr. Pennings:
Hi, I'm Dr. Nick Pennings. I am a Family Physician and Obesity Medicine Specialist. I also serve as Chair and Professor of Family Medicine at the Campbell University School of Osteopathic Medicine.

Jennifer:
I'm Jennifer Berg, and I'm a patient living with MASH.

Dr. Bril:
Hi, I'm Fernando Bril. I'm an Assistant Professor in the Division of Endocrinology, Diabetes and Metabolism at the University of Alabama in Birmingham and Associate Scientist of the UAB Comprehensive Diabetes Center.

Dr. Bansal:
These are our disclosures, and these are our learning objectives.

And now, Nick's going to kick us off on why we are here on Global Fatty Liver Day.

Dr. Pennings:
Thank you, Meena.

So if you're a clinician seeing patients in the clinical setting, you're likely seeing a lot of patients with MASLD and MASH. The challenge is that we have a hard time identifying it. It's not easy to see. But just because you don't see it doesn't mean it's not there. MASLD and MASH is common. Looking at data from NHANES 2017 to 2020 and in honor of Global Fatty Liver Day, we're looking at the [prevalence] of steatotic liver disease, and we see it's very high, 37.8%, with the vast majority of those having MASLD—32.45% of patients have MASLD. So we're seeing it's very common.

And who is at risk? Well, it affects all ages. It affects both genders. It affects all races, but Hispanic males over 40 are a particular risk for having MASLD and MASH.

So why is it important? Well, it impacts life expectancy. Life expectancy is shorter for patients with MASLD. Cardiovascular disease risk

is higher in patients with MASLD, and, in fact, cardiovascular disease is the number one cause of death in patients with MASLD. So we're very concerned about the impact on metabolic health and on the health of our patients, particularly those who are diagnosed earlier. The earlier you're identified with MASLD, the more likely it is to progress to fibrosis and other complications of fatty liver disease. And the challenge as clinicians is, the symptoms are vague. They rarely have any symptoms, and maybe they have symptoms of fatigue, which is really very nonspecific, or some right-upper quadrant pain.

So with us today is a patient who's living with MASLD and MASH. Jen is a 53-year-old female living in San Antonio, Texas, and you struggled much of your life with your weight, haven't you?

Jennifer:
All my life. I came from a family of three older sisters and three older brothers, and I kind of lovingly refer to them as my ghosts of Christmas future. So I really tried to see what was happening to them and like, pull back in my lifestyle. But there were some things that weren't made quite clear how serious they were. I was told in 1995 that I had fatty liver disease, but that didn't really mean anything. The doctor was like, oh, everybody has it, don't worry about it. And then fast forward to 2009, my oldest sister started having complications and dying from fatty liver disease.

Dr. Pennings:
And it wasn't just fatty liver disease. Also, diabetes.

Jennifer:
Diabetes, high blood pressure, high cholesterol, and just the whole metabolic—

Dr. Pennings:
Right. But the fatty liver wasn't really given any attention?

Jennifer:
Correct. Yeah.

Dr. Pennings:
Okay. And then you had a pretty life-changing event. You had bariatric surgery.

Jennifer:
I did because of my sister in 2009. My youngest older sister and I decided to have weight loss surgery in 2011, and so we both did. My sister then went on to pass away at the end of 2011, and my liver didn't really—my numbers didn't get any better. But I still didn't have a true diagnosis. And then my youngest older sister that had surgery actually ended up progressing to cirrhosis between 2011 and 2019. So her weight loss didn't really—

Dr. Pennings:
And So you had lost a lot of weight with bariatric surgery, right?

Jennifer:
Yeah. A little over 100 pounds, like 101.

Dr. Pennings:
But you didn't see a significant improvement with the liver, which is kind of unusual because weight loss usually has a pretty profound effect upon that. Then you started gaining weight again subsequent to that. Is that correct?

Jennifer:
Yeah, about 2019. I stayed at almost within 5 pounds from 2011 to 2019, and then, at the end of 2019, for some reason I just, I couldn't lose weight. I could gain it incrementally and I could maintain, but I just kept gaining it. And all the way up to 60 extra pounds.

Dr. Pennings:
And then you started medication—anti-obesity medication. Is that correct?

Jennifer:
Correct. Last year, I started anti-obesity medication.

Dr. Pennings:
And when we talked before, you described how the after the bariatric surgery, you kind of get this feeling of fullness, and that kind of gradually faded over time, and when you went on the medication treatment for obesity that came back, that was restored. Is that right?

Jennifer:

Yes, that was one of my first observations was that, it's like it was like a chemical weight loss surgery. I felt like I did when I first had my weight loss surgery when it was like, don't eat that last bite. You're good. Stop. So—

Dr. Pennings:
And then that helps you bring your weight down and also, at the same time, you started treatment for fatty liver disease.

Jennifer: Correct. Yeah. Yeah, a few months later, I started treatment for fatty liver disease.

Dr. Pennings:
It's a very interesting story, and it speaks to the challenge that patients have when they lose weight with bariatric surgery, still a chance of gaining their weight back again, and the role of anti-obesity medications and treating that.

