Rounding@IOWA: Making Sense of MASH

Transcript

[Upbeat theme music plays]

Dr. Clancy

Welcome to Rounding@IOWA, a continuing medical education podcast developed by and for healthcare teams. I'm your host, Dr. Gerry Clancy, Senior Associate Dean of External Affairs for the Carver College of Medicine here at the University of Iowa. Today we'll delve into MASH, or metabolic dysfunction-associated steatohepatitis, a condition with lots of television advertisements for new treatment options. We will start our discussion on a set of liver conditions that have had various names over the past several decades. As well, we will talk about how the progression of this form of liver disease can be quite serious. We will then move on to several very promising treatment options for those at risk for MASH and those who have MASH as well. Our objectives today include, first, we want our participants to be able to recognize the past and current nomenclature for metabolic-associated liver diseases. Second, we hope our participants will then be able to acknowledge the staging and progression of MASH. Third, we will then be able to recognize the risks, signs, symptoms, and lab findings for MASH. And finally, we'll finish with describing non-pharmacologic and pharmacologic treatment options and how to guide our patients. Fortunately, we have two University of Iowa liver specialists, Dr. Alan Gunderson and Dr. Marta Tejedor Bravo, to help us sort all this out. Dr. Marta Tejedor Bravo is an associate professor of internal medicine in the Division of Gastroenterology and Hepatology at the University of Iowa. Her education and training background include: First, she earned her medical degree from the Universidad of Autónoma de Madrid School of Medicine in Madrid. She then completed specialized training in gastroenterology and hepatology at the Hospital Universitario Ramon Cajal in Madrid. She completed a Masters of Science from the Universidad de Ocala in Madrid and a Doctor of Philosophy from the Universidad Complutense de Madrid. This was then followed by completing a liver fellowship in transplantation at St. James University Hospital in Leeds, England. Marta, how did I do with some of that Spanish there?

Dr. Tejedor Bravo

Yeah, I have to congratulate you. You're all ready for your Spanish boards. That was amazing. Thank you.

Dr. Clancy

Today at the University of Iowa, she's the clinic director of the James A. Clifton Digestive Health Center at the University of Iowa Health Care Program and the program director of the Iowa Liver Wellness Program at the University of Iowa. Dr. Alan Gunderson is an associate professor of internal medicine in the Division of Gastroenterology and Hepatology at the University of Iowa. His educational background and training includes he earned his medical degree from New York Medical College in Valhalla, New York. He then completed residency in internal medicine at the University of Wisconsin. He served as chief resident at the William H. Middleton Memorial VA Hospital in Madison. He completed fellowships in gastroenterology and hepatology and transplant hepatology at the University of Wisconsin School of Medicine. Here at the University of Iowa, he is the director of the Transplant Hepatology Clinic and is the associate program director of the University of Iowa Gastroenterology Fellowship Program. Dr. Tejedor Bravo and Dr. Gunderson, welcome to Rounding@IOWA.

Dr. Gunderson

Thanks for having me.

Dr. Tejedor Bravo

Yeah, thank you for having us. It's our pleasure.

Dr. Clancy

We're glad you're here. So I just provided our listeners an overview of your education and training. Could you tell us what a typical work week might look like for you? And Marta, let's start with you.

Dr. Tejedor Bravo

Yeah, so I mean, after sending the kids to school and all that mayhem in the morning, I usually run late. And then I get to see a bunch of patients, liver patients in the clinic. Sometimes I scope. We also do inpatient consultations. Every now and again, we get to see transplant hepatology. So a little bit of everything, and it's always busy, as you know, and we just love what we do.

Dr. Clancy

Great. I imagine you have residents and students and fellows with you most of the time as well.

Dr. Tejedor Bravo

Yes, we do.

Dr. Clancy

Very much so. Alan, how about you? What does a work week look like for you?

Dr. Gunderson

Remarkably similar, but every week includes some combination of general hepatology clinics, where we'll meet people with MASH or MASLD, transplant clinics on many, but not all weeks, where we'll meet people who are going to get a transplant or have already had one, and maybe they have MASH or MASLD of their post-transplant liver, some gastrointestinal endoscopy, and of course, medical students, residents, fellows, and hepatology fellows in our clinics.

Dr. Clancy

Great. And do you have the morning chaos as well?

Dr. Gunderson

I'd like to tell you that my mornings are footloose and fancy free, but it's, I mean, wake up and it's burning until I'm at work and kids are at school. It's a thing.

Dr. Clancy

Yeah. So in a similar kind of question, could you both tell us what drew you to liver health as an area of focus for your career? And Alan, let's start with you.

Dr. Gunderson

A bunch of things. So first off, the liver is a remarkable organ. It's really cool. When you study internal medicine, there's a lot of that that's liver. All of biochemistry is in the liver. So people who are in their undergraduate studies or medical school, they are already getting some training steeped in the underlying factors important in liver disease. It's great. Plus, everything for a liver is pretty objective. If there's a problem with the liver, we can typically see it on a blood test, on an imaging test, or on a liver biopsy. If it's not on those things, it's not a problem.

Dr. Clancy

Great. Well, you're talking to a biochemistry undergraduate who was fully in nerd mode during undergraduate days as far as in the laboratory. So I get it.

Dr. Gunderson

We're among friends.

Dr. Clancy

Marta, how about you? What drew you to liver health?

