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Leveraging Metabolic-Driven Treatment Strategies to Target the Origins of NASH

Announcer:

Welcome to CME on ReachMD. This activity, titled “Strategies for Optimizing Liver Health in Diabetic Patients,” is provided by Clinical Care Options, LLC and is supported by an educational grant from Novo Nordisk, Incorporated. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

(Music fadeout)

Dr. Abdelmalek:

Thank you very much for joining us for the Clinical Care Options symposium, entitled “Leveraging Metabolic-Driven Treatment Strategies to Target the Origin of NASH.” I’d very much welcome you here. I also would like to thank our sponsor for this educational grant from Novo Nordisk, that without their support this program would not be possible. So my name is Manal Abdelmalek. I’m a Professor of Medicine and Director of Hepatobiliary Diseases at the Mayo Clinic in Rochester, and I have the distinct pleasure of having Dr. Rohit Loomba, also Professor of Medicine at UCSD and Director of Hepatology, as well as long-term colleague and friend, Dr. Brent Tetri. Dr. Tetri is Professor of Medicine, also Director of Hepatobiliary Diseases at St. Louis University. So, here are disclosures.

So, the objectives of tonight’s symposium are to:

1. Detail the pathophysiology shared by obesity, type 2 diabetes, dyslipidemia that really contributes to the pathogenesis of NAFLD and NASH;
2. To summarize key recommendations for the latest clinical care guidelines for NASH regarding the early therapeutic interventions aimed at improving the metabolic processes for our patients with NAFLD and NASH;
3. And to compare the efficacy and safety outcomes for NASH drugs in late-phase investigations and the potential implications on our management of patients with NASH.

So let’s move on to our quick survey. How many patients with NASH do you provide care for in a typical week? #1 – less than 10; #2 – 10-25; #3 – 26-50; #4 – 51-100; or greater than 100. Alright, let’s move on.

Next question: What is the most likely relationship between NASH and other metabolic disturbances? #1 – hyperlipidemia causes NASH; #2 – obesity causes NASH; #3 - type 2 diabetes causes NASH; #4 – obesity and type 2 diabetes cause NASH; and #5 – obesity, type 2 diabetes and NASH share underlying causes. Please vote. Alright. Excellent.

Next question. According to current guidelines, which class of medication should be considered for treating a patient with obesity, type 2 diabetes and coexisting NASH due to potential liver and cardiovascular benefits? #1 – DPP-4 inhibitors; #2 – GLP-1 receptor agonists; #3 – metformin; #4 – SGLT2 inhibitor. Please vote. Alright. GLP-1 receptor agonists.

In the phase 2 study, semaglutide was found to have which of the following outcomes in patients with NASH, when compared to placebo? #1 – resolution of NASH with improvement in fibrosis; #2 – resolution in NASH without improvement in fibrosis; #3 –

resolution of NASH but high rates of pruritis; or #4 – significant weight gain, greater than 5% but resolution of NASH. Please vote. Alright. Resolution of NASH without improvement in fibrosis. Okay.

So, I'm going to be starting us off here tonight, and we are going to give you a snapshot of NAFLD and NASH epidemiology. So clearly we've come to understand that the prevalence of NAFLD is increasing globally. A huge problem, as you could see, averaging around anywhere between 20 to as high as 30%, in some countries, specifically an enrichment of NAFLD in South America and even the Middle East. The highest country in the world – even Turkey, having a 31% prevalence of NAFLD. So this is a global problem. This is not a western problem, and of most concern with the rise in both obesity and type 2 diabetes. Studies suggest that the prevalence of NAFLD in patients with type 2 diabetes is nearly twice the prevalence of NAFLD in the general population, so amongst patients with type 2 diabetes, about 50% will have nonalcoholic fatty liver disease, and you could see it doubles nearly everywhere, in every country globally, in a cohort of patients with type 2 diabetes.

And certainly, we've come to recognize that this is a systemic disease. Nonalcoholic fatty liver disease is the hepatic manifestation of metabolic syndrome and our patients are enriched with other comorbidities such as type 2 diabetes, polycystic ovarian disease, obstructive sleep apnea, and yes, in keeping with complications and metabolic syndrome, there's increased risk for cardiovascular disease or even chronic liver disease, and the pathogenic processes for chronic – not only liver injury but tissue injury in other organ systems go hand in hand.

But at least for the liver, fibrosis – and really not fat, not inflammation, not ballooning – but fibrosis and fibrosis alone predicts overall mortality and liver disease mortality, and as you could see here, in almost a stage-dependent manner, so that patients with stage 3 and stage 4 bridging fibrosis or cirrhosis are at highest risk for overall mortality, as well as liver disease mortality. But we've also come to recognize this is a very dynamic disease. This is not a one-way track. It can flux, and it can flux with not only diet and exercise, but it can flux with intervention. But in accordance with the cohort of patients we care most about, it's those patients who have this intermediate progressive stage of nonalcoholic steatohepatitis, that's characterized not only by the presence of fat in liver, but also the presence of necroinflammation and ballooned hepatocytes, which are the primary predictor for fibrosis progression. And it's this cohort of patients that not only is at risk for progressing to fibrosis, but which the regulatory authorities, both in Europe and in the U.S. has defined as the at-risk cohort that really could be, and should be, targeted for pharmacologic therapies.

Now, given this dynamic process, we certainly have also come to recognize that it's not all about myself. There are unique epigenetic and genetic modifiers for this disease that define one's inherent risk for not only developing disease progression, but also for developing the clinically meaningful outcome of hepatic decompensation, liver cancer, all-cause morbidity and mortality. And this, in fact, is what regulatory authorities have deemed have to be improved with any pharmacological therapy, is a clinically meaningful outcome. And there are disparities in NAFLD outcomes. Patients who are of Hispanic ethnicity are at increased risk for NAFLD compared to whites, and black patients seem to be protected from NAFLD but are at increased risk for cirrhosis and hepatic decompensation. So clearly, one size and one pathogenic process doesn't fit all, and we're still trying to define all these nuances and variables.

But the factors contributing to health disparities may be more complex than just the biology of the disease itself. There's trust in the healthcare system. There's access to the healthcare system. There's socioeconomic status that may impact diet and exercise. And of course, there's the underdiagnosis of NAFLD and NASH at early stages that facilitate early intervention, and of course, unique genetic polymorphisms which will be discussed later by my colleagues that promote or protect against NAFLD, NASH or fibrosis progression.

So in the past year or two, certainly there has been a wide call to action for early intervention with patients with NAFLD and NASH, and a call for really integrated models of care. Multidisciplinary practices that are partnered relationships between a hepatologist and an endocrinologist or nutritionist.

And even a behavioral psychologist to address eating disorders or clinical pharmacologist to address the polypharmacy that our patients are on, or approaches to facilitate increased exercise. Now certainly, while we focus on liver disease within our practice, cardiovascular risk reduction is essential because this remains the primary clinical outcome our patients are more inclined to have complications of cardiovascular outcomes, potentially even before their liver-related outcomes. So managing dyslipidemia and diabetes and hypertension and smoking becomes important. And of course, screening and managing their comorbidities such as sleep apnea or PCOS, because eliminating metabolic stress may in fact also be helpful for our patients. There's a lot of focus on integrated weight loss initiatives that integrate pharmacotherapy, weight loss drugs, bariatric surgery, and partnering with an endoscopic or approaches to weight loss with advanced endoscopists, and even individualized pharmacologic approach for targeting prediabetes and diabetes, with an overall goal to improve glycemic control because that has been defined as a predictor for fibrosis progression as well. And we'll get into these therapeutics. And lastly, of course, prevention of strategies, for which our patients with advanced hepatic fibrosis and cirrhosis can even get into trouble, such as vaccination not only for COVID, but also for hepatitis A and B.

So with that being said, I'm going to turn this podium over to Dr. Brent Tetri, who's going to talk to us and walk us through NASH

pathogenesis.

Dr. Tetri:

Well that was a great, whirlwind tour. Thanks, Manal, that's awesome. Alright, pathogenesis. Let's talk about it, because it gives us a sense of where we've come in our understanding of this disease. And if you think about it, the primary issue is really the fat supply exceeds adipose tissue storage, and – but there's other factors. There's – certainly what we eat makes a difference – not the amount, but just the components, you know, high saturated fats and other issues are contributors. And then there are, of course, the genetic contributions and I'll touch a little bit on that. Rohit, here, has done great work in that area. But let's just talk a little bit about that right now – just very briefly. I'm way out of my field here. And we know this predisposing genetic polymorphisms listed here, and there's also some that have been recognized to be predictive. And there was this nice study, and – and I grab my glasses here, to see the fine print.