So in the pathophysiology of obesity in MASLD and MASH, dietary intervention is really a key component. And while there's many different factors that contribute to fatty liver disease, the diet plays an important role. And in a standard American diet, we see a higher carbohydrate intake. Those carbohydrates are converted into glucose, and normally, that glucose should be taken up by the muscles, typically about 70% or more. But when we have insulin resistance, the glucose is not taken up by the muscle, and it goes back to the liver where it undergoes de novo lipogenesis. We also, with a high sugar intake, often have a high intake of fructose. And fructose should be able to be converted to glucose in smaller portions, but with larger exposures, that stays in the liver, gets converted into fat. And then we have a high-fat component to the diet as well. And again, the fat should be absorbed by the subcutaneous adipose tissue where it can be a healthy reservoir for fat, but when we are consuming excess amounts of fat, or our fat consumption is too high, or we overload our adipose cells, they become dysfunctional, and they become insulin resistant. And the insulin-resistant fat tissues, whether it be visceral fat or excess subcutaneous fat, then are releasing free fatty acids into the circulation, which is going to contribute more to fatty liver disease, as well as insulin resistance.

But one of the other challenges that we have when treating both obesity and fatty liver disease is the inherent bias that we see toward patients with obesity. And while the dietary component is very important, if we just think of it as just being calories in and calories out, that's really a gross oversimplification. Really what we should be asking is, why are calories in greater than calories out? And, typically, if we don't have an education in obesity, we will tend to blame the patient. They're lazy, unmotivated, not compliant. They're weak-willed. That really doesn't appreciate the physiology that is behind obesity. That, as we calorie restrict, and I think we all feel that, when we skip meals, when we don't eat, we feel hungry. And so when patients are calorie-restricting, when they're creating a negative energy balance, the normal physiologic response of the body is to increase hunger signals, decrease satiety signals, and increase hunger. And that's not a good feeling. We use a term for that sometimes. We call it "hangry."

We combine that with metabolic adaptation, which also slows our basal metabolic rate down as we lose weight. So that makes it harder to maintain that weight loss. And so we have these physiologic drivers that promote consumption. We have this metabolic adaptation. And then, living in an obesogenic environment, where it is easy to consume excess calories, poses great challenges. But our same society that promotes food as a way of fellowship and connection also judges individuals for having obesity, feeling that they lack self-discipline or that they're just not trying hard enough. Even health professionals have negative attitudes towards patients with obesity, blaming the patients for their weight or not trying hard enough.

Our staff can sometimes make negative comments, so we have an office environment that makes the patient feel stigmatized. So these are all things we need to be cognizant of when treating patients with obesity.

I wanted to ask you. As a patient living with obesity for much of your life, what were your experiences with stigma and bias in the health profession? Is that something that you did experience?

Jennifer:
Oh, for sure. Being overweight and going to the doctor for just about anything. That was the first go-to. It's your weight. It's your weight. It's your weight. And so that's another reason why I decided to go for the weight-loss surgery because it's like, well, if everything is my weight, let's really hit the big guns to get this under control.

The most clear-cut story I have about that is I went—I was having trouble with, I thought, my shoulder, and so I got an MRI. I went to a doctor—a orthopedic doctor, and he said "It's your weight. I can't see anything structurally wrong with your shoulder. It's your weight. Take ibuprofen. Call me in 6 weeks to tell me how great you feel, and hopefully you'll walk and lose some weight by then."

And I was—

Dr. Pennings:
It wasn't your weight.

Jennifer:
I was flabbergasted. And so I had gone back to my doctor. She sent me to a different orthopedic doctor, and that doctor looked at my shoulder and was like, "Oh," he's like, "I don't think it's your shoulder. I think you have something in your neck." So they did an MRI on my neck, and I had three bulging discs in my neck that had to be treated, and I was then, fine. But the other doctor was just like, "Oh no, it's your weight. You just take ibuprofen, you'll be fine."

Dr. Pennings:
And that is a challenge that I think that many healthcare professionals—there's a tendency to just blame the patient and not really look and see what is causing their symptoms, just quickly blame it on their weight. And that really is a reflection of a lack of training that students have in health professional educational fields. The residents are not getting trained in obesity medicine. So this, I think, is very important to understand: that obesity is a complex disease and that that complex disease has multiple medical complications associated with it. But also, it is a disease that's a chronic condition that really needs long-term treatment.

And that one of the challenges that we have is having enough time to treat patients with obesity because we're treating the diabetes, we're treating the liver disease, we're treating the osteoarthritis. But the truth is, when we treat obesity, we treat all of those conditions. So, really, it is important to be able to treat those. Because of the lack of training and understanding, both patients and providers may not really consider the importance of treating obesity.

But one of the key things for treating obesity is the treatment of MASLD and MASH because MASLD and MASH are progressive diseases. It starts with fat deposition in the liver. It progresses to inflammation in the liver, and that inflammation then could lead to fibrosis at various stages and even to cirrhosis. And this progresses generally, about every 7 to 10 years. But it's going to vary by individual. So I think it's important to be able to evaluate patients for that, be mindful of that, and be able to treat that.

So it really is important for both endocrinologists and PCPs to treat MASLD and MASH. And why is it important? Well, one is because type 2 diabetes is strongly associated with MASLD and MASH. It's very common in patients with type 2 diabetes, and endocrinologists and PCPs are treating type 2 diabetes. So we need to be looking for it. We need to be thinking about it. And being able to treat those common origins, both the dietary interventions and the treatment of insulin resistance.

Which then leads us to our next speaker, who is an endocrinologist. Tell us about your experience with treating MASLD and MASH in patients with diabetes.

Dr. Bril:
Yeah. Thank you, Nick. So yeah, in the next section, we are going to talk about what can PCPs and endocrinologists do about it.