Dr. Tejedor Bravo

Yeah, so I didn't understand the liver, so I made it my job to truly understand it. It all started with trying to figure out hyponatremia, and then it went on to understanding the pathophysiology behind MASLD and a bunch of other things, and I just love it. I love the complexity of it. I love how every system in the body gets involved and starts to fail when the liver doesn't work. I just find that really fascinating how it all is intertwined. And yeah, as Alan said, it's a lot of internal medicine within an organ.

Dr. Clancy

Those are great answers. I didn't understand the kidney and so I took several renal electives as a fourth year medical student and I still didn't understand it. So I did not go into renal, went all the way over to psychiatry. So let's start with defining MASH and the evolution of names for MASH. First question, and I'd love to hear from both of you, what is metabolic dysfunction-associated steatohepatitis or MASH and how does it fit into the broader spectrum of liver diseases?

Dr. Tejedor Bravo

So MASH is one of the categories of steatotic liver disease, which is just like an umbrella term to include anything where fat plays a role in the pathophysiology. There is fat infiltration of the liver from a number of different origins. MASH is when this is from metabolic conditions. We also have alcohol, so that would be ALD. There's a combination of most. That's MetALD. This is the new kid on the block. And then of course we have other steatotic liver diseases that include things like different drugs like methotrexate or genetic conditions, et cetera. And I'm going to let Alan take over and complete that response to how he sees MASH fitting into the general hepatology spectrum.

Dr. Gunderson

Yeah, no, I mean, I just full agree, right? So all MASH is for people who have a metabolic risk factor. They've got fat in their liver. That's a problem. That's all it is. And under the microscope, you can see some inflammation. That's it. And Marta's exactly right. There's basically three types of fatty liver. And the clinical word is steatosis, right? So fatty liver from alcohol, really common. Fatty liver that's from metabolic risks in your genetics being

the second broad category, and then other, which could be other stuff that's pretty common, medicines like tamoxifen, amiodarone, methotrexate, hepatitis C, genotype 3, you name it. There's a bunch of other things can do it that happen very rarely.

Dr. Clancy

For those of us who say graduated from medical school in 1988, what other medical terms might have been used in the past for MASH?

Dr. Gunderson

Boy, I'm sure everybody's familiar with the old NASH. So it used to be NASH and NAFLD. NAFLD was the fatty liver that didn't seem to cause as much problem. That became MASLD or MASL, I guess. And then NASH became MASH. You know, and I'm interested in what Marta says, but you know, it went through a couple intermediate variations on the way to becoming MASH. But the basics, it used to be kind of called by what it wasn't. It was fatty liver that wasn't from alcohol. And I think they're just trying to hit it a little more on the head that this is fatty liver for a reason. It's fatty liver because you have the right genetics, sort of the right risk factors. And so it's an affirmative diagnosis instead of one of exclusion. And I think that's the important parts.

Dr. Clancy

You good with that, Marta?

Dr. Tejedor Bravo

Yeah, I was just going to comment. There was a period of time where we were all in the congresses thinking, what did he say? Did he say NASH? Did he say MASH? Did he say MASLD or NASLD? And there was a bit of confusion there until the nomenclature changed for the 100th time.

Dr. Clancy

So tell me, did all the hepatologists get together and say, this is what we're going to do? Or what was the sifting of the naming process? Love to know how it all ended. It seems like we've settled down at least on it.

Dr. Gunderson

Yeah, I mean, you'd like to think. I mean, even now they permit both terms for clinical trials and stuff. So, it takes a while to really filter down. The rough, I think they met and had a consensus conference and they sort of decided that, hey, there's probably clinical terms that are more useful. The second part, they were trying to get fatty out of the nomenclature,

they polled some people and they found they didn't like the word fatty, which is weird, right? Because it makes it very clinical and easy for us, but it's not accessible language for everybody else out there. I mean, how do you explain steatosis without saying the word fat? So it gets to be hard.

Dr. Tejedor Bravo

Yeah, the change in nomenclature was driven by, as Alan was pointing out, it used to be a negative diagnosis and that was creating some confusion. And as Alan was mentioning, we wanted like just to point out what the main drivers were, but also the terms fatty and non-alcoholic brought some stigma to the name. And in particular, when we talk about MASH in children, it's telling them, hey, this is not from alcohol, it kind of sounds so weird. Like, why would a kid be, told something like that? And that was a big part of it. And also fatty, although it makes our life easier in terms of explaining it, does come with some sort of stigma and negative connotations, again, back to children. And also by bringing, pointing out what the risk factors are, we're able to differentiate it a bit better from other diseases like the ones that we mentioned before that also come with steatosis infiltration.

Dr. Clancy

Great. So. When you're looking at MASH, are there specific cardio and metabolic criteria that a patient must meet to fulfill the formal diagnosis? What gets you the formal diagnosis of MASH?

Dr. Tejedor Bravo

So it's like the definition is steatosis of more than 5% of the hepatocytes accompanied by at least one cardiometabolic risk factor, namely hypertension, diabetes, dyslipidemia, and here for the diagnosis, we're talking about high triglycerides or low HDL. For the definition, we're not looking at LDL or obesity in the absence of significant alcohol consumption.

Dr. Clancy

And is it a bright line between hepatic steatosis or MASLD and inflammatory steatohepatitis, or is it a blurry line?

Dr. Gunderson

It's a blurry line. Oh, good gracious. If we were great at deciding, we'd be famous. Probably the best way to figure it out is under the microscope, because in the end, MASH, the difference between sort of more benign fatty liver and MASH is inflammation. It's typically inflammation you can see under the microscope. And it's inflammation that matters, right? Inflammation is what leads to scarring. So if you have MASH, you might make a fibrosis

stage of scar over around sevenish years. So go from zero to 1 to 2, you name it. In the more benign fatty liver, it might take double that if it moves at all.