This is a study with UK Biobank, and what they did is they looked at a European subset of the UK Biobank, and they sorted out a score they called the GEMS score, and I've defined it down here in the fine print. It's a function of the at-risk mutations – the 3 major at-risk mutations – plus sex, diabetes, age, HDL cholesterol, albumin and platelet count. You put all that into some fancy equation and you calculate this GEMS score.

And you can see that the higher the score, the higher the risk of liver-related events, and this was tested in a cohort of 549 Italians from Palermo with a median follow-up of about 6 years. So that tracks really nicely, and again, this is a mix of the genetics and sort of the standard risks that we know about.

Here is another, newer study I thought was really pretty cool – very informative. Again, the US Biobank, looking at a much larger cohort with a median follow-up of 9 years, and they looked at the risk of liver-related events based on a polygenic risk score – hepatic fat content is what all that stands for. And they put it into quartiles – this risk score. So, the low number is really low risk – low risk of genetic risk of NASH, and the high number is a high risk of genetic – genetic risk of NASH. And you can see in the folks with diabetes, it goes up. So bad genetics – bad genes plus diabetes, much higher hazard ratio from liver-related events. Same thing for obesity – not quite as striking, but pretty strong.

But here's what really interesting to me. When I looked at this graph, it's totally flat, so no metabolic risk factors whatsoever. You got bad genes, you're not going to have liver-related events, which is just fascinating. We see the lean NAFLD patients, but they'll often have metabolic risk factors, who have really liver disease or NAFLD. So you take away all the metabolic risk factors – the diabetes, hypertension, hypertriglyceridemia – and you can have a high genetic risk score, and no NAFLD events over time. I thought that was really interesting.

So going back to my little diagram here, we'll just focus now on the fat supply and the storage capacity related to NAFLD. So, in the literature, there's a lot of epidemiologic studies that tried to link NAFLD as a cause of insulin resistance, and these papers were never very good at explaining this mechanistically. And it's really hard with epidemiologic studies to show causation. But there's quite a few papers out there that says NAFLD – you have fat in your liver, it makes you insulin resistant. And it – that's not the case. So I'll try to do it justice here, but beyond that there's also literature that says NAFLD causes hypertension, it causes hyperuricemia, dyslipidemia, hyperglycemia, type 2 diabetes, macrovascular disease. So I put 2 big question marks over there. Again, epidemiology studies. Not that epidemiology studies are bad thing. They're good. Very informative.

But let's just focus on this connection here, and switch the order around a little bit. I just wanted to say, to emphasize this point, that the data shows correlations not causations. And I just give a couple examples here – this polymorphisms of the ApoB gene, that block fat from getting out of the liver, and also PNPLA3, that are associated with fatty liver, but not insulin resistance.

And Jerry, on his slides today, had a whole bunch of other examples of things that cause fatty liver, that don't cause insulin resistance, so I think over time, we've really been able to disentangle that, and show that that's not an issue. So we flip it around the way we think about it now, and we really think about the insulin resistance, increasing circulating fatty acids, and a lot of other things. This is incredibly overly simplistic, as an underlying cause of all these consequences. So that's the underlying metabolic disease.

Now historically, in terms of treatment, we know that we've, you know, come up with, you know, pretty good therapy for all of these aspects – the hypertension, the elevated uric acid, the lipids, the hyperglycemia, diabetes and the macrovascular disease. So we've been pecking away at this, and of course in NAFLD, or I should say NASH – it's what we really worry about, it's been a tough one to crack. So it makes you wonder if the ideal metabolic – or ideal therapy is actually metabolic therapy that addresses the underlying cause, and so could potentially treat all of these aspects.

I'll get back, just to say a little bit about the fat supply. I sort of glossed over that to begin with. I think this is really important, because to me, this is – really gets to the crux of where metabolic disease comes from. You know, we have fat stores and we try to stuff fat into

them, and at some point they say no more, or they get stressed, and they have an inflammatory response. That can happen at different BMIs. I think – this is hypothetical, but it's one interpretation of the literature. So, in patients with lipodystrophy, they don't have very much fat stored, so you have very limited ability to store fat, and you can get metabolic disease with a relatively low BMI because you're not safely storing it away – typically, fat in the buttocks and the legs, and not the visceral fat. And then on the flip side, of course, is we see some individuals who can store fat very well, without metabolic problems. They have a very high BMI.

And just a word about what goes on in the fat. You know, once thought to be this inner tissue, it's just storage. It's incredible – this Roncon JCI paper here, discussed through a few of the things. You know, fat puts out free fatty acids, and that's what I focused on, and here's all the other things it can send out that cause insulin resistance. It sends out cytokines that can cause inflammation, and contribute further to insulin resistance. Sends out some lipid metabolites that have effects as well, and not to mention, the micro-RNAs that affect gene expression everywhere. Various proteins, and angiotensinogen which may explain the hypertension, and then the other peptides – adiponectin is a big one. It actually drops down. Adiponectin release, in my mind, is a sign of healthy adipose tissue. When it gets stressed, it really drops down because adiponectin has a lot of beneficial effects.

You see FGF21 on here. You hear about the trials that – a whole bunch of different FGF21 drugs for NASH. This FGF21, coming from adipose tissues, really just acts locally. The FGF that acts systemically actually comes from the liver, but it has a lot of local effects there. So clearly, adipose tissue – a very metabolically active tissue, and we stress it has a lot of effects on metabolism.

So wrote about the lean patients. I was asked to, you know, to comment on whether it's different or not, so I just thought I'd highlight this one study, look at NHANES data, and this is adults with fatty liver disease by ultrasound, and also metabolic disease. And I though this is – this looks really complicated, so let me walk you through it. So this is the NHANES patients – 9,341 NHANES patients. In the first ring out, is the non-NAFLD – about two thirds. That's a third of patients with NAFLD. Just what Manal was just talking about. That's from NHANES, and then if you look at those with a normal BMI with NAFLD, then you start to get into the lean NAFLD. Some of them had – most of them had lean waist circumference. A few were obese by waist circumference, but basically this is your lean NAFLD. But then you look out here, and what do they have for metabolic abnormalities? Most of them, or two-thirds of them, are metabolically abnormal. You know, hypertension, hyperlipidemia, and all that. So, even though they are lean, they have a lot of metabolic things going on that contribute, and the metabolically normal probably have high genetic loading for fat buildup in the liver. So I thought that was a – really nice data.

So, bottom line is metabolic components are common in our – the lean patients, but it's a reminder too, and Rohit's really written beautifully on this, that we should look for other causes for fatty liver, and keep in mind Wilson's. I send a lot of 24-hour urines. You know, the ceruloplasmin is like 20 or something, and 22 – I have yet to find one, but I always look. ApoB mutations – something to think about. The tipoff here is low serum lipids – cholesterol or LDL cholesterol, whatever you want to look at, they're all low. You know, I – so if I have a patient, certainly with a cholesterol under 100, and they have fatty liver, I'm thinking hypobetalipoproteinemia. And then, lysosomal acid, lipase deficiency has been thrown out as a possible cause as well. Uh, celiac disease, hypothyroidism, of course covert alcohol and drugs. Just things we have to keep in mind.

So this relationship between the metabolic components and NASH. I've obviously talked a little bit about that. Epidemiologic data suggests that bidirectional relationship. I'm going to – we're going to have a debate here with Manat, and see. That's okay, it's all good. Treating the type 2 diabetes, at least with traditional therapies, with insulin sulfonylureas does not have a clear benefit in NASH.

So it's really, in my mind, still unclear what the role of glycemic control has in controlling NASH. You obviously want to do it for vascular disease and all the other known – known bad things about diabetes. And in treating NASH, we'll never have an answer to this question. Can it independently benefit diabetes? Just because all of our treatments now are hitting both, or hitting the underlying pathophysiology. So if we had a pure NASH drug, maybe we'll – it's hard to know. Some of the drugs that come out might be there, but I think it's going to be really hard to disentangle that relationship.

As I said, the mechanistic data really tells us – and as you identified on the quiz, metabolic disease underlies both of these. So what about the hyperlipidemia? The simple point I wanted to make here is the – in the fasting state, it's when our patients get their lipids drawn, right? The lipids come out of the liver. Those are lipids from the liver, not going to the liver. There's this beautiful picture of a VLDL molecule here, and the way I show it here is you have all these substrates – free fatty acids, glucose, especially fructose – going into the liver. The liver processes it, turns it into triglyceride, packages it up with an ApoB-100 protein, and puts it out in the serum as a particle of VLDL. Bunch of cholesterol in there as well. And it gets delipidated peripherally and some of it – a small fraction – comes back as intermediate and low density lipoproteins and chylomicron remnants. Stable isotope studies tell us that's a pretty small fraction of the fat going in through the liver, so it's really created in the liver by the substrates – the triglyceride is. So yeah, it doesn't go backwards. So it's – the high VLDL doesn't go back to the liver, by and large.