So as you can see in this graph, and the point I want to make here is, we need to think of MASLD as a systemic condition. You can see how, as we go from increased adiposity, patients are overweight and obese, as they progress to the classical cardiometabolic risk factors such as type 2 diabetes, hypertension, dyslipidemia. So it takes time to develop those classic cardiometabolic risk factors, but MASLD is already there. It's an early marker that something is wrong from a metabolic standpoint and that these patients are metabolically sick.

And you can see, and Nick alluded to this, how closely linked is MASLD to this dysfunctional adipose tissue. So as we store up those abnormal amounts of fat in those adipocytes, they become inflamed, they become insulin resistant, and they release excess free fatty acids into circulation.

So the liver has an enormous capacity for accumulating those free fatty acids in the form of triglycerides, and we have MASLD. But we need to think that those free fatty acids are going everywhere. They're being stored in the skeletal muscle, in the heart, in the kidney, in the pancreas. This is a systemic lipotoxic condition.

And as I'm also showing in this graph, there is a bidirectional relationship between MASLD and these classic cardiometabolic risk factors. Not only having MASLD puts you at risk of developing type 2 diabetes, dyslipidemia, hypertension, but also, if you have more cardiometabolic risk factors, you are at higher risk of progressing to liver disease. So this is important. This is highly prevalent, as Nick said, and this is a systemic condition that needs to be addressed comprehensively.

So if we look at who needs to be screened for liver disease, most guidelines out there usually suggest the same populations. Even if we look at clinical endocrinologists, hepatology or American Diabetes Association guidelines, usually are the same profiles of individuals we are looking at that are at increased risk of liver disease.

If we take the clinical endocrinologist guideline, we see prediabetes or type 2 diabetes, the presence of obesity, the presence of other cardiometabolic risk factors. Or if we already know that the patient has steatosis because somebody did a CT or an ultrasound for

another reason, and we learned that that patient has steatosis. Or if just in routine labs, we found elevated liver enzymes, those are signals that those patients may be at increased risk of liver disease, and we need to start looking for those patients.

So in the last week, for example, if you've seen, let's say, 11 patients with type 2 diabetes. Statistically speaking, one probably already has clinically significant fibrosis. So if you haven't identified one of those, you're already missing it.

And, as I said, they are aligned pretty well through the different societies. They call it in different ways, but it's kind of the same patients. Although, the hepatology guidelines also recognize that if you are drinking more than what we usually say is mild alcohol consumption, and that means 20 grams daily for females or 30 grams daily for males, then you are at increased risk of liver disease, and we should be screening. And then, if you already have family history of MASH, cirrhosis, that's another red flag that you are at increased risk and we need to screen. Same with the ADA guidelines.

So what we need to be doing when we are in front of patients is incorporating into our ABC, which is basically looking at A1C, blood pressure, and cholesterol. Start adding—and we did this decades ago—where we started adding diabetes complications, and we do a pretty good job at screening for nephropathy, neuropathy, retinopathy, including the EGFR. But now, we need to start thinking of the next step, which is fibrosis DF, or liver fibrosis.

So I said this steatotic liver disease is very common, to the point that if you are in front of a patient with diabetes, you kind of assume they are—or you know already they are metabolically unhealthy and they have higher chances of having fat. So we are not looking for that fat or that steatosis, we are focusing on seeing if there is a liver damage, fibrosis, that we can identify early on.

And how are we going to do that in the primary care clinic or in the endocrinology clinic? Well, what we need to do is try to first exclude whether patients have clinically significant fibrosis—F2 or higher. And the first tool that we have that is relatively easy to apply, you have the formula there. There are different apps online or on the internet where you can just automatically calculate. Some labs already provide it automatically if you have ALT, AST, platelets, and the age of the patient. It's called FIB-4 index.

And the number to remember is 1.3. If you are below 1.3. And there's another number to remember, which is 2 if you are over the age of 65 because age is in the formula. We know that if age is above 65 years old, then the number to remember of the cutoff point is 2. But let's go with 1.3. If the patient is below 1.3, then this is not perfect, but the chances of having clinically significant fibrosis are quite low, so we can just repeat this on a yearly basis, although there's no clear data as to suggest whether we need to do it on a yearly basis versus every 2 years. Or even 3, based on some guidelines.

Now, if you're on the other extreme and you are above 1.3, or remember, 2, if you are older or if your patient is older than 65, then we need to start thinking of a second test. And again, as I said, FIB-4 is not perfect. We are going to miss some patients, and we are going to over-diagnose some others. But it's a first screening tool to kind of divide the waters. And even if we miss a patient, we are repeating it every year, so we may catch them later if we continue to use it.

Now, if we already have an abnormal number, it's time to move to the second-tier test. Either a vibration-controlled transient elastography or an enhanced liver fibrosis, which is a serum biomarker. It's a blood test. Three inflammatory biomarkers are measured, and you get a number if you order that in the lab.

If you don't have access to vibration-controlled transient elastography, the common brand name is FibroScan, you can use any other ultrasound elastography to the shear wave or what you have accessible.

These are the cutoff points to remember if you go for VCTE, and it's less than 8, or ELF less than 9.8—although, these cutoff points are changing, and you may start seeing 9.2 for the ELF—then you can rest assured that the chances of clinically significant fibrosis are low. You can repeat those tests yearly or every 2 years.