Dr. Clancy

Got it. So here's the biochemistry nerd in me. Can you provide us with an overview of the pathophysiology of MASH and kind of that loop around elevated blood sugars and insulin resistance and lipid dysfunction? How does it all come together? Like the Krebs cycle, is there a drawing that explains it all?

Dr. Tejedor Bravo

Alan, is it okay if I take this one?

Dr. Gunderson

Marta, that looks like an incredible set of notes. You're all over it. You got it.

Dr. Tejedor Bravo

Yeah, okay. So I gave a lecture about this last year, so I'm all in for it. Essentially, there's two big pillars in the pathophysiology. The first one is insulin resistance and the second one is intrahepatic de novo lipogenesis. And they're intertwined. But let's start with insulin resistance. So when we eat too much with hypercaloric nutrition, that excess calorie is stored in the adipose tissue. And when there's too much energy to be stored, then there's hypertrophy or expansion of that adipose tissue. And then the vessels that need to grow just can't keep up. So there's hypoxia. And the hypoxia will induce inflammation. That inflammation is going to spill over some toxic metabolites from that adipose tissue and some inflammatory markers that will then travel around the organism, promoting insulin resistance and oxidative stress in other tissues such as the liver or the muscle. When we talk about the insulin resistance, in particular in the liver, insulin stimulates 2 different pathways inside the liver. One is the gluconeogenesis and the other one is the de novo lipogenesis. And what's really interesting about this insulin resistance in MASH is that it only affects the gluconeogenesis pathway. So the de novo lipogenesis is preserved, meaning that even when you have this insulin resistance, all the effects of the insulin are going to still stimulate the de novo lipogenesis pathway inside the liver, stimulating that deposition of fat inside the liver. Also, this decreased glucose uptake by the liver and the muscles, secondary to this insulin resistance, is going to worsen the hyperglycemia, inducing more hyperinsulinemia and placing our patients at risk for type 2 diabetes. And then the second pillar is the de novo lipogenesis. So this excess caloric intake, the excess carbohydrates and the free fatty acids are going to increase the beta-oxidation that Gerry was mentioning and also the Krebs cycle. So all those two pathways are like hyper-

enhanced, so to say. And ultimately, we have an increased substrate for the de novo lipogenesis, which is the acetyl-CoA. That's the first molecule in the de novo lipogenesis pathway, and it's the end product of both the beta oxidation and the Krebs cycle. So therefore, we're feeding directly into the de novo lipogenesis pathway. And also this excess free fatty acids and carbohydrates are also stimulating the transcription of different lipogenic genes also involved in the de novo lipogenesis pathway. So ultimately, we're increasing our intrahepatic triglycerides. In that pathway, in that excess production of triglycerides, we're producing toxic lipid species that are inducing oxidative stress of different organelles like the mitochondria or the endoplasmic reticulum. Then just to complete the picture, those are the two most important ones. As Alan was pointing out before, this is modulated by a genetic background. There are certain genotypes that are going to be more prone to the toxicities and to the increased fibrosis with fewer metabolic risk factors. And then there's other two players, the gut and the brain. So it all comes to a very intricate pathway and multi-organ interaction. So that's kind of the overview.

Dr. Clancy

That was great. I have never heard it broken down that way, first of all, how complex it is, but second of all, how it all fits together. So that was wonderful. Great job. Great job. I hope the students enjoyed that lecture because that was really good. Really good. So let's move over a little bit and talk about epidemiology and symptoms and screening. MASH is sometimes referred to as a silent disease, as are several liver diseases, unfortunately. What are patients typically, or why are patients typically asymptomatic early on, even into the moderate stages? And what vague symptoms might they present with that gets your attention early on?

Dr. Gunderson

Yeah, I mean, liver diseases in general are under the radar because the liver is such a big, sturdy organ. I mean, the mass of a liver is big, so you have to lose a lot of functioning hepatocytes to really notice a lot. When you finally lose a functioning mass of hepatocytes or it has enough scar that blood doesn't flow through it correctly, you finally have symptomatic liver disease and that changes everything. So livers are fine until they fall off a cliff. So in liver disease, it's usually screening for a problem before you can feel it, before you have symptoms. By the time you have symptoms, you have a real problem. Fatty liver disease is an important kind of silent disease because so many people have risk factors for it. For this specifically, I mean, most Americans now are overweight or obese. That's a risk factor. So many Americans have pre-diabetes or diabetes, dyslipidemia, hypertension, you name it. So screening for it gets to be the way it's identified before, hopefully before it's a problem so we can intervene and keep people well.

Dr. Clancy

Great. So out in the primary care world, are there certain demographics or comorbid conditions that when you look at a patient's past medical history or problem list, you might start thinking, all right, this adds up to enough severity in these areas that it might be pointing toward MASH? What do you look for as far as other diagnoses that then suddenly raise the alarm that it might be there?

Dr. Gunderson

Well, if you were just looking at a list of stuff, you could find the profile of somebody who likely had MASH before you found MASH. If you found diabetes, you got a great chance of finding MASH, type 2 diabetes. If you find someone who's overweight, as they are progressively more overweight, so as they tend towards obesity or significant obesity, morbid obesity, they're very likely to have it. Those are the two biggest. Probably the third is having more than one cardiometabolic risk factor. So having obesity and diabetes is worse than either one, adding to it dyslipidemia worse, adding to it hypertension worse. So two risk factors, but the chief one would be diabetes.