So just to wrap things up, in terms of the summary, the epidemiologic data suggests bidirectional relationship. The mechanistic data

says this underlying metabolic disease, and now we have genetic contributions adding to that. And therapies that seem to under – address the underlying metabolic disease may be the best. And I think that's what we're starting to see in our treatment trials, because the early treatment trials – you know, pharma loved the inflammatory pathways, the fibrosis pathways, and they just haven't worked out well. And the metaphor I have for that is it's like you're flying down the freeway in the car. If you want to stop your car, and you don't take your foot off the gas and you have crappy brakes, you know, you've got to put your foot on the brake pedal but if you've still got the gas pedal down, you're going to keep going. The gas pedal is the metabolic driver, okay.

So now we have the therapies that take the foot off the gas pedal – the metabolic driver. And we're seeing gradual slowing of the car – gradual resolution of NASH. Of course, the future may hold that we'll do dual therapy, at least temporarily, and try to put the brake on, too.

Do some directly additive anti-NASH therapy – anti-inflammatory, anti-fibrotic – while we treat with a metabolic drug. But that's in the future. That's totally hypothetical. So thank you for your attention. That's a brief survey, and I look forward to Rohit.

Dr. Abdelmalek:

Thank you, Brent. And yes, as a lead to introduce the vital information that Rohit is going to share with you, kind of like to walk us through the latest guidelines. The AGA 2021 Care Pathway for NAFLD and NASH, and the ACE 2022 guidelines.

So we have all come to understand clearly, the limitations, the imperfect nature of what we've historically called the gold standard, right? The liver biopsy – it's invasive, it's painful, it's expensive. It could potentially be associated, although rarely, with morbidity and mortality and it's fraught, as we've seen even in our clinical trials, with sampling variability, and interpretation variability, and observer variability. And it requires experts to interpret and with a highly prevalent disease such as this, we just don't have that global level of expertise, and it's just impractical for population-based screening. So, we've been very fortunate to see the emergence of noninvasive tests, in the – these past several years, and I would like to just kind of put them into three categories for you. There are clinical and laboratory-based noninvasive tests. There's simple scores such as the FIB-4 score, the FIB-4 index, the NAFLD fibrosis score, the AST to platelet ratio- the APRI score. And there are also proprietary tests, such as the ALF score which could be ordered, the NIS4, all blood-based biomarkers – the FibroSURE, the HEP score. And of course, imaging biomarkers – Rohit is also an expert in and will be sharing his expertise with you – both Fibroscan (transient elastography), MRE, T1-weighted imaging, MRI-PDFF for quantitation of fat, and even combination biomarkers, such as combining Fibroscan with an AST score – the FAST score.

So the cli – the AGA, the American Gastroenterology Association, recently published clinical care pathways. Now this is a modification of that pathway, and I thank Rohit for actually making these modifications, and being able to speak to it. But – and I'm going to ask him to comment here because I'm going to briefly pass this podium on to him. As you could see here, there is initially the identification of patients at risk, as Brent has shared with you. Two or more risk factors in metabolic syndrome, patients with type 2 diabetes or steatosis on an imaging study, and you couple that with the appropriate history and laboratory tests. The exclusion of alcohol, the assessment of what liver function and liver aminotransferases is, and as clinicians the next job is risk stratification. Who do we care about? Who do we not care about? Because in, you know, 30% prevalence of this disease, we have to empower ourselves with the right tools for appropriate risk stratification. So Rohit, you want to take it over from here and tell us how to do this?

Dr. Tetri:

Yeah, thank you, Manal and thanks Brent. So, we call this modified. So how is it modified? So, I've added 2 additional parameters that are not in the AGA document, and those are related to MR elastography cut point and the ELF – enhanced liver fibrosis panel cut point. If you can see here, you're looking for a patient who's got metabolic risk factors. The most important one would be type 2 diabetes, typically a patient 50 or older, and then you have detailed history on them, about, you know, what they drink, what medications they might be on. You've got complete blood count and complete metabolic profile. Based upon that, you can come up with a FIB-4 assessment. FIB-4, if it is 1.3 or higher, that's a patient who needs to be, you know, further assessed with a second test. The FIB-4 is already 2.67 or higher, these patients have elevated ALT, AST – typically over a very long period of time, and they should probably come and see a hepatologist regardless. Because you start looking at about 50% of these patients may have severe liver problems. Some of them may even have cirrhosis. Those who are in the middle need further risk stratification.

And, we've added additional parameters for MR elastography. One cut point that's actually very stable is here. If you see a FibroScan of 12 or higher, or MR elastography of 3.63 or higher, or an ELF of 9.8 or higher, these patients are looking at somewhere between 80-90% or more, likely to having stage 3 or stage 4 fibrosis. So this is really helpful. And then, once you are in the intermediate risk, here again, these patients might need additional assessment. Some of them might be getting a liver biopsy. Those that are lower risk could potentially be followed every 2-3 years, based upon some of the data that we have, and might need a repeat assessment. If the FIB-4 is going up, you probably may want to bring them in earlier.

Dr. Abdelmalek:

That's a secure pathway.

Dr. Tetri:

Sure.

Dr. Abdelmalek:

You know, it's really easy for providers when we're on one extreme of the spectrum or the other. How often are you experiencing the initial algorithm following an indeterminate range, and what are your next steps?

Dr. Tetri:

Yeah, I think I would say even in my clinic, you would say at least 50% will be in the lower range. So you probably would be able to exclude those that are a FIB-4 of 1.3 or below.

Once you are looking at those that are above, I think if I'm de novo seeing patients for the first time, a FIB-4 of 2.67 or 3, typically that alcohol history is very useful, and routinely doing PES testing also in my patient. That's another biomarker for recent alcohol use quantification that helps. And – but, I would say, you know, 30 or 40% would be in the intermediate range, up to 50%, who would need further assessment. And typically, they are going to get, you know, advanced assessment – maybe a FibroScan, but majority of them get an MR elastography at UCSD. These are among – if you were to pick just one, I – we, you know, Manal showed you 3 different clinical prediction rules. If you just need to pick one, you can just choose FIB-4. It's easy to use, and easily appliable, so in Epic – most places that have Epic as your EMR, are able to develop something called DOD FIB-4. We are working on that, and once you have that – because it's easier to incorporate that in your note. And so, these type of things may become easier.

NAFLD fibrosis score is also fine. You may not be able to really apply that in a practice because it has much greater number of components. This test has a good negative predictive value, but one thing you need to remember is if the metabolic risk goes up, you may have to push the lower limit cut point further down. So, what I mean by that, if you were looking at a diabetic who's got multiple metabolic risk factor, then even if the FIB-4 is slightly lower – say 1 – that patient probably has NASH, and may have significant fibrosis.

This is a calculator, and basically, FIB-4 can be calculated using age, platelet count, AST and ALT. And you can plug that in and, you know, if you go to this website you can actually calculate. Pretty easy to do in your clinic. Doesn't take long, and you can do it in front of the patient.

We discussed that, you know, you are basically ruling out, or reduced likelihood, of stage 3 or stage 4 fibrosis. Doesn't mean that this patient doesn't have NASH. Doesn't mean this patient doesn't have stage 1 fibrosis, or may even have stage 2 fibrosis. Thinking about that is, I think, important, but you don't miss those things. Now, those that are here – this test doesn't have a very high positive predictive value, but 50% of these patients may have significant disease, so it's helpful. In the intermediate range, we basically apply another test, and those tests could be here or here.

Now, what about enhanced liver fibrosis panel? I told you about 9.8 or higher. Why is that important? This study – they had patients who had bridging fibrosis, so stage 3 fibrosis at baseline. They followed them over 2-3 years, and what they found was those who had an ELF of 9.8 or higher had significantly greater progression to cirrhosis.

If the patients had lower ELF, they did not progress to cirrhosis compared to those who had higher. So this is helpful if you had a patient with stage 3 fibrosis. If their ELF was higher, you would be seeing that patient much more often. Probably that patient should be included into a clinical trial – your event rate will be faster. So we're utilizing these type of data in our clinical trial to assess how many outcomes we are likely to get, based upon what the baseline biomarker status is for the patient.