Now, if again, you have these diagnostic tools that come up normal, it's time to start thinking something is happening in the liver. You already know about the metabolic health and we are going to talk about that. But now, there is damage in the liver. We need to start thinking about what's happening in the liver. And let's remember that, while only a minority of patients with all these cardiometabolic risk factors will eventually develop cirrhosis (because most of them will die before from cardiovascular disease), it's still a significant percentage of patients that develop cirrhosis, and we want to identify them early on to use effective therapies and change the natural history of this disease.

Now, if you have a patient with these two abnormalities, you follow the pathway, it's time to refer to hepatology, where they can do other sequential testing like a magnetic resonance elastography. They will consider biopsy and in many times, we also need to think well, are we ruling out other liver conditions? And sometimes, as PCPs or endocrinologists, we don't have the expertise, and a hepatologist needs to examine these patients to see, well, are we missing something? Are we missing autoimmune conditions, drugs that could be associated with these abnormal tests?

And questions that we will discuss as we move forward is, well, I said FIB-4 is not perfect, so we will discuss, well, should we skip it in patients that we know are high risk, and do we want to go directly to VCTE or ELF? And then, can we consider MRE early on if we have availability of it? And I already alluded to this, cutoff points are changing, so you need to stay tuned for how the field is moving.

And I always get asked, is there any role to ALT and AST, as we have now FIB-4, which is indicated by most guidelines. And I still use ALT and AST, so even if you don't have platelets and you can't calculate it, I would suggest you order those platelets to calculate. But AST and ALT are still useful. And the way I use them is the following. So if ALT is higher than AST, that's usually more indicative of fat accumulation. There can be inflammation and ballooning, the MASH component, but usually, it doesn't allude to fibrosis development.

And this is especially interesting or useful if you have long-term data of patients, and you see—because this fluctuates all the time—so if you have a pinpoint ALT/AST, they may be normal, but then you recheck it after 6 months, they may be abnormal. So if I see a patient that from time to time, had elevated ALT, higher than AST, that repeats after a month or so forth, and then I see if I can see years of that, I see that that starts to change, where AST now becomes higher than ALT, that can either mean they started drinking alcohol—remember, that alcohol increases more AST than ALT—or they are developing fibrosis.

So they're still useful, but patients can have this disease and can have advanced disease even with normal liver enzymes. So first we need to start thinking of lower cutoff points. Usually, when we order them, the normal range goes up to 40 or 50. We need to start thinking of lower cutoff points if we want to use liver enzymes as a red flag of something happening in the liver.

And then, how do we approach in the clinic, these patients? Well, I already alluded this is a systemic disease, and it needs a comprehensive and holistic approach where we focus on lifestyle intervention, quitting alcohol, and a Mediterranean or other type of diet that we will decide on an individual basis. We need to focus on weight loss, and we need to consider medications for that because success rate with lifestyle may not be as good as what we intend or what the patient needs. We need to consider bariatric surgery, and then we need to treat all other cardiometabolic risk factors, diabetes, dyslipidemia. And at that point, remember, studies are safe even if your liver enzymes are abnormal.

With that, I want to move to Jen. So how was, for you, this diagnosis of fatty liver? How did you get there? Were you explained of the process, were you understanding what was happening?

Jennifer:
Not at all, until much later. Again, 1995, my doctor said, Oh yeah, fatty liver. But everybody has it, don't worry about it. Then my sister got diagnosed. I continued to just follow with a GI doctor, just checking my AST and ALT. It didn't occur to me that I needed to do more, and oddly enough, my rheumatologist actually sent me to talk to Pinnacle Clinical Research because he knew how serious I took my liver, and with my sisters having issues. So he's the one that actually kind of, like, spurred my journey to actually get a diagnosis. So I didn't get the actual diagnosis till 2021. And really, no doctor that I've gone to has talked about, like, the whole picture of it. I've kind of taken that on myself, coming to things like this and to different meetings and things, learning about the different components of it, because I really didn't know all of the ins and outs of the disease.

Dr. Bril:
Yeah. And while we like that patients advocate for themselves, we also need providers to be advocating for this increased cardiometabolic risk. And do you think the approach that providers had with you, was it holistically? Did they discuss diabetes management, dyslipidemia, hypertension? How do you see it?

Jennifer:
Yeah. I was going to say, each specific doctor that I went to, discussed their piece of it. I don't think I was ever told by any doctor, even up to this point. I guess my liver doctor now, who is a hepatologist, he talks about, like, the whole picture. But up until I went to him a couple of years ago and started seeing him, no doctor had ever said, oh, your diabetes can cause issues with your liver. Your liver can cause issues with other things. It had never been put together as a whole puzzle. I just had all these little pieces that were hanging out there.

Dr. Bril:
Well, talking about hepatology. Meena, can you drive us on what to do?

Dr. Bansal:
Yeah, absolutely. Absolutely. So, Jen, it's great, because I think it was Dr. Stephen Harrison, right, that you met at Pinnacle?

Jennifer:
Correct.

Dr. Bansal:
And who we greatly miss, actually today, who's done a tremendous amount for the field. Did you ever calculate your FIB-4? Out of curiosity?

Jennifer:
So just on my own, and I don't remember the actual number. I was doing all the calculations on my own after I went to—because he was my introduction to advocacy. They called me to go to his Program Mosaic. And so then, I was sitting in Mosaic in 2022, calculating all of my numbers that I could get out of my blood work and things like that. So I don't remember the exact numbers at that point, but I did do it myself.