Dr. Tejedor Bravo

Yeah, and just to give you a little bit of context about that, the prevalence of MASLD among patients with type 2 diabetes is around 55%. And the global prevalence of MASH, so steatohepatitis, among patients with type 2 diabetes is 37%.

Dr. Clancy

Yeah, got it. So pretty routine in primary care. My primary care physician routinely screens me for electrolytes and sugar and liver enzymes. Tell me about the liver enzyme as a clue versus the liver enzyme as sometimes not pointing you in the right direction at all.

Dr. Tejedor Bravo

So who to screen? So if we look at the AASLD guidelines from 2023, basically we would have to screen everyone by the sounds of things. They suggest screening people with cardiometabolic risk factors, people who have steatosis on imaging, and people with abnormal LFTs. And I think that amounts to probably all of our people, all of our patients. And then the type of tests that we can use is something like a stepwise thing. So we would start with easy ones like FIB-4, which is just the non-invasive based on AST, ALT, platelet count, and age. And if the FIB-4 is high, above 1.3, then we move to a second test like FibroScan, for example, to try to refine our risk assessment. If the FibroScan is above 8, then the patient should be seen in hepatology to try to pin down if the patient has what we call at-risk MASH, which are patients with some degree of fibrosis in whom we want to give

pharmacological treatment to prevent progression. But if the patient doesn't have either an elevated FIB-4 or an elevated FibroScan, then they could potentially remain in primary care with intensive lifestyle changes and repeating those non-invasive tests every other year.

Dr. Gunderson

Gerry, I think when I hear your question, I think I'm imagining somebody who's in primary care and has somebody made with some risk factors and sees an abnormal set of liver blood tests like an ALT or an AST. And the hard part about that is like Marta's saying, that's not how you stage MASH. It's important, it tells you about some necroinflammatory inflammation, but it doesn't tell you really what you care about. And like Marta is saying, there's all sorts of ways to tell you about scar. Abnormal liver enzymes are important. They might mark who could have a problem, but you don't really know if you have a problem until you know if you have scar.

Dr. Clancy

Yeah. So let's talk about staging. Being from the outside looking in on hepatology, do you have a scoring and a staging system for MASH?

Dr. Tejedor Bravo

Yeah, like the scarring staging is pretty similar across all sorts of etiologies. It doesn't really matter if it's MASH or anything else. And the way I always explain it to my patients is think of this process of damage and repair that happens in the liver as if you always scratch yourself in the same place, you scratch it heals, you scratch it heals, eventually you'll get a scar. So the same thing happens in the liver. Over time, that repeat process of inflammation and reparation will cause some degree of scarring. And that scarring will progress from an F0, meaning there's no significant scarring at all, to an F4, meaning there's so much scarring, so much fibrosis that we call it cirrhosis. So cirrhosis is just a fancy term to say that the liver is very scarred. And one thing that I want to point out is that the same way we can go up the ladder, we can come down the ladder. So whatever our staging system shows, like say a FibroScan value, that is just a number for the most part. It's something that's dynamic. It doesn't mean there's no way around it for the most part, unless it's very, very advanced.

Dr. Clancy

Great, great. So a liver biopsy is not a minor procedure. I do remember that from internal medicine. So when do you say it's time for a biopsy?

Dr. Gunderson

Not all that often anymore. You know, and I'm interested in what Marta's practice is. I think there's general agreement between hepatologists on who deserves a biopsy. And it's people where you can't make a good clinical diagnosis. If you can't estimate scar accurately because your tests are giving you gray zone level results or disparate results, some saying no scar, some saying lots, or if there's a competing diagnosis that could look similar, whatever that might be, autoimmune liver disease, hemochromatosis, you name it. That's probably the time where biopsy comes back as sort of the decider. It's still really the only way to make a formal diagnosis, but most people have a clinical diagnosis.

Dr. Tejedor Bravo

Yeah, I totally agree with that. It's just for the diagnostic uncertainty. And we have more and more non-invasive tools, for example, the MRE, MR elastography, which is currently the most accurate non-invasive testing to assess scarring and steatosis. So that really, if what you want is a very precise fibrosis staging, you're going to prefer MRE as opposed to a biopsy, if that's the only thing that you want to get out of it.

Dr. Clancy

So from the outside looking in, is the MRE a blood test or is it a scan? What is the MRE?

Dr. Tejedor Bravo

It's a magnetic resonance elastography. And the advantages are that it allows you to assess the whole liver. It's able to detect fibrosis earlier than, for example, the FibroScan. And it's also effective in obese people, which is the limitation of FibroScan.

Dr. Clancy

Sure, and do you have any other blood biomarkers that you would rely on beyond liver function?

Dr. Gunderson

Yeah, I mean, you know, we're big into...

Dr. Clancy

Expensive stuff? [laughter]

Dr. Gunderson

Yeah, oh, sure. Yeah, more expensive the better, right? I mean, honestly, generally we want something that doesn't cost anything. So if we can get by with a FIB-4 test, like Marta's

saying, that's probably where you start. Then there are proprietary tests. Here we don't have the ELF, the estimation of liver fibrosis. So there's FibroTest-Acti-Test, there's FibroSURE, FIBROSpect. There's a bunch of proprietary tests. They all perform pretty well. But in general, liver-related blood tests are good at telling you who doesn't have much scar. They're pretty good at that. Where they're not as good is the stuff Marta's talking about, like the MRI elastography or the FibroScan, where they do it with ultrasound, is telling you who clearly has lots of scar. Like for all the stuff in the middle to advanced, that's really where the imaging tests are better. But for ruling out, the blood tests are great.