Now if the patient has cirrhosis, can we predict which patient with cirrhosis, who's totally compensated today, will develop hepatic decompensation over the next 2-3 years? Again, an ELF of 11.3 or higher may be predictive of future decompensation over 2-3 years. And that's another idea that even in cirrhotics who are well-compensated, we have tools to determine future risk for progression.

What about imaging tests? And these are some of those that we have listed. We'll focus mainly on transient elastography and then MR elastography. This is vibration control transient elastography, available on the FibroScan machine. This is routinely available in a hepatologist clinic, but it may not be available in a primary care or an endocrine clinic. But understanding these results would be important, and typically we have patients come in fasting, at least 3-4 hours, when they come for this test. Why? When we eat, you have greater blood supply going to the liver and that may interfere with your liver stiffness assessments.

This is data from France from Jerome Boursier's group, looking at baseline liver stiffness and long-term survival in patients with NAFLD.

So greater the liver stiffness, worse the survival. And that's really true because these patients really have cirrhosis and decompensated cirrhosis. That's what we are picking, with advanced liver stiffness.

This is a study done at UCSD, where we had patients with biopsy-proven NAFLD, and who underwent contemporaneous MR elastography. And we found that a cut point of 3.63 kilopascal had a diagnostic accuracy of about 0.92 for detection of stage 3 and stage 4 fibrosis. These data have now been widely replicated and validated, and this is now going to be, in the future, NAFLD practice guidelines that might be coming in the next couple days.

Now how best can we identify a patient who needs to be treated without a liver biopsy? Can we do that today? The answer is yes, we can, and I'll give you parameters around those measures. One test is fast, as previously alluded to.

And where we include CAP, which is controlled attenuation parameter, it's a test on FibroScan machine that tells you how much fat you may have in the liver, the liver stiffness on VCTE, and serum AST on labs. MAST includes MRI proton density fat fraction to – for liver fat quantification, MRE and AST – so similar to it, replacing with MR variables. If you have simply somebody who is a FIB-4 of 1.6, then you do an MR elastography, and if it is 3.3 kilopascal or higher, that patient has advanced fibrosis. So we're picking people who have at-risk NASH, which is NASH with stage 2 fibrosis or higher.

What about FAST? So, FAST – if it is 0.67 or higher, it is associated with higher odds of having higher likelihood of having at-risk NASH, which is NASH with stage 2 fibrosis, or higher. If it is 0.35 or below, this patient is less likely to have it. The main problem of this test is that the positive predictive value is low, which means even if you are 0.67 or higher, your positive predictive value is ranging between 0.33 and 0.83. So, less helpful but it still helps with enrichment into a study or a trial. So can be a better test, where when they're positive, we are absolutely certain that this patient has a disease that we are interested in. The answer is yes.

And so here's another test that we developed at UCSD, and then validated that in Japan, and we wanted a high positive predictive value. As a clinician, we wanted to ask when it is positive, we know exactly what to do. Can you imagine – you did a COVID test, came back positive, but you weren't sure if this patient really has COVID? That would be a bad test to have. Here, you're talking about also a major problem, which is, you know, whether you need to be treated or not. And you want a test that gives you a pretty good certainty to then go on a treatment, that you may be placed lifelong. So, this gives you a positive predictive value about 97%, and in validation cohort in Japan, geographically and ethically distinct cohort, a 91% positive predictive value. And the key factor that has the greatest effect on this model is, of course, MR elastography. So why even put the FIB-4? Well, FIB-4 helps because if it is below 1.6, you could probably save a lot of cost, by doing MR elastography in only those that are still in the intermediate category, but above those. So this way you could probably reduce cost and still capture the patients who need to be treated. None of these tests are ideal, because you're going to still miss patients who may not qualify this criteria. They may need further assessment.

This is one example of how you could actually use this assessment, in terms of rule out and rule in, and this can probably help you assess patients who have stage 2-4 fibrosis, with a pretty high positive predictive value. Here, we compared Method versus FAST in a head-to-head comparison, where Method had a higher diagnostic accuracy compared to FAST.

And then, when MAST score came out, we then compared head-to-head between Method, FAST and MAST, where you can show that Method had the highest diagnostic accuracy for detection of stage 2 fibrosis or higher.

And this was also true for addressed NASH. Now these are some of the common imaging tests for hepatic fibrosis. Of course, FibroScan is most reliable, and in terms of ruling out advanced fibrosis. This test is useful because it's available right in the clinic. MR elastography is much more specific, but of course is more expensive, and may not be routinely available. So I'm not recommending that you do MR exams on everybody, but it's just important to understand when you get a result back, what that actually means for a particular patient.

Shear wave elastography is also being utilized on ultrasound machines, and those results are typically similar to what we see on FibroScan. What about disease progression? So, when the FibroScan – if you start seeing an increase, so today suppose the FibroScan was 15 kilopascal, patient comes back 2 years later and it's 20 kilopascal. That's a 25 or 30% increase in liver stiffness. There is some data that that is associated with worsening of disease. We also know that patients who have bridging fibrosis who have liver stiffness and FibroScan of 16.6 kilopascal, have high risk for progression to cirrhosis. So this is similar to what I showed you on ELF. So now you have data on ELF, you have data on FibroScan, so how you can risk stratify a patient with bridging fibrosis. What about patient with cirrhosis? Yes, if liver stiffness on VCTE was 31 kilopascal, this patient has high risk for hepatic decompensation. Similarly, on MR elastography, a 15-19% increase is associated with worsening of disease. And about 15-20% reduction may be associated with improvement, although we are soft on data on that. Further studies are needed. So I'll pass it on to Manal for discussing this patient's patient journey.

Dr. Abdelmalek:

So, let's talk through a case here. A real case. So, Marianne, a 43-year-old Hispanic woman, single mother of a teenager, eats on the run, has little time. She is working full time and raising kids, and the doctors have been following her liver enzymes for years. Mildly elevated, she has been reassured that they are "nothing to worry about" and just to diet and exercise. So, she's developed in the interim, over all these years of being followed, borderline high blood pressure, and early impairments of glycemic control, but doesn't really identify herself as being diabetic. Her father was recently diagnosed with cirrhosis, and since her father's diagnosis, of course, she's become more anxious, and now she's starting to pay attention. And her BMI is 28, her labs – again, nothing to speak of – AST of 45, ALT of 50, hemoglobin A1C 6.8%, LDL cholesterol 230, HDL 23, triglycerides of 350, and her platelet count's 180. And her FIB-4 is 1.52. So, what should we do next?

Dr. Tetri:

Yeah, so this patient, as you see, she's got a – first of all – family history of cirrhosis, so this is a big risk factor for having advanced fibrosis, and the risk would be about 15%, although the risk is higher in men than in women, but she's got a first-degree relative with cirrhosis, so that puts her at 15% right away. She's Hispanic, which also increases the risk because of PNPLA3 homozygosity. On top of it, there is overweight, and elevated triglyceride levels. And platelet are on the lower side and hemoglobin A1C is 6.8, so diabetes would put her risk again about 14% for advanced fibrosis. So yeah, this patient is at pretty high risk, for having advanced fibrosis or at least stage 2 fibrosis.

Dr. Abdelmalek:

So Brent, let me turn to you and ask you. I mean, yeah, your reference lab in your – in your hospital probably goes to an upper limits along those AST of 45 or 50. What are your thoughts about that, not to mention her – her laboratory parameters and…

Dr. Tetri:

That's a good point. I'm not happy with these numbers at all. You know, and we studied reference laboratories, and we did a survey and asked the reference laboratories if they exclude people with obesity from the reference population, and none of the laboratories did so I think what we're doing, is we're seeing a lot of patients with fatty liver disease in the reference range. And those of us that have been doing this for a long time have seen this reference range go up, up, up, up over the decades, and I think that's what's going on. And I've studied the study out of Italy, suggested that normal, healthy ALT for a woman should be below 19, for a man below 29. So, I mean, these are very elevated. And I have this discussion all the time with my patients. I just tell them to ignore what the lab says. It's not a healthy range.

Dr. Abdelmalek:

Any thoughts about those lipids? Is that already raising a flag in your mind, about anything else we should be considering or approach to management? And I guess we could get in that…

Dr. Tetri:

I think it's just – it's all consistent with metabolic risk factors. You know, they – it all just adds up in my mind, and this is a patient – well, we'll talk about what we're going to do.

Dr. Abdelmalek:

Yeah. So this is a patient, if I were to see her in my clinic, I mean, you – you're going to size everybody up for their own individual risks, right? And as Rohit alluded to, her father's risk, having cirrhosis, is probably a flag right then and there.