Dr. Bansal:
But I think it's important for patients to know their FIB-4, right? So you can advocate for yourself, empower yourself. If you're out there listening, you have your numbers. There's an app that's available on your phone. Just calculate it, and that way you can bring that to your physician and say, hey, I'm a little bit concerned. My FIB-4 is 2.8, and we need to do something about it. So it definitely is great to have patients engaged.

So as everybody's mentioned, fibrosis, fibrosis, fibrosis. That is the most important determinant of liver-related outcomes and associated with even some of the cardiovascular outcomes, as was mentioned. So by the time you have stage 2 fibrosis, you have a 10-fold increased risk of liver-related mortality that increases to 17-fold at F3, and 40-fold as you approach cirrhosis. So where you are in this fibrosis continuum really can drive the therapies that you want to focus on.

So when you're earlier on, and you have steatosis, maybe a minimal fibrosis, that's when we're focusing on either pharmacologic weight loss or surgical weight loss, or sometimes you need both. And that changes over time. It's very dynamic. But as you march along, and you have increasing levels of liver fibrosis, you then need to have a liver-directed or liver-targeted therapy.

But even as a hepatologist, it is our job to talk about this with our patients, as your doctor did. So we still need to tackle overweight and obese status through weight loss, exercise. And I tell patients that, don't get stuck on the scale because exercise alone helps cardiometabolic health independent of weight loss with increasing step count, decreasing cardiovascular and overall mortality. We also focus on diet. Nick mentioned fructose, and I think you were saying the Dr. Pepper, right? Like it was something that you used a lot. And we see that a lot. People love their soda. They don't realize right that that fructose is causing some of that steatosis. We also recommend if you have any degree of fibrosis, you should not be drinking alcohol. With no fibrosis, that's kind of up for debate. No smoking. Coffee; we recommend 2 to 3 cups of black coffee a day which is protective for the liver, and a Mediterranean diet.

And, again, we also, as hepatologists, need to treat comorbidities. So I'm actually also boarded in obesity medicine, so I'm very comfortable in managing patients living with overweight or obesity by starting them on GLP-1s or the duals that are available now for those indications. Of course, getting the diabetes under control with those agents. And Fernando mentioned this a little bit, dyslipidemia is quite common. As a hepatologist, what I will see is patients have abnormal liver enzymes, so there's a hesitancy to start a statin.

I would say, don't fear the statin. Even if the patient has liver enzyme 70, 80, start the statin. You will see a blip, but expect it, but then it will come down and, ultimately, your liver enzymes may be lower than what they were when you initially started. So definitely do not fear the statin. Management of hypertension and sleep apnea.

So we now have the first FDA-approved therapy that had an early approval on March 14th, 2024. And this study is still ongoing. So they met their primary endpoint, which was a 52-week biopsy endpoint, and they demonstrated statistically significant MASH resolution, as well as improvement in fibrosis by one stage. As I said, this study is ongoing because we need to now see that that translates into improved clinical outcomes. Because if the fibrosis goes away but you still have esophageal variceal bleed, we haven't really achieved anything. So it's going to come down to clinical outcomes.

It's important to note that resmetirom, which I didn't mention earlier, is a thyroid hormone receptor beta agonist and it actually also decreases LDL. So when we talk about the wholistic approach, you don't want to start a medication that then may worsen some of the other things that we're concerned about in this patient population. So looking for those positive lipid effects is also reassuring.

In patients who had some elevated liver enzymes at baseline. This was a paper published in *The New England Journal of Medicine*, you see that patients have a reduction ALT, AST, and GGT. Sex hormone binding globulin is simply a neutral protein that reflects target engagement, so you know that your drug is getting to the liver and turning on those pathways that it's supposed to.

Now, we've talked about incretins. The class of incretins, which has really revolutionized how we manage many of these complications. But we know that there's pleiotropic effects of the incretins. They have cardioprotective effects, renal protective effects. They have an effect on weight loss, both by central-acting mechanisms, as well as peripherally acting mechanisms. GLP-1 receptors are probably not

expressed in the liver, so any effect that we see on the liver is likely due to kind of the global metabolic improvement. And so there's some research kind of happening in this, but right now that is kind of what is thought.

The biggest news this year at the liver meeting was the report out of the phase 3 ESSENCE trial. So this was the use of semaglutide over a 72-week period. Fifty-six percent of patients had type 2 diabetes, 43% were living with obesity, and they hit their dual endpoints of both MASH resolution without worsening of fibrosis, as well as a reduction in one stage of fibrosis, which, again, is the most important thing, and really great news.

In addition, Fernando mentioned some other assessments of liver fibrosis because, in reality, I don't do a liver biopsy to stage a patient. Right? I do a liver biopsy if I'm trying to rule out autoimmune hepatitis. I'm like, kind of scratching my head. I'm not sure this is what this is in disease. And so that's the only time really, as a hepatologist in this day and age, or if you're in a clinical trial. Otherwise, there's no role for liver biopsy.

So in this study, what they saw correlating with improvements, they also saw improvement in the Enhanced Liver Fibrosis Score that Fernando mentioned. And the key kind of delta there is kind of meeting a 0.5 reduction, which they did, as well as improvement in VCTE, or liver stiffness. So when everything is moving in the right direction, liver enzymes are getting better, VCTE is improving, ELF score is getting better, you're really feeling very confident that you're kind of moving the needle here.

Now, there's a number of double G's and triple G's. So we have the dual GIP/GLP-1 receptor agonist. And this was the phase 2 study for tirzepatide, where they showed MASH resolution without worsening of fibrosis. They saw a trend towards improved fibrosis small numbers. So we await potential phase 3 data.