Dr. Clancy

Okay, great. So let's move on to disease progression and complications and frankly trying to get the attention of the patient when you're concerned about them. In talking with the patient, what kind of things do you discuss with them as far as the progression of the illness and the importance to act in protecting the liver further? What kind of things do you let them know may be on the horizon if this isn't taken care of in an aggressive way?

Dr. Tejedor Bravo

I tend to tell them the ladder story, like to kind of give them like, a setting, like a framework, like where you are in this ladder type of thing. And if I really want to scare them to see if they do something about it, then I'll jump into what cirrhosis means and what decompensated cirrhosis looks like and how miserable it is actually. And then I give them like that bit of hope that this is, you're not there and we can come down the ladder, but we need to put in the hard work. And we're going to be discussing drugs in a minute, but anything that we do needs to go hand in hand with lifestyle changes. So we're going to be talking about diet and exercise. Those need to be hand in hand with anything else that we do.

Dr. Clancy

Got it. Got it. How about hepatocellular carcinoma? Let's talk about that as far as MASH and its relationship. We know that all sorts of hepatitis sets you up for hepatocellular cancer. Is MASH in the mix as well?

Dr. Gunderson

Sure, yeah. When it comes to things that make cancers, on top of the list for liver is usually hepatitis C. That's still on the top. Number 2 is hepatitis B worldwide. That kind of makes the most because there's so many people who get it from their mom at the time of birth. After that, it gets to be a pretty close race between MASH and alpha-1 antitrypsin. And generally our biggest risk factor for making primary liver cancer is cirrhosis, generally from those four things, viral hepatitis, MASH, and alpha-1. The difference about maybe some of

those is those four leading causes probably have some risk of making liver cancer before you have cirrhosis. And that's what makes them pretty important. So even if scar is what we're worried about for staging MASH, there's other stuff too that makes a huge difference in someone's health and your advice. I'd say liver cancer is a good scary one.

Dr. Clancy

Yeah. So let's not move on yet. Let's tie in one more scary disease. Let's talk about the relationship with MASH and progressive cardiovascular disease and how those two are related.

Dr. Tejedor Bravo

So it's interesting because in early stages of MASH, you die of cardiovascular disease and liver outcomes are not as relevant. So that's something that we need to stress to our patients, especially in early stages. We need to get control of all the cardiometabolic risk factors. And as fibrosis progresses, in particular F2 and above, is when you start being at risk of liver related events like progression to cirrhosis, decompensation or HCC or hepatocellular carcinoma. And that's why we also focus our drug therapy in F2s and above when we target specifically the MASH. Alan, do you want to make any comments about the cardiovascular?

Dr. Gunderson

Sure. Everything in MASH that we talk about is a cardiovascular risk. Obesity is a risk. Diabetes is a risk. Hyperlipidemia is a risk. Hypertension is a risk. It's all a risk. So it should be no secret. It should be no surprise that there's so many cardiac risks and it's the number one reason people die with MASH, right? It's before you get liver disease, which is generally many, many years, you have all those risks for heart disease. So it makes sense. It's atherogenic dyslipidemia, I guess we should say that, inflammation with fats flying around. Yep.

Dr. Tejedor Bravo

Yeah, and circling back to the pathophysiology, once you have steatohepatitis, once you have MASH, the liver works like an inflammatory hub. So once the liver is inflamed and is suffering from all this oxidative stress, it starts to kind of spill over inflammatory markers to the system, to the whole organism. And that in turn will worsen systemic inflammation affecting and worsening your cardio, like your cardiovascular risk, your risk of cognitive impairment even, and things like that. So it's just like an inflammatory hub once the liver is inflamed.

Dr. Clancy

All right, before we get into pharmacology and some of the new options, let's talk about non-pharmacologic management and lifestyle interventions, something that can be particularly hard to gain ground on. But do you, kind of in the early mid stages, do you have a body weight loss target for the patients? How do you approach getting them serious about weight loss and turning things around?

Dr. Tejedor Bravo

So any weight loss is better than no weight loss. The guidelines do suggest that losing more than 5% of your body weight will reduce your liver fat. When you go up to 7 to 10% of body weight loss, you're improving your inflammation. But if you really want to improve your fibrosis, then you need to lose more than 10% of your weight.

Dr. Gunderson

Yeah, full agree, right? So the target is almost always more. This gets to be an important thing when you're talking to people because that gives you something real to talk about, real to target. The hard part is when you're doing lifestyle modifications, which everybody should do, right? It saves you from having to take an important medicine, it saves you from an important bariatric surgery. The problem is... They're not very successful. About one in 10 people gets any kind of durable response from that. But that's one person you're saving from having to be on an important or expensive medicine or need a surgery or all that. So it should be tried on everybody. It's low risk, potential high reward.

Dr. Tejedor Bravo

Yeah, and even, I'll just say this, even if you don't achieve weight loss by changing your lifestyle to a healthier diet and increasing your exercise, meaning you have a healthier muscle with less fatty infiltration of the muscle, you're having more mitochondria, more functional mitochondria, your overall functional status is going to improve. All of that has a positive impact in the liver on its own, regardless of the weight loss.

Dr. Gunderson

Yeah. Healthy muscles are sink for glucose, right? So people who exercise more have more functional or larger muscle masses have less high blood glucoses. They have less fat in their liver. Yeah, exactly.