But it – to each person his own, and individualized and personalized care is important, so you know, as patients come in, identifying their family history, their social history and their, you know, individualized risk for recent weight gain, longstanding obesity, what they do, what they diet – clearly this is a very busy mom. She doesn't have time, she's raising a teenager, she's eating on the run. So you already can potentially target diet as one modifiable intervention to tackle, and help put those building blocks in for her. Now there are other dietary cofactors that we didn't drill into with her – even modest to social alcohol use, and what is that standard for individual patients? Can it be modified? If patients are smokers, that could be a risk factor, not only for NASH, but fibrosis progression. And of course, you know, anybody eating on the run is probably getting not only a diet that's enriched with hydrogenated fats, but also very enriched with complex sugars and fructose, and I will drill down and talk to my patients about that, and try and change that and encourage them, actually, to drink more coffee. So, coffee is good. (Laughs) The more coffee, the more the better. But, and then of course, in the absence of FDA-approved therapies, early identify – early identification of each and every one of the metabolic variables that we're seeing, even in her laboratory parameters – the impaired glycemic control, the dyslipidemia, the high LDL – is a potential early intervention strategy for targeting prediabetes and diabetes, with the armamentarium of therapies we have at our disposal, or the

dyslipidemia consideration of lipid-lowering therapies, or statins. Working on modification of the hyper – hypertension, which we'll talk about, and of course, addressing other variables which may be contributing to her metabolic syndrome, like sleep apnea.

So, Rohit, you kind of want to talk to us about the recent guidelines and what your thoughts are about the ACE guidelines that are coming out?

Dr. Loomba:

Yeah, I think this is just going back to the cartoon I showed you, in a different matter. These guidelines are telling you you've got metabolic risk factors, and those are associated with NAFLD, and you want to start thinking about not only liver disease, but of course, prevention of cardiovascular disease, because #1 cause of mortality in our patients with NASH is cardiovascular disease. And the way to think about cirrhosis and/or liver disease related morbidity and mortality prevention, is to think about fibrosis risk stratification, that we already discussed, in terms of low risk, intermediate or high risk.

Quickly, that that ACE is the American Association for Clinical Endocrinologists, so this is really geared towards the diabetologists managing their patients with diabetes with guidelines that…

Dr. Abdelmalek:

Yeah, exactly. And so the – so they're very, you know, focused on what really is the underroots of – of this disorder. The identifying early, the metabolic risk factors, both in history and exam, is of course, you know, shouldn't fail to exclude other factors, and – and miss other diagnoses of chronic liver disease. And so, excluding secondary causes of hepatic steatosis, whether it's alcohol or concomitant medications, and really striving to improve overall morbidity and mortality for targeting prevention of cardiovascular disease, and then of course, prevention of progressive – progression of chronic liver disease, and identifying those, as Dr. Loomba has already alluded to, at highest risk of stage 2 or higher, and managing these comorbidities effectively.

So, in these care guidelines – and this comes from the American Association of Endocrinology – they have outlined very detailed, potentially plans for various elements of these metabolic complications we can address. Weight management, for example, and all across the entire foundation of this disease, whether anybody is low risk, intermediate risk or high risk, you know, our strive is to decrease the sedentary time and increase daily movement, irrespective of whether it's aerobic or resistance, and targeting diet in an energy-efficient manner so that we could potentially even associate the dietary interventions with effective, sustained weight loss strategies that aren't just dieting. It's really a lifelong dietary modification. But beyond that, I mean, we've kind of changed our thoughts about how much alcohol is too much alcohol. Give me your thoughts on that.

Dr. Tetri:

Let's just put a plug in for our sister association, the AGA, which published their weight loss guidelines.

Dr. Abdelmalek:

That's correct. Yes.

Dr. Tetri:

So look for those. It's similar. And it really comes out strongly in favor of pharmacotherapy with some of the new agents that are out there now, so be aware of that. As far as alcohol, you know, I think that we went through a period 10 years ago, where we were a little more lenient, and now we're saying anybody who has any significant fibrosis, they really should abstain. And it's tough – you know, you have the patient who says, "Can I just have a good glass of wine once a week?" And I'm like, eh, probably best not to.

Dr. Abdelmalek:

Yeah. Especially for anybody with fibrosis already.

Dr. Tetri:

Correct.

Dr. Abdelmalek:

I advise against abstinence as well. And you could see here that the algorithms for weight loss tools that are at disposal increases the disease severity increase – certainly everybody potentially needs behavioral modification – but as you can see for intermediate and high risk cohorts, that the greater intensity of weight loss we may need to achieve opens up avenues for more specialized obesity management, multidisciplinary teams, consideration of structured programs, or even pharmacotherapy or bariatric surgery. So Rohit,

what are your thoughts about more advanced endoscopic or bariatric approaches?

Dr. Loomba:

I think we – we have to start thinking about whether these are happening in hepatologists' clinic or they're happening in the primary care setting. You know, one of the things you don't want any confusion as to – what is the intent of whatever therapy or intervention we are doing. So, I think if somebody had a significant fibrosis, I'm not sure if, you know, there is enough data to say that for their fibrosis I would do a bariatric surgery. Definitely, if they've got, you know, obstructive sleep apnea, they have type 2 diabetes, hypertension, cardiometabolic risk – for those, and improving or reducing those risks, I think it would be beneficial. So I'll frame it around that, and that's how I think we've framed our question.

Dr. Tetri:

I'm sorry – another plug for the Bariatric Surgery Society. Had combined society recommendations just published, that now includes from their perspective NAFLD as one of the metabolic comorbidities that justifies surgery. Whether the insurance – insurance companies are onboard, we'll see.

Dr. Abdelmalek:

It is – it is one step, because now it is included in the surgical guidelines as an indication for bariatric surgery. You know, from a medical standpoint, how often are you using weight loss agents in your patients, and – and how do you target that?

Dr. Tetri:

Yeah, they've got to come around to that. You know, I'm so old-school, but now that we have such good drugs out there, I think the GLP-1s, and now we have tirzepatide that hits the glucagon receptor as well. The data is just so impressive, you know, and we have the GI side effects of lower dose, and you ramp up slowly. So I'm going to come around, you know.

Dr. Abdelmalek:

Yeah. And the ACE guidelines do, you know, say, you know, weight loss pharmacotherapies for those that can't achieve it necessarily with diet and exercise alone, is indicated, and GLP-1 certainly is a class. It's been very effective in helping not only with some of the under – drivers of the metabolic syndrome and diabe – glycemic control and diabetes as indication for the use, but also a weight loss agent. And as Rohit talked about, there certainly is a role for bariatric surgery, and you know, when my patients have, you know significant indications – very advanced metabolic complications at a young age, and bariatric surgery could potentially be life-saving for some of our patients – it certainly is something I do engage with and even discuss.

Dr. Tetri:

My approach is to let the patient bring it up, because I – where I've seen the biggest disasters with bariatric surgery is when patients get talked into it.

Dr. Abdelmalek:

Agreed. Now.

Dr. Tetri:

Yeah, if they're onboard and they – they understand it, and they're willing to do it, then great, and I support it. I said the data – as far as your liver, it'll be great. Yeah.

Dr. Abdelmalek:

So, diabetes management of our patients. Now, we have an armamentarium of drugs, and we'll talk about that, both in emerging therapies as well as for co-management of diabetes. So, Rohit, how do you approach your – I mean, our patient is, in fact, by definition, diabetic?

Dr. Loomba:

Yeah. I think in terms of diabetes management, things are really changed for the good in the last, I would say, 5-7 years. Back in the days, you know, a patient comes in, we will typically go ground up with metformin, and then, you know, add DPP-4. At this time, if somebody was obese and had type 2 diabetes, I think it's very reasonable to think about a GLP-1 analogs. You could still use metformin, but typically you're going to get benefit above 0.5-1% in hemoglobin A1C reduction. And after that, I think you will stabilize. So you know, thinking about GLP-1 analogs in that setting would be very helpful, and frankly, it wasn't the case 2 years ago, but now I

see many of my patients with type 2 diabetes are getting started, and within the last 6 months, I've seen a lot more uptake, in terms of acceptance from the insurance for approval as well.

Dr. Abdelmalek:

And the guidelines speak to the fact that our primary goal should be to optimize glycemic control. Even with driving down glycemia, if you can get it by diet and exercise, a Mediterranean-style diet, more avoidance of carbohydrates that are – induce higher levels of insulin secretion, maybe higher protein diets. But the foundation of a lower glycemic index diet, to drive – maybe in combination with pharmacotherapy – the glycosylated hemoglobin to under 6.5 is what these guidances would advocate for, because there is data that not only the higher levels of glycemia could potentially be associated with fibrosis, but certainly many of the other comorbid conditions our patients struggle with, which do ultimately result in increased morbidity and mortality. We're seeing a lot of data at this meeting about chronic kidney disease in our patients, as well as their cardiovascular outcomes as well.