Now, servodutide is quite interesting because it's a GLP-1 receptor agonist, but also a glucagon receptor agonist. And importantly, glucagon receptors are expressed on hepatocytes. So this molecule may have both a metabolic effect through weight loss but also a liver-directed or -targeted effect because that improvement in hepatocyte metabolism. So we look forward to the phase 3 studies.

So there are a number of double G's and triple G's. These are the big guns coming in, here. We mentioned servodutide and tirzepatide, but there are a number that are coming down the pike, so it's a very exciting time for incretin targets and therapies. So now, moving on to lanifibranor, which is a pan-PPAR. So this is an alpha, a delta, and a gamma. The alpha attacks the steatotic hepatocyte, the delta hits infiltrating macrophages, and the gamma has a direct stellate cell or antifibrotic effect.

So in this 24-week study, lanifibranor, at the highest dose of 1,200 milligrams, hit MASH resolution as well as fibrosis improvement, so we look forward to phase 3 data. Also, again, everything moving in the right direction. Reduction in liver enzymes, improvement in glycemic indices, improvement in some of the lipid parameters, the non-invasive assessment. Keep in mind that this does cause a little weight gain, and that's really the gamma effect, like you also see with higher doses of pioglitazone. So just keep that in mind, and so maybe some combo therapies could be helpful to offset that weight gain.

I should mention that that weight gain is really more of a redistribution. You do lose the fat in the liver, but it kind of goes more peripherally.

Now, we have the FGF21 molecules, which are really fascinating. FGF21 is a pleiotropic hormone, endogenous hormone, that has very positive glycemic and lipid effects. The problem is, is that half-life is 2 hours, and so there's been a number of kind of modulations to lengthen the half-life. So this is efruxifermin, which is a long-acting FGF21 analog, and after 96-weeks, they saw very significant improvement in fibrosis reduction, as well as MASH resolution.

Pegozafermin, again, here, now another modulation. This is a long-acting fusion protein. Same concept. Improvement in fibrosis as well as MASH resolution. So all of these are hitting, they're in their phase 3 stages.

So the take-home points here is that we do have our first FDA-approved therapy for MASH, resmetirom. Phase 3 ESSENCE data is extremely promising, and we anticipate FDA approval. If I had my crystal ball, I would anticipate approval this year. And so we have, we're going to have, a full armamentarium.

Weight loss improves MASH and fibrosis in most people. Clearly, not everybody. Whether you achieve that through bariatric surgery or through pharmacologic approaches, diet changes. We have a rich pipeline of emerging therapies, and the most important point thing is to personalize the approach. Each patient has different comorbidities. You have to prioritize what you're trying to attack. What kind of stone can kill multiple birds, if you will.

Exercise can improve MASH independent of weight loss, and so, as I mentioned, we want to think about improvement in cardiovascular disease, which is the number one cause of death in these patients, kidney disease, alcohol use disorder—we didn't go into at all—but some of these incretins may also have effects there, as well as obstructive sleep apnea.

So I think we are going to open this up for some Q&A, and we'll take questions from the audience. While we're waiting for that, I'll ask if at your institutions, do you have, kind of, care pathways in primary care and endocrine to be screening with kind of either auto-calculating FIB-4 or FIB-4 calculations, and then doing all of this risk stratification? I'll start with you, Nick.

Dr. Pennings:
So I'm still doing them manually. I plug them into an app to be able to calculate that. And I think that's probably where many primary care providers are. That it would be nice if it was auto-generated when we ordered the sets of labs, that it would be able to be calculated for us. But I currently do that manually.

Dr. Bansal:
Yeah. How about you, Fernando?

Dr. Bril:
Yeah, we started with first flagging patients that had an increased FIB-4, so it would alert physicians. We targeted endocrinology and PCP clinics. If you had a patient with pre-diabetes or diabetes or obesity, and the FIB-4 was high, they would get an alert.

We are still analyzing the data, but I would say that didn't seem to help a whole lot on referral. Just I think we get a little bit of fatigue with all these alerts and red warnings. So we are working into implementing this automatic FIB-4 calculation. Just to avoid, but I will tell you it only takes 30 seconds to calculate it with any of those apps out there. I think AGA, the American Gastroenterological Association, also has an app where you can calculate the FIB-4. So different apps, it only takes 30 seconds, but we need to do it to screen these patients and to know and learn about how our patients are doing liver-wise.

Dr. Pennings:
I have a patient who had a liver ultrasound that showed increased fat in the liver. So I went back. I hadn't calculated her FIB-4 before, and I went back, and I looked at her LFTs and they weren't elevated. And actually, her AST was a little bit higher than her ALT, so I'm thinking, well, this is not going to come out positive. But when I put in the calculation, she actually had an elevated number that warranted doing further testing. And we did a VCTE test on her. But it speaks to the need to check it on everyone, right? And that would make it nice if it was automatically generated. But in particular, this was the case that I didn't expect it.

Dr. Bansal:
Well, I think you just described the FIB-4 sniff test. So when you see that reversal, as Fernando also pointed out, then things that make you go hmm. You're like, okay, maybe there's something going on here.

And even when the liver enzymes are normal. So you mentioned 30 and 19 or 20. So the key is, is that even it was red for you, right? You were like, why is my number red? But it doesn't have to be red to be abnormal. So even if it's 35, 40, and then you have that reversal, that's likely going to be a positive FIB-4.