Dr. Clancy

Totally makes sense. And do you have a diet style that you find at least science wise is best supported?

Dr. Tejedor Bravo

I come from Spain, so I'm all for Mediterranean diet. I'll just say that.

[laughter]

Dr. Clancy

And as am I. Absolutely.

Dr. Tejedor Bravo

But to be perfectly honest, any diet that helps you lose weight will work. And then we have to tailor the diet to something that the patient will actually follow. So if I was like a meat potato community and I come talking about, lentils and fish, they're gonna, like many of my patients will look at me like, yeah.

Dr. Clancy

That's not gonna happen.

Dr. Tejedor Bravo

Yeah.

Dr. Gunderson

It's one of those things where it really does take a little bit of work in the clinic, right? It's easy to say, please start a Mediterranean diet because generally that means something, generally you can look it up or you name the diet. What's hard is to meet someone where they are and identify their biggest risk factors and cut it out. That takes time in the clinic. That takes work. Generally, there's some places you can really buff up most people's diets, right, trying to meet them where they are. If they're already having real sugary beverages, you can probably cut down, cut some of those out. They're eating a lot of packaged processed foods that are, you know, add a lot of high fructose corn syrup. Try to cut those down. But honestly, many people have something they eat out of habit that works for their day and their life because they got kids or they're on the job site or you name it. And so there's some things they can do, but they may not be able to pull lentils around with them. But you know, different food products prepared in different ways can make a big impact, right? So we know that potatoes are the most satisfying food for someone's hunger. There are studies, they are the most satisfying food. But how you take your potato sure matters, right? Clearly a baked potato with nothing added is going to be a lot different than the French fries you get at a fast food joint. They're both going to satisfy your hunger great, but they are not the same.

Dr. Clancy

So the Irish were right. Yep.

Dr. Gunderson

The Irish were right.

Dr. Clancy

Yeah. So Marta, you know, you're from Spain. My roots are from Ireland. So yeah. My father, born and raised in Ireland, had to have potatoes at every meal. Yeah. So Alan, you mentioned it, but just is the various bariatric surgeries on the list as well as far as something you would recommend it from time to time?

Dr. Gunderson

Oh, for sure. So bariatric surgeries, it should be said, still are the most successful at long-term weight loss, right? There are the potential downsides of great medicines that can save you from a surgery, but that you'll have to maybe keep taking forever. That should be no secret. If the medicines are the only thing that changed and you take them away, you may revert back to how things were before. It should be said on this podcast that bariatric surgery's roots are here in Iowa. I mean, Dr. Mason in the 1960s really pioneered those and started the modern Roux-en-Y gastric bypass after that in the 70s. But they have the most durable effect. There are some people that can't get the desired effect still with the medicines. There are some people whose diseases are so advanced that the medicines still may not be adequate. So there's still a role for this. It's just a smaller role than maybe it used to be.

Dr. Clancy

Great, great. So let's move on to something that's quite hopeful, and that is the new pharmacologic options that we have with the landmark approval of resmetirom as the first targeted drug for MASH with moderate to advanced fibrosis. How does this drug work? This is a new one for me, and frankly, I haven't asked AI, how does this work? What does it do?

[laughter]

Dr. Tejedor Bravo

So you know what's really interesting? The molecule it targets, the receptor it targets, it's not directly implicated in the pathophysiology of MASH development. And I find this fascinating. What it does is it's an agonist of the thyroid hormone receptor beta that only exists inside the liver. So it's very liver specific. It won't trigger like thyroid response like

things elsewhere. And by binding to this receptor, it increases gene transcription of genes that are actually improving mitochondrial function, increasing beta oxidation of the free fatty acids, increasing lipophagy and cholesterol catabolism. So all of this in turn will improve your mitochondrial function, decrease your intrahepatic triglycerides, reduce the lipotoxicity, and all of that translates into decreased inflammation and decreased fibrosis.

Dr. Clancy

Great. So I mentioned it that it's for moderate to advanced fibrosis. Is this a difficult medication to take? Is it a difficult medication to get people approved for?

Dr. Gunderson

Because it's new, it's expensive, right? So they come with all sorts of rules. So you sort of have to meet the trial criteria that they sort of satisfied. So you have to have enough fibrosis, not too little, not too much. And if you meet all the criteria and your insurance says yes, then you can get it. It's an easy medicine to take. It's just a once daily pill. It's based on weight. Either take 80 milligrams or 100. It's real easy. The hard parts with resmetirom are only a couple. It's in the potential side effects because it gets fats out of the liver for all the reason Marta says, you burn them up, you get them out. One of the ways you get them out is in your bile. Since bile is made-up of water, bile acids, and lipids, it increases lipids in your bile secretion. So you might get more gallstones. No one's shown that, but that's a potential thing. In some people, it might make your liver enzymes actually look worse. Those are some people that we have some worry about, so there's a monitoring strategy for that. And then we can't give it to people who have thyroid cancer or a close family history of thyroid cancer. Marta's right, it's supposed to really only be working on the liver, but there's a potential risk of making thyroid cancer bloom. So if they have that in their history, it's really our only historical point we have to really get out of people before we get the medicine for them. Those are the only things we have to watch out for.

Dr. Clancy

And how long have you both been able to work with it? Is it new for you or have you been able to have some at least months under your belt with it or years?