Dr. Tetri:

I think a very practical question is, what do you do with a patient referred to you, or you're following for a long time, and is still on a sulfonylurea? I mean, I – granted, they're dirt cheap, and sometimes for insurance reasons that's all they've been able to be on, but I – I'm sending a lot of letters back saying, "Look at the ACE guidelines," and you know, do everything we can to get this patient off.

Dr. Abdelmalek:

Yeah, I – I send them – I send them from their primary care physicians to a diabetologist, and I really advocate for consideration of SGLT-2, and/or GLP-1 receptor agonists. I mean, because those have also been associated with reduction of cardiovascular risk. So I really do partner with an endocrinologist who can also advocate for my patients and their needs.

So, hypertension co-management. This is an interesting area. Do you think this really matters, Brent?

Dr. Tetri:

Of course it does. You know, as you were quick to point out, you know, cardiovascular death is the number one reason our fatty liver disease patients die, so, you know, they've got to manage their hypertension. And you know, it's very common that I see patients' blood pressures way up when they're into clinic, and you never know – white coat syndrome, they just drove in through traffic, whatever – so I'm always telling patients, go home, take your blood pressure regularly, tell your primary what the numbers are.

Dr. Abdelmalek:

I was very intrigued at the guidelines, that actually wrote as first-line therapy, consideration of an ACE inhibitor and ARB.

Now, there's some very intriguing, basic science data in this realm, as it relates to nonalcoholic steatohepatitis, but I also think they have implications on other clinical outcomes as well.

Dr. Tetri:

Yeah, we'd sure hope that it would have an anti-NASH effect and anti-fibrotic effect, but you know, the trial that was in of losartan in children, unfortunately was a negative trial for fatty liver disease, so…

Dr. Abdelmalek:

Yeah, and it's only currently animal data that suggests that maybe that they have an anti-NASH and anti-fibrotic effect, but I think, first and foremost, if we…

Dr. Tetri:

Yeah, hypertensive pet mouse could be great.

Dr. Abdelmalek:

Yeah, yeah. (laughs) But if we can decrease, of course, their – these, and these agents also have benefit from a cardiovascular outcome, and – and also a renal outcome. So, don't be intimidated by treating all their medical complications very aggressively. What are your thoughts on this dyslipidemia and the role of statins, Rohit?

Dr. Loomba:

I think out of all the things that we've discussed, this is something that you could make a difference, and I always take care of that, and so if a patient is not on statin, first question is why the patient is not on statin. And I think that's something that I pay good attention to,

and 80% of my patients are on a statin or need to be on a statin. So that's something that we should definitely consider strongly.

Dr. Abdelmalek:

I agree. I'll – I'll – I am a strong advocate for use of statins in our patients. There is really no reason not to utilize a statin, and increase to tolerances…

Dr. Tetri:

Yeah, it's very well-supported in guideline statements that you know, underlying liver disease is not a contraindication of statin use.

Dr. Abdelmalek:

That's absolutely right, and our patients are too at high risk for cardiovascular disease, and this is clearly resonated in the recent guidelines. Alright, let's go into the phase 2 studies, here.

Dr. Tetri:

So this is the GLP-1 receptor agonist, and as you recall, GLP-1 is a peptide hormone made by our pancreas food, especially carbohydrates, and it tells the pancreas to make more insulin, but it does so much more than that. I mean, that was sort of the canonical view of it. This little dotted line down here with increased insulin, decreased glucagon. But now we know this incredible CNS effects that decrease food intake, that lead to weight loss, and there's effects on the liver. It might be indirect. It might be through the CNS affecting metabolism, and there is, of course, effects on the gut and slowed gastric emptying. That could be beneficial as well, so there's a lot of things that go on with the GLP-1 receptor agonists. You know, the gut effects are probably why we see the nausea and vomiting with them, but that's – patients get used to that over time.

Dr. Abdelmalek:

Clearly the, you know, semaglutide has been studied for NASH. There was a 72-week, phase 2 study of 320 patients with biopsy-proven NASH, fibrosis stage 1-3, and the intervention was placebo versus semaglutide at 3 different doses – 0.1, 0.2, 0.4 – subcutaneously, once daily. And the primary outcome of this trial, which was published in October of last year – Phil Newsom is the first author – was the resolution of NASH without worsening of fibrosis, and as you could see here, at every dose of semaglutide studied, there was an improvement in NASH. Um, the primary endpoint was met at all the doses. However, semaglutide despite 72 weeks of treatment did not improve the fibrosis endpoint. And the side effects, even in patients with NASH, was comparable to side effects of GLP-1 as a class, as we've otherwise observed in obesity or type 2 diabetes, with the most common side effect, as also we've seen with liraglutide, being early gastrointestinal symptoms. And as you could see here, semaglutide in a dose-dependent manner improved weight manner, and in dose-dependent manner improved glycemic control in patients with NASH. So it was almost a win-win, so if we get reduction in weight, and an improvement in glycemia, one would anticipate also an improvement in liver fat and necroinflammation.

And, while the fibrosis endpoint was not achieved at 72 weeks, if you look at the data a little bit differently, you'll notice that fewer patients in a dose-dependent manner actually had fibrosis worsening, compared to placebo. 18% on placebo versus 4.5% at semaglutide 0.4, so now semaglutide has moved into a global, phase 3 trial, as a therapeutic for NASH.

Dr. Tetri:

Just to point out here, you know, some of this worsening and then the improvement in placebo, could just be sampling artifact. Vlad Ratsiu did that study a number of years ago, when he did 2 pairs, or paired biopsies and had them analyzed separately, and it's like 20% better, 20% worse.

I call it the therapeutic trial of being supine for 30 seconds – you know, between the time you get the 2 cores. So it – that can just be sampling, when I see numbers like this.

Dr. Abdelmalek:

Agreed. Agreed. But at least it's encouraging, wouldn't you agree?

Dr. Tetri:

Ab – you know, oh, yeah the fact that, I mean, you look at placebo, that's sort of like Vlad's study. And then you see how much less that purple triangle is, of worsening fibrosis. I think it's having an effect.

Dr. Abdelmalek:

Okay.

Dr. Tetri:

Alright. Obeticholic acid. So, it's FXR ligand. What's FXR? It's a nuclear receptor, and it pairs up with its partner, RXR, to bind DNA and regulate gene transcription. And what does it regulate? A lot of things that have to do with bile transport. But it also increases FGF19 in humans, 15 in the mouse. And it increases SHP. Now, SHP is an inhibitory thing, so it turns off a lot of things, that – including SREBP-1, which is the master driver of de novo lipogenesis. So the liver making fat from sugar – de novo lipogenesis is regulated by this. So, I think there's probably a lot of things going on here that explain potentially beneficial metabolic effects, in addition to its canonical effects on bile acid transport.

Dr. Abdelmalek:

Alright, you want to share the regeneration?

Dr. Loomba:

So, looking at this data, if you see – actually, Brent did the phase 2B trial in NASH CRN. We – the three of us participated in it, where we looked at obeticholic acid at 25 milligram orally daily versus placebo, for 72 weeks in patients with NASH. And then, that positive data led to initiation of this phase 3 program, with obeticholic acid in two different doses – 25 milligram orally daily, 10 milligram orally daily – and placebo. And this is the subpart, H-18 month data, on approximately 900 or so patients. You can see, obeticholic acid at 25 milligram was better than the 10 or the placebo, for 72 weeks in terms of one-stage improvement in fibrosis. When we look at NASH resolution without worsening of fibrosis, there wasn't a significant difference, but when we looked at individual components of NAFLD activity score, we did see improvements. We also saw improvements on ALT, AST and some of the other biomarkers of liver inflammation as well as fibrosis. So overall, I think in terms of efficacy, obeticholic acid was shown to reduce fibrosis, both in the FLINT trial as well as in the the 18-month point.