Dr. Pennings:
And I think that's an interesting point because generally, we're taught that if ALT is elevated, you need to be thinking about fatty liver disease, right? But if it's not and AST is higher, you should be thinking about alcohol. But really, what you're talking about is that you also have to be suspicious for fibrosis when AST is higher than ALT.

Dr. Bansal:
Yeah. And we should always ask about alcohol use. In a non-stigmatizing way, we do AUDIT-C, and now PEth testing has become very popular, to have a much more quantitative assessment of liver/alcohol use.

So we have some questions from the group. So what changes could you make? Oh, so this is—So, Jen, if you could. So the question is about, what can we do as physicians to be less stigmatizing when we are addressing these comorbidities? So if you had to give advice to the doctors that are out there, what would you tell them?

Jennifer:
Yeah. I think the one thing for me was just the physical thing that can happen is that whenever I went into a doctor's office, they only had the regular cuff always, and my arms are pretty big. So I would kind of joke with the technician, you know you need to bring the chubby cuff. Like let's do that. And it always felt like, not great to have to. They'll force to put on the small one and you can hear it. Like, the Velcro ripping off as it pumps up. Always embarrassing.

And then, the other thing I would say is just like, as far as like from the doctor perspective, eat less, move more. Like, I could buy a house probably with the number of times I was told eat less, move more, but never given specific instructions or ways to do that. Everything was kind of all on my own, so.

Dr. Bansal:
Right, right, right.

Jennifer:
Except for my weight loss surgeon. He was very clear. Do not eat bread, do not eat sugar ever again and you'll be fine. Which was almost the case.

Dr. Bansal:
Alright. We have some questions about how to order VCTE and ELF testing. So VCTE, the most common is FibroScan. And so there are a number of places across the country that do have FibroScan, but if you don't have that, basically what it is, is sending a pressure wave through the liver and measuring how fast the wave propagates. A healthy liver, the wave propagates very slowly. In a liver that's stiff from inflammation or scaring, the wave goes very quickly. And so that's one such way to do it. There are ultrasound machines, and you can get shear wave elastography through radiology. Personally, it's very heterogeneous across the country. The values are different, so the values that—you can't compare apple to apple in terms of values.

And then, ELF, you can order that through LabCorp, and insurance coverage is improving rapidly and it really depends on where you are in the country. But it's a simple blood test.

We also have a question about screening for alcohol use. So, Nick, do you screen for alcohol use in your primary care practice?

Dr. Pennings:
Certainly, it's a question that we ask. And I think one of the most important parts about that is to make the patient feel that they're not being judged in asking that question, so they feel comfortable in giving an honest answer to be able to assess what their actual alcohol intake is. But certainly, it's a very important part of taking any patient history. So being able to make a patient feel comfortable to answer those questions.

Dr. Bansal:
Yeah, how about you, Fernando?

Dr. Bril:
Yeah, we do screen for alcohol. Actually, all the patients that we see in clinic, that I have also patients that have diabetes with no liver disease, but those with liver disease, they all get PEth testing in our clinic. But the first screening audit is three questions. Kind of to identify alcohol misuse, but then we get PEth testing in all patients, which is a blood test. There are more and more studies looking at how that can give you a quantification and distinction between MASLD and MET ALD that we didn't talk much today. But this new condition that patients that have, or would fulfill like a diagnosis of MASLD, but also drink more than these mild amounts that I mentioned before; 20 grams daily for females, 30 for males, grams daily. If they have met ALD, we have cutoff points kind of to distinguish between those two.

Dr. Bansal:
Once they come to us in hepatology, like, someone's worried about their liver, so we've kind of made PEth the standard test so that I'm getting it in everyone. I'm not choosing to get it in you or you, and it's part of our work up. It's part of the work up. And I think that then, you can at least have conversations. Sometimes the patient was just at a wedding in Mexico for the past week, and that's not their typical PEth value, but at least it gives an opportunity. And you're just, I mean, sometimes I will also say there are gut bacteria that can produce alcohol. And so you're just kind of trying to assess if there is an effect of alcohol, ethanol, whatever its source, that could be contributing to the liver disease.

So, Jen, we have a question specifically. During this course, did you ever get tested for alpha-1 antitrypsin deficiency?

Jennifer:
So I believe my hepatologist is the one that ordered the test for me. I don't know about my family as much. They don't really—they're not into the genetic testing or anything like that. I'm kind of the black sheep in my family in that way, I want to know. But I don't have alpha-1.

Dr. Bansal:
But I think that listener is picking up on something about the rapid fiber, the genetics and multiple cofactors that could be contributing to kind of the rapid fibrosis in your family history. Like, having cirrhosis at such a young age. And so we know genetics, so obviously, alpha-1 antitrypsin is one thing that is known, even the heterozygote state, to contribute or be a synergistic factor in fibrosis development. But there's others. We said that the Hispanic men over 40, but it was Hispanics, specifically, that have some genetics; PNPLA3 polymorphisms that increase the risk of liver fibrosis.

Now, insurance. So in Ohio, it's very hard to cover GLP-1 agonists. I don't think that's limited to Ohio, based on our conversations. But any pearls with appeals, so any guidance you guys could give and what's the key wording?