Dr. Gunderson

It's a couple years. So I think it came out around AASLD 2023 or 24. So we've had a couple years of it. To be honest, and I'm interested what Marta says, it's in the guidelines. It's something we should talk about. It would be on a board question scenario thing. It's just not my go-to medicine. And the reason for that, and I'm interested in what Marta says, because I bet we overlap, but it only works in the liver, right? It only works on the liver-

related fat problem. It doesn't work on everything. And since MASH comes with all sorts of problems, you want to modify all of them. And so if I had a choice, I'd probably pick something else. I'd pick one of the GLP-1 or double or triple GLP agonist medicines because they'd get everything I care about instead of one thing I care about.

Dr. Clancy

Well, it does seem to fit Marta's lecture that we had on how the illness, yes.

Dr. Tejedor Bravo

Yeah, and I totally agree with Alan. It only works on the de novo lipogenesis side of things, so to say, although it doesn't impact directly that pathway. So it really like experts are kind of finding that there's like two big phenotypes, so to say, one where insulin resistance is predominant, and those are the patients that are really going to benefit the most from GLP-1s and that kind of strategies. But then there's other patients, in particular, certain genotypes, certain high-risk genotypes that are more at risk of developing or having faster progression of fibrosis because of that genetic background where it's more important to target the intrahepatic part of things. So for example, just to give you an example, this is the mutation I'm thinking of is the PNPLA3. I mean, it doesn't really matter if it's the most important one. That is particularly prevalent in Latino people, for example. Like 50% of the Latino population will have the high risk genetic variant. And it has been shown that these people have more advanced liver disease in the presence of fewer cardiometabolic risk factors. So maybe for a patient whose BMI is not all that high or in whom you can't identify all those many cardiometabolic risk factors, those would be probably the patients where I would maybe consider resmetirom first as opposed to a GLP-1. And I totally agree with Alan in that a GLP-1 would be preferable if you have a lot of insulin resistance on board.

Dr. Clancy

Sure. And just again, trying to keep up with what the FDA says versus what you practice. Is there any of the GLP-1sthat have been FDA approved for MASH?

Dr. Gunderson

I mean, we got one that's FDA approved. So we got semaglutide has a bunch of preparations, a bunch of trade names, Ozempic included, but the trade name of semaglutide that's approved is Wegovy. It won't be the only one. There's a lot of interest in the market from that. So the mixed receptor agonists tirzepatide, GLP-1 and GIP, they're going to be approved sometime. I think they're in phase 3 trials. And so it's going to get flooded with other medicines that do it. But right now, that's the only medicine, the Wegovy formulation of semaglutide that's approved for it.

Dr. Clancy

So on the practical side of that, then for getting a patient a GLP-1, do you have to turn to Wegovy or can you essentially go off label with the other ones, but they're going to have to pay cash for it?

Dr. Gunderson

Man. So this is, it's such a quagmire. So honestly, in my clinic, I can get someone resmetirom, which isn't a GLP-1. If I need a GLP-1 and they just have liver associated disease, I'm kind of out of luck. It's going to be really hard for me to get. Generally, I just can't get it. So I don't want people to have diabetes, but if they have diabetes, now they have a real chance of getting what they really need. And even though the approved one is Wegovy, the right GLP-1 to be on is the one you can get. So if insurance pays for one, you should have it and you can feel pretty good that it's going to work on exactly what you need.

Dr. Tejedor Bravo

I've been pretty successful prescribing semaglutide for F2s and F3s. That's the FDA approval, sema for F2s and F3s. And I have been successful with a few patients. If for whatever reason they can't get it, it's what Alan says, we need to try, we try to find another indication. So do they have diabetes? Do they have OSA? And then can we get them on tirzepatide even if we don't have yet a phase 3 trial? Because ultimately we have phase 2 trials that already show that tirzepatide helps with fibrosis and inflammation.

Dr. Clancy

Sure. So are there times when you use Rezdiffra and you use a GLP? Use them both.

Dr. Gunderson

I never have, but you can.

Dr. Clancy

Marta?

Dr. Tejedor Bravo

Yeah, the same like, the trial, the phase 3 trial, it was the MAESTRO-NASH. There were people who were already on semaglutide and were also given resmetirom. I can't remember what the breakdown was. I usually choose one or the other. I've never started intentionally a combination therapy.

Dr. Clancy

So with a year or two under your wing as far as these meds used for MASH, are you seeing stopping of the illness or are you seeing any reversal?

Dr. Gunderson

Yeah. So resmetirom is a little harder for me because it's hard to know when to stop the resmetirom, but it seems like in some people it sort of calms down their liver enzymes and you hope that means something. I haven't been using it long enough to know if fibrosis improves, so I don't have any idea. But for the GLP-1s, some people have serious weight reduction and you can see improvements. I mean, you can see improvements across the board. They're on fewer medicines. They used to be on insulin and they're not. And since diabetes is a huge risk factor for putting fat in your liver, you bet you that matters for your liver. You can see on their scans, their FibroScans that quantify what your liver is made out of, how much fat, how much scar, you can see that their liver is less stiff, so it seems less scarred. You can see that it looks less fatty than it used to. And you could guess by looking at them, you don't need the fibro scan to tell that, but it's nice to get the confirmation.

Dr. Clancy

Marta, how about you? What have you seen as far as some success stories?

Dr. Tejedor Bravo

So kind of the same thing. Like we don't have enough long-term follow-up with resmetirom. I've had like mixed results. I had one particular patient in whom I chose it because her BMI was only like 30. And after a year of taking it, the FibroScan hadn't budged. If anything, it had worsened some. So we just switched and we're trying to get her on sema right now. And then some of the patients, I've had a couple who've had to discontinue it due to side effects. But again, if the patient has a lot of cardiometabolic risk factors and a lot of insulin resistance, we're going with sema as well. And yes, we do see a reduction in LFTs, which is the, it's supposed to translate a reduction in inflammation.