In terms of the safety issues, we noticed pruritis which was most frequently seen within the first 90 days. It's dose-dependent again, and you saw it higher with the 25 milligram dose. And if you reduce the dose, the pruritis actually decreases. This is something that you could actually predict, and you are able to manage, because you know when it's going to come. Increase in LDL was also noted with obeticholic acid. It's thought to be related to internalization of LDL receptor versus placebo, and there is a new press release based upon little bit long-term data, that just came out a few weeks ago. Based upon that, the LDL that goes up initially, does return to baseline levels after continued therapy with obeticholic acid. LDL increases are responsive to statin. In terms of it, the LDL goes up, you started somebody on statin, they do go down and respond very well to it. We also noticed that there were patients who developed gallstones, or episodes where there were elevations in liver enzyme associated with pain and in – and a presentation for gallstone formation. And that's something that is a mechanism of FXR, in terms of formation of gallstones, and that's also noticed slightly higher in the 25-milligram, compared to placebo.

Dr. Abdelmalek:

Yeah. As a last compound in phase 3 clinical trials, is the thyroid hormone data ligands.

Dr. Tetri:

Yeah, Resmetirom. So, this is a much simpler diagram, and obviously, way over-simplified. So to remind you of your medical school endocrinology, T4 is an inactive hormone. It gets activated in the liver to T3, and that hits the thyroid hormone beta receptor in the liver. And of course, it comes out in the blood and does everything else thyroid hormone is supposed to do. But it can also be inactivated to the reverse T3, and it's been shown in patients with NASH that they have a much higher activity of inactivation, and sort of a defect in the deiodinase that takes the iodine off to make T3. So, by boosting this up with a ligand for the receptor in the liver, the thyroid hormone beta receptor, there's been shown to be favorable effects on lipid metabolism, and it may do this through mitochondrial biogenesis and just increasing fat oxidation. And by hitting beta and not alpha, we don't run into the unfavorable side effects of thyroid hormone. You know, why don't you just give a patient a bunch of thyroid arma? Because then the alpha in the heart gets overstimulated, which is not good for the heart. Plus, this drug is liver-targeted, in the way it's released.

Dr. Abdelmalek:

Yep.

Dr. Loomba:

Thank you, Brent. Resmetirom now is in the phase 3 trial. We might be hearing about those data in the next few weeks, at least the top-line data. So this is a very exciting juncture for our field, to see what the next phase of this development with thyroid hormone beta receptor agonists would do. This is just data looking at what we know, based upon the previous phase 2B program. The – one of the key

pharmacodynamic parameters associated with this particular drug is, thyroid hormone beta receptor agonism leads to significant reduction in liver fat. And you would be able to receive that, or predict that, in say, 12 weeks, and that predicts your response on histology at 9 months. And that's really helpful in development, because you could look at the dose and you can also look at which patients are responding to treatment. So this might be something unique that may become a way to monitor whether your patients are responding or not. These studies, and other trials, also led us to develop what could be a predictor of response with, say, thyroid hormone beta receptor agonists, or other drugs that leads to significant reduction of liver fat. One of factors is, 30% reduction in MRI proton density fat fraction. So Resmetirom responders who had 30% reduction in liver fat, had high rates of natural evolution. They had higher improvements across the board, for all 3 features of NAFLD activity score as well as fibrosis. For NASH resolution achievement, if you achieve 30% reduction, you have 5 times higher odds of achieving NASH resolution on histology. So these results are helpful in translating these changes in noninvasive biomarkers, and predicting what might be the histologic response that we will see.

Another feature of thyroid hormone beta receptor agonism as a class, is reduction in LDL cholesterol. So you are also getting potential benefits on cardiovascular disease, as well as liver disease. So, we look forward to seeing what we find in phase 3 programs.

Dr. Abdelmalek:

And our last compound that's in phase 3 clinical trials is the PPAR.

Dr. Tetri:

Yeah, that's the pan-PPAR, Lanifibranor. So it hits alpha, delta and gamma. Gamma, you know, we have the drug pioglitazone. We've been hitting that for NASH. That's one of the options over here, PPAR-gamma, and it has its beneficial effect, primarily probably in the adipose tissue, by telling adipose tissue to be healthier, and store more fat so it's not so stressed in releasing bad things into the blood. And then, the PPAR-alpha will increase oxidation of fat in the liver, and delta probably has effects on flammatory cells, plus on the muscles. So, very diverse effects by hitting all 3, which is what Lanifibranor does. You know, we have drugs that hit gamma with the pio, and drugs that hit delta alone. But it turns out, maybe hitting all 3 together is – by activating all these pathways will be beneficial.

Dr. Abdelmalek:

And Lanifibranor was studied in a phase 2 trial – the NATIVE study. And actually, by hitting all the, you know, targets of alpha, delta and gamma, this was the first drug to actually both dual surrogate regulatory endpoints of resolution of NASH, without worsening of fibrosis, in a dose-dependent manner, and also, improvement in fibrosis without worsening of NASH. The side effect profile of Lanifibranor was mild to moderate adverse events, that were again, some gastrointestinal symptoms – a little nausea or loose stools, and a very modest weight gain in about 3% from baseline. So on average, patients gained about 2.7 kilograms. So the side effects were comparable to what we've otherwise seen with pioglitazone or PPAR-gammas. So there is more to come with this compound as it's also moved into phase 3 clinical trials.

So, a lot of reason to be really excited here. (laughs) About a future, and as you can see, a huge armamentarium of compounds, of which 70% of this slide are actually drug targets that address metabolic drivers of disease, whether it be lipid metabolism or glucose metabolism. So, clearly the metabolic armamentarium that we have – will have – could have at our disposal, is huge, and about 25% are still really targets that are addressing apoptosis – anti-inflammatory, potentially anti-fibrotic targets. So, time projections to these coming to fruition?

Dr. Loomba:

Yeah, so it'll be interesting to see if we come around to a time of combination therapy, of combining those, like I said earlier on, you know, metabolic drug plus a drug that hits the NASH. So, we'll see.

Dr. Abdelmalek:

I – I would agree. So let's move on, back to the assessment. Here we're going to readdress the questions that you were initially given, and what are the most likely relationships between NASH and other metabolic disturbances? Okay. (laughs) Yes, and the right answer is, indeed, number 5 – obesity, diabetes and NASH.

Dr. Loomba:

I know it's late.

Dr. Abdelmalek:

Okay. According to the current guidelines, which class of medications should be considered for treating a patient with obesity, type 2 diabetes, coexisting NASH due to potential liver and cardiovascular benefits?

Dr. Loomba:

I gave a hint on this one. So, let's see.

Dr. Abdelmalek:

Alright. Great. Fabulous. Okay. Next question. In a phase 2 study, semaglutide was found which – to have which of the following outcomes in patients with NASH when compared to placebo? Resolution of NASH without – with improvement in fibrosis? Or without improvement in fibrosis? Resolution of NASH but high rates of pruritis? Or significant weight gain but resolution of NASH? Please vote.

Fabulous. Great. And our – okay. Now, I'd like to address a few questions that came from our audience, and please – Rohit. Do you recommend that patients actually be sent the liver fibrosis serum panels? How often are you using those over a FIB-4 or any other modality?

Dr. Loomba:

ELF – we are trying to set it up for our clinical patients, and for research patients we do get ELF, and – but that's usually in batches that we get. But for clinical patients, we are trying to set that up.

Dr. Abdelmalek:

Okay, fabulous. So, Brent, is the effect of semaglutide on NASH due to non-liver metabolic effects or is there a direct effect on the liver? I've read that there is no GLP-1 receptors in the liver. Can you comment?

Dr. Tetri:

Yeah, that's a very good question. I think it's the – for that reason, its indirect effect on metabolism, that it benefits the liver, not directly.

Dr. Abdelmalek:

Yeah. I'd agree. It's all indirect. What aspect of fibrosis done on a 4-point or 6-point scale – was it done on a 4-point or 6-point scale in the semaglutide study? Uh, I believe it was actually done on both, so there was initially – it was designed as a – the 4-point scale.

Dr. Tetri:

And then modified Ishak…

Dr. Abdelmalek:

And then the modified Ishak was used.

Dr. Tetri:

When we just stretch out the advanced fibrosis. Feel of a more granular and…

Dr. Abdelmalek:

Okay, here a question that – which I'll take. What is the role of fructose in NASH? Children given fructose slowed developed fatty liver. Brent, you're laugh…

Dr. Tetri:

No, that's you.

Dr. Abdelmalek:

I think this is poison. (laughs) It's an absolute toxin to the – to the liver in my opinion. It is a direct and potent inducer of de novo lipogenesis. And in doing so, can be a environmental risk factor for the lipotoxicity, so I absolutely inform my patients and their children to avoid the sweetened beverages – eat the fruits but don't drink the fruit juice. You'll…

Dr. Tetri:

Yeah, and keep in mind table sugar – sucrose – is half fructose, and rapidly broken down into glucose and fructose in the gut. So that – it's essentially the same.