Dr. Bril:
Yeah, I had a whole lecture on understanding the waters of insurance. So I feel with that question. So I would say that there are no secrets in the sense, they're insurance is, in general speaking, are being restrictive. But you need to know your indications, so you need to know what you are prescribing it for. I think obesity is what we struggle with the most. If we want to indicate it for obesity, insurance may not cover obesity as an entity. So I usually tell patients, find out if your insurance covers obesity as an entity. But if that's not an option, then you still have to know that GLP-1s are indicated for other reasons. Diabetes is the obvious. I think everybody knows that if you have diabetes, you would probably qualify for it. But then, cardiovascular disease. So if patients have cardiovascular disease, even if they don't have diabetes, then they may qualify for it. And now, sleep apnea. If it's moderate to severe, AHI above 15, then you would qualify for sleep apnea, so that's another opportunity. And we are waiting eagerly to see if liver becomes an indication. And this would be another reason to screen patients because then we may have another indication and hopefully we'll be covered for liver disease.

Dr. Bansal:
Absolutely, absolutely. I think the field is rapidly evolving and the pressure is mounting because when you have so many benefits on multiple organs, and you have so much data from cardiovascular in and of itself, that I think the data is mounting and the pressure is going to be mounting, and that might also cause prices to come down as the competition ramps up.

So there's a question about calculating BMI for all patients. I think that a lot of places with an EMR do have that. I would say waist circumference. We don't do it because it just kind of—but that would be actually, even a better way to look for visceral adiposity because if you're an apple versus a pear, your BMI could be the same but it's the visceral adiposity that's really associated with the outcomes and the deposition. So it is a good idea just to get your indication. Right? If you are overweight with 1, 2, or more metabolic, so to get your GLP-1 approved, you definitely need a BMI if you're going for that indication.

But do you guys measure waist circumference at all in your clinics?

Dr. Bril:
We don't. So we do it for research purposes, but in the clinic, I think that the issue is how reliable is the measurement? I don't do it myself. And then, if I have to explain it to someone, are they always measuring at the same height, versus not. And we do have bioimpedance in the clinic, so we do get a percentage of fat, which is another tool. And sometimes we use it with insurance, if BMI cutoff points don't go the way we need them for approval, we use the percentage adiposity.

Dr. Bansal:
How about you?

Dr. Pennings:
And I do waist circumference all the time in my office and monitor my patients with it, so it's another feedback. And it's really exciting when you see an 8-inch decrease in waist circumference. And then, you see all the metabolic benefits. But it is important that you do it consistently and you do it correctly. So there's a couple of different recommendations. The most common, I think, is measuring at the level of the iliac crest and parallel to the floor. I typically have the patient breathe in, breathe out, and relax, so that they're not sucking it in. Which is something some patients will do. And I think that helps with the consistency of the measurement.

Dr. Bansal:
Right. Right. Yeah, I think people are pointing out, kind of, you're a little bit unusual in the sense that the weight loss did not improve the fatty liver. I think that's, just to be clear, that's really the exception, not the rule. I think, from bariatric surgery data, from all the pharmacologic studies, weight loss does. So maybe the genetics, something else coming in. Yeah, Fernando?

Dr. Bril:
Yeah, I would say, so we need to think of it the way we think of diabetes, hypertension, and dyslipidemia. So weight loss helps, but patients respond to it differently, right? And even patients after bariatric surgery with significant amount of weight loss, some may still need medications for diabetes, some may still need medication for dyslipidemia, and some may still need medication for the liver. And even in studies looking at data from bariatric surgery, regression of fibrosis is around 40%. So that means 60% actually, didn't have regression of fibrosis.

Which speaks that, at the end, we need to treat this condition holistically, but also try to think of combination therapies and not just for—so focusing on weight loss for sure, but also thinking that some patients may need something else other than that.

Dr. Bansal:

So you just teed off the next question, right? So if you don't get the Fib—Go ahead, Jen.

Jennifer:
Can I just say real quick? I'm actually, the only one of my siblings that beat diabetes after weight loss surgery or after because my oldest sister had lost a significant amount of weight but never changed her eating habits enough to get rid of the diabetes. Also, my sister that progressed to cirrhosis, she still had to take diabetic medication. I haven't had diabetes since 2011. My A1C is 5 or under.

Dr. Bansal:
So weight loss improved probably that aspect. Nick, you were going to make another comment?

Dr. Pennings:
Well, just that you didn't really have a liver fibrosis evaluation back then, either. So really what we're looking at was liver enzymes and that by itself is not really a measure of improvement or advancement.

Dr. Bansal:
Right. But I think the point is, is that none of these trials have shown 100% response, whether you need to wait longer. A year of fibrosis takes time. So it may be that you need to wait longer. But we know that there's responders and non-responders, and I think part of the exciting part of the field is to define those people as early as possible or to pre-know based on AI and genetics, etc., that you're more likely to respond to drug A, you're more likely to respond to drug B, so you kind of lead with that one. And I think that if you aren't getting —So in your case, right, you were on anti-obesity medication, but you also got the liver-targeted therapy, right? Because maybe it wasn't enough for you. And so, for you, that add-on therapy was what did help you. And so I think you have to see how people respond, if we don't yet get to the predictive algorithms.

The other comment was about I would say the FGF21 showed the greatest antifibrotic effect. So if somebody's really teetering in that cirrhotic stage, you might want to start with that strongest antifibrotic to bring them back from cirrhosis. And so combining a tight antifibrotic with a metabolic approach is going to be great.

So that's all the time we have for today. I'd like to thank my friends for joining me. Thank you for tuning in and have a great rest of your day. And please continue to celebrate Global Fatty Liver Day. Raise awareness, awareness, awareness. That is our charge.

So enjoy the day. Bye-Bye.

Announcer:
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