Dr. Clancy

So what are you seeing out there in the future as far as pharmacologic options? Is there other stuff being staged that looks pretty promising.

Dr. Tejedor Bravo

Yeah, we have a lot of phase 3 trials in the works. And there's different categories of medications being developed. We have de novo lipogenesis inhibitors. These are drugs that are going to inhibit particular enzymes inside that de novo lipogenesis pathways. The ones

that have phase 3 trials right now are denifanstat and Aramchol. Then we have a different class, the PPAR agonists, like lanifibranor. That one is a medication that we use, for example, for PPC, and it's being trialed for MASH as well in a phase 3 trial. We have FGF21 analogs, like efruxifermin, pegozafermin, and efimosfermin. And finally, we have the incretin analogs that Alan was mentioning, like tirzepatide, survodutide, and retatrutide. Those are the ones on phase 3. And probably we're going to be looking at combination therapies down the line.

Dr. Clancy

Great. Nice and hopeful, but unfortunately probably very expensive as well.

Dr. Gunderson

Yeah. But there's good news about that stuff coming. I mean, since we already have good treatments, especially with the current GLP-1s, when the new ones flood the market, it might decrease some of the costs for some of the older ones. They might try to find a new market niche being the affordable GLP-1. And we might get benefits across the board for that. So there's a lot of reasons for optimism with the new medicines coming, especially the new GLP-1 double and triple agonist therapies. There's a lot of reason.

Dr. Clancy

It is pretty amazing. Pretty amazing. I have to give a lecture on the future of healthcare and I've got a whole section on peptides. It's just going to make a huge difference in certain areas. Right. So kind of in that same vein, what does the future look like for MASH recognition and early diagnosis and treatment? You both have got many more years to practice. What's it going to look like 5 or 10 years from now?

Dr. Tejedor Bravo

I think we're going to die of success, to be honest.

[laughter]

Dr. Gunderson

That would be great. I want that future. That's the future I want. But I think we'll have success when something changes so broadly across the population that fatty liver disease, MASH isn't so much a problem. So either wide access to medicines when people need them, that's a potential change, or just lots of bike trails, just lots of bike trails, and that's how we get it done. But it'll take a population level, like a widespread difference in how this works to really put a big dent in this. Marta had a conference about this last year. She invited world experts. It was great. It was a lot of fun. But in Iowa, roughly, if you do the

math, about 16% of the population will have important MASH, MASH with enough scar to make a difference in how long and how well you live. If there's 3 million and some people in Iowa, that's 500,000 people. There's five liver docs. There's no way we can do that. So it's gonna take a really big measure and it's gonna have to be implemented and exist for a while before we put a real dent in it.

Dr. Tejedor Bravo

Is a cultural thing. We need a cultural change about lifestyle. Yeah, I agree.

Dr. Clancy

We really do. We really do. You know, the concept of blue zones and diet and exercise as fully part of a culture. Yeah, absolutely. Well, you both have been outstanding in explaining this and the time has just flown by. As we close, what are some of the take-home points you'd like to leave with our listeners? And Marta, we'll start with you.

Dr. Tejedor Bravo

Yeah, so I want to make one more comment. I want to stress how important it is to stay away from alcohol if you have cardiometabolic risk factors. They don't just add their risk, they multiply each other. Okay, so alcohol multiplies the liver damage from cardiometabolic risk factors. And the more number of cardiometabolic risk factors, the more dangerous even small amounts of alcohol become. So this is something that needs to be stressed. So that's one. Then the second thing that I want to say, and then I'm going to pass it over to Alan to kind of give the take-home messages, but I can't finish this without inviting everyone to our conference, our liver conference in September. That's going to be on September 25th. That's a Friday. There is an online option. Last year we talked about MASH. This year we're going to talk about cirrhosis and all things advanced liver disease. There was the Bavino 8 conference held in Italy in April, and that's a five-yearly conference for portal hypertension. So we're bringing world experts again to kind of give a summary of what's new in the field. So I want to invite everyone. It's not too expensive. There is an online option and all the videos will be available for a month after the conference. We will leave the link at the bottom of the podcast. And also two days later on Sunday the 27th, we're hosting our Run for Your Liver, Run for Your Life 5K in Centennial Park to raise awareness on all things liver related on the importance of liver disease. So please, everyone is invited. Again, the link will be in the comments.

Dr. Clancy

Really good. Alan, take home points for our listeners.

Dr. Gunderson

Just a couple. Just a couple. So I think the first is that important MASH is pretty common. You shouldn't screen everybody. You should screen the right people. So it's going to be people who have cardiometabolic risk factors. The next is ALT isn't what tells you who's important. It's who's got scar. And in clinic, you can probably just do your FIB-4 to figure that out. The ones who look like they probably have important scar should send to a liver doctor or a gastroenterologist if they're performing that role. The rest, you can probably just keep screening, keep treating cardiometabolic risk factors, and you'll be doing a good job. Give the common good advice, and hopefully that works out well. So about diet, eating as well as they can, and then activity, exercise, generally, the more the better.

Dr. Clancy

Well, Dr. Tejedor Bravo and Dr. Gunderson, thank you so much for joining us today and for your great work in liver health and wellness and advancing the treatment options that we have for our patients.

[Upbeat theme music plays}

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