Dr. Abdelmalek:

Yep. Um, would you start with weight loss medications first, before bariatric surgery? What is a good plan of action before considering

anybody for bariatric surgery?

Dr. Loomba:

Absolutely, the bariatric surgery, if done without lifestyle intervention, is a very painful life. And so, it's really important, because they have the surgery done, and now they cannot eat. So it's really important to get used to it, and I think that is why it's very important to give people time so they can adjust to it. Typically, I'm giving my patients at least 6 months, sometimes a year, before they actually undergo the surgery or a procedure.

Dr. Tetri:

I think an unknown area there is what's going to be the role of the GLP-1 drugs in the bariatric surgery patients? Because you know, they don't all get down to some skinny weight. They'll plateau out, and, you know – because they'll still have the biological drivers of hunger and all that, so I think it'll be really interesting to see if they get an extra boost out of this.

Dr. Abdelmalek:

I think there's going to be a lot of utility to this class, and def – in different clinical settings for sure. This is an interesting question. Would you continue or start a statin in the setting of high – now that's not defined, but I'll say high. I've seen patients with ALTs 5 times the upper limits of normal, like a true normal of 20, but we've all seen patients with an AFT of 150. Would you start a statin in the setting of what you consider in high L – ALT?

Dr. Tetri:

That's a great question, and in the right patient, I would – that they clearly have a high risk, with the profile, and obviously a very close monitoring to make sure those liver enzymes don't go any higher.

Dr. Loomba:

I wouldn't start. You know, a patient comes to me, their ALT is 200. Don't mess around. Try to figure out why it is. And so, I am not starting that patient on day 1 on a statin. A patient comes in, his ALT is routine – 30, 40, 50, 60, 70 – that patient does get statin on my first visit. That's my approach, is to – what is the urgency for me to start, and what is the risk benefit ratio? At – if somebody walks in at 200, I want to figure out why it is 200 first. Now it could be – I have some patients who may have it, but then I may work on their – you know, how much sugar they may be taking, how much fructose they take, how many smoothies they drink, how much alcohol they drink. Maybe stop that completely, and then bring them back, and then I might consider that.

Dr. Abdelmalek:

Okay. Rohit, I have a – a really good question for you. So, our practitioners are going to be starting these interventions – lifestyle modification, diet and exercise, maybe GLP-1, whatever. How are they going to monitor for NASH resolution? When do they know that their patient has kind of moved out of the weeds, if you will? Is there a biomarker we can use for NASH resolution?

Dr. Loomba:

Yeah, I think what we will have is – recently we had a paper – depending on the therapy, so if you have a thyroid hormone beta receptor agonist, you've got the liver fat reduction and then you've got the ALT responses to be added to it. Similarly, with GLP-1, you've got the liver fat reduction, which is probably similar to what you see with that, and the ALT reduction. Both of those together will increase your odds. If you really normalize ALT, that patient has improved, so you know, remember we wrote a paper from a few years ago that was, if the ALT ran down 30% and your ALT was also normal, then that patient had a response on histology. So things like that, I think, will come to the practice guidance, once we have a therapy that's approved.

Dr. Abdelmalek:

So, yeah, I agree. Brent, maybe a question for you. I – I know how you feel about ultrasound, but (laughs). And, do you – if a patient comes to you and the abdominal ultrasound indicates hepatic steatosis, do you always pursue additional diagnostic evaluation? What's your threshold?

Dr. Tetri:

If the ultrasound shows steatosis?

Dr. Abdelmalek:

Yep. When do you – do – should we be pursuing? Should we be pursuing further evaluation of everybody?

Dr. Tetri:

Yeah, it's a great question. I – I do FibroScans regularly, so you know, you can ask this. They don't have any other metabolic risk factors, would you do a FibroScan? I – you know, a FibroScan doesn't cost much more than a CNP or a CBC, so I…

Dr. Abdelmalek:

FibroScan's cheaper than an ultrasound, you know?

Dr. Tetri:

Oh, yeah. Lots, yeah.

Dr. Abdelmalek:

So, so to answer that – that's exactly my clinical practice. I'll, you know, size up their metabolic, do a FIB-4 and a FibroScan. So, and if – if the FibroScan stiffness score is low – less than 7 – I, I really…

Dr. Tetri:

Back to primary care.

Dr. Abdelmalek:

…back to primary care, and I'll see that patient back.

Dr. Tetri:

Let's flip that around. So they come in to you saying, you know, obesity, diabetes, whatever, and ALT of 50. Do you do an ultrasound?

Dr. Abdelmalek:

Not necessarily.

Dr. Tetri:

I don't. I – you know, because it's – it's relatively insensitive, so the ultrasound – they don't say there's any fat, I don't trust it.

Dr. Abdelmalek:

Yeah. I do do the ultrasound as screening for hepatocellular carcinoma…

Dr. Tetri:

Sure. Fair enough.

Dr. Abdelmalek:

…if I am absolutely concerned that the platelet count is less than 150, or there are significant predictors for…

Dr. Tetri:

…and you're worried about their biliary tracking.

Dr. Abdelmalek:

That's exactly right. So – but I – I agree. It's not indicated.

Dr. Tetri:

Yeah, so it's fallen off the guidelines, too. It's the initial evaluation, so all those textbooks that say elevated liver enzymes, do ultrasound – it's not in that – not in our guidelines anymore.

Dr. Loomba:

That's – Dr. Tetri, you got it out. The ultrasound is out.

Dr. Tetri:

Am I wrong?

Dr. Loomba:

No, no, you're never wrong.

Dr. Abdelmalek:

You're never wrong. Never wrong.

Dr. Loomba:

I'm just giving you credit for that. You know, that piece is yours.

Dr. Abdelmalek:

Okay. So maybe Brent, you could take this. You brought it up, so maybe question's yours. What do you recommend for the treatment of the lean NASH patient, without metabolic abnormalities?

Dr. Tetri:

Yeah, so it – somebody with lean NASH without any metabolic abnormalities is going to be really rare. Like I showed that – that study, the NHANES study, usually they have some, and I – you know, and they'll often have a little bit of centrifugal fat, and increased waist-hip ratio. So I still recommend lifestyle modification, realizing that they have probably some, but it was some significant genetic loading. But that doesn't mean they shouldn't eat healthy and exercise.

Dr. Tetri:

Right.

Dr. Abdelmalek:

Let me repeat the question, please.

Dr. Loomba:

Yeah, the question is: When the BMI is more than 35 kg/meter squared, the FibroScan is almost always overestimating, and too high. And – and that's true. You know, we wrote a paper where we did a head-to-head comparison on FibroScan, the same day as MR elastography and MRI PDFF, and CAP. And what we found is that as your BMI goes up, these tests becomes separate from each other. And, the infliction point is about 35 kg/per meter squared. And so, in people with BMI 40, 45, you're over estimating, and this overestimation – so if you see somebody exactly as you mentioned, may have 15 kilopascal, they may actually have normal liver. So those are the patient who might need another test. If you otherwise think they probably are low risk, and those would be good candidates for say, MR elastography or ELF, and those tests might be able to sort them out. Otherwise, if they're discordancy – these type of patients end up getting a liver biopsy.

Dr. Abdelmalek:

Absolutely. There's actually one last. This is the last question, but I think it's a very interesting question. I said, for – for either one of you or both of you, do you think there is going to be any role for a liver biopsy in the management of the NASH patient in the future?

Dr. Loomba:

Absolutely.

Dr. Tetri:

I'm old school – I say yes, too. And there's still all the things we've learned. You know, iron – you didn't expect to see, you know, some autoimmune, you know, plasma cells, things like that. Biliary stuff.

Dr. Abdelmalek:

So you're not convinced that the noninvasive nits – noninvasive test will replace biopsy…

Dr. Loomba:

Well – how the question is framed – will liver biopsy, any role in management of NASH? The answer is yes, absolutely it will have a role. But, it would – I think if you freeze it, in 90% of patients, we're not going to need a liver biopsy. So, that was your question.

Dr. Tetri:

I think that's all that is happening, frankly.

Dr. Abdelmalek:

And I would agree with that. It's not going to be completely absolved in the evaluation of the indeterminate patient, or where you're considering or concerned about overlap syndromes or phenomenas. But I think in a majority of patients who we historically have biopsied, we may be able to proceed without it.

Dr. Tetri:

Yeah.

Dr. Abdelmalek:

I agree. I – I can't thank you all enough for the time you've spent with us today. I can't thank Novo Nordisk enough for their gracious educational grant that made this program possible. We thank you very much. Thank you. (applause)

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