[MUSIC PLAYING]

JAIDEEP BEHARI: My name's Jai Behari. I'm one of the herpetologists. So this morning, you've heard from Shahid and Ramone, who've taken away your alcohol. And I'm here to take away your sugar and fat. And I also realize I'm the last man standing between you and lunch. So we'll make it short and sweet.

I think this morning's session was mainly transplant, but we're talking about problems, like alcohol, that Shahid and Ramone talked about, and then NAFLD, where transplants simply cannot be the solution when 90 million people are suffering from that problem in this country and who knows how many untold hundreds of millions around the world.

So clearly, we need solutions that go beyond liver transplant. So I think most of our afternoon sessions now are focusing on preventing advanced liver disease and cirrhosis. And so I think that's an important thing to keep in mind, as we do talk about very sick patients that do need transplant to save their lives.

I just do have some disclosures. And I will talk about off-label use for medications, because there is currently no FDA-approved medicine for NAFLD and NASH. So nothing focuses the mind than having a patient with real problems sitting in front of you. So let's start with a real case.

A few months ago, when Susan first emailed me about talking at this conference, this was a patient I was seeing in clinic that day. So I thought it was very relevant to start with that particular patient, who I see in our NASH clinic.

This is a 58-year-old female. She was referred for liver injury tests. That's what the referral said. She was 43 when she was initially diagnosed with fatty liver, and she had a CT scan, went into the ER with abdominal pain, had a CT showing kidney stones. And then since then, she'd been getting annual blood, religiously following up with her PCP.

As you can see, her transaminases were in a range that, depending on which lab you're talking about, could be considered quite normal. Even now at Presby, up to 55-- or even sometimes 64 if you go to one of those smaller hospitals-- is considered a normal range for ALT.

She always was in the normal arranged for her lab, and so her PCP told her not to worry. And the advice he gave her was, portion size control, increase your physical activity. Lose weight, come back and see me next year. And when you think about this, all of our patients who get this advice. Go home, eat less, move more. Come back and see me in six months.

So that's exactly what she did. She joined Weight Watchers. She went on diets off and on for a while. She started a gym. Something happened to her life. She stopped exercising and went on for quite a few years. And during this time, her weight, depending on what she was doing, was plus, minus 5 pounds. And she had a BMI of 36 and remained pretty stably at 36 for a period of time from the age of 43 onwards.

So then just before she was referred to us, she went back, as she had been doing for many, many years. But this time, there was a change in her blood work. And her PCP noted that her ALT was 45. That was still within normal range for that lab. But her AST was a little bit higher. And since they had recently decreased the reference range for the ALT, now, that came back as positive. It was 35 or something for that lab.

So now, suddenly, that caught the PCP's attention. And for the first time, her platelet count was 148,000. So the reaction there was this is thrombocytopenia, and this patient was referred to a hematologist, who did a full workup, and then couldn't find anything and ordered a CT scan, suspecting liver disease. And, lo and behold, she has cirrhosis with splenomegaly. That would explain her enzyme abnormalities, as well as the thrombocytopenia.

So all of us are seeing these patients almost every day in clinic. And of course, the answer to all of her problems was NAFLD or NASH-related cirrhosis. And at that point, she was referred to the liver clinic. So I am using this case as an illustration to make the point that perhaps in 2019, we've got to move beyond telling our patients to move more and eat less and perhaps to have a more formal framework for risk stratification and management. Because simply, we can't wait for these patients to decompensate to transplant them.

So I'm going to focus my talk on five different topics, and we'll work our way through it of increasing degrees of complexity from the very simple to the very complex and try to give you some specific take-home points that you can start implementing, hopefully, today in your clinic. So we'll talk first about some ways of risk stratification. Not every patient needs to be referred to us. Not every patient needs a sub-specialist to see them. Not every patient needs a liver transplant evaluation.

How do we decide in 2019 how to manage these patients? How do we avoid unnecessary testing? How do we avoid anxiety that our patients face when they first find out that there is an organ called liver that happens to be fatty for them?

And then what specific goals and recommendations can we tell patients rather than just telling them to go home and lose weight, which very few are able to do successfully? What specific dietary recommendations work? Are there any medicines that we could consider? And then what are the surgical options?

So let's start with the first question, which is, what's available to us? Does every patient really need a liver biopsy? Or does every patient need to be told to come back in a year? So what's between those two extremes of doing nothing or sticking a needle in someone?

So just to refresh your memory-- for those of you who are used to seeing these, it's probably not new information. But I just wanted to bring everyone up to speed about what does it mean when we say someone has NASH versus someone has NAFLD?

So NAFLD is just an umbrella term-- non-alcoholic fatty liver disease-- which includes any stage of the disease throughout that spectrum. so someone that has very mild, 5% liver steatosis all the way to someone that may have cirrhosis from NAFLD is considered to be NAFLD. So that's the big umbrella term.

But the term NASH is used very specifically for those patients who've had a liver biopsy with specific histological features. And I've got to tell you, pathologists debate each other very, very aggressively about what exactly constitutes NASH. So in general, there are three features that constitute NASH.

One is very obvious. All of you could see these big white holes. And this is where fat globules are within hepatocytes. So you take a biopsy, stick it in formalin. The fat gets absorbed because it's an organic solvent, leaves behind a little hole there. And the pathologist can see it right away. So these are big globules of fat now leaving behind a hole. So its steatosis is very easy to recognize. So that's what a fatty liver looks like.

But there are some other features that make it not just steatosis, or simple fat, fatty liver, but NASH, or nonalcoholic steatohepatitis, and that's the presence of inflammatory full size, shown here with a green arrow, where there are these lymphocytes in the hepatic lobule, and then these cells, which look like balloons, and so very creatively they are called balloon hepatocytes.

And they are different from normal-looking hepatocytes all around it, but it's an extraordinarily hard thing to find two pathologists who will agree on what's a balloon hepatocyte or not. So kappa, or inter-observer agreement, is actually surprisingly low for balloon degeneration. So this scoring system, unfortunately, has not been very helpful in predicting who has a poor outcome and who does not.

But there is one feature in a biopsy that's very helpful in determining who is going to head towards trouble and who is probably going to have a very favorable course from the liver's perspective. And that is the presence of fibrosis, shown here in the blue, by using a stain called a trichrome stain. And so when we start to see this-- and here's a patient that would be considered as having bridging fibrosis, perhaps even some early cirrhotic nodules, stage F3, which would be pretty advanced fibrosis, would be someone that I would consider to be at very high risk for developing cirrhosis.

So until recently, this was the only way we could tell someone whether they were at very high risk or not at high risk. And this is a very important thing to keep in mind, because many studies have shown-- and I have a bunch of references here-- but the bottom line is, the more the fibrosis, the higher risk of dying. And here's the kicker-- not just dying from liver disease, but from all cause mortality.

So it turns out that in NASH, fibrosis increases your risk not just of dying of liver decompensation and liver-related complications, but also of cardiovascular outcomes, as well as, perhaps, even extrahepatic cancers. Now it's a little hard to tease out, because there are so many shared risk factors, like diabetes and obesity. But in general, there seems to be something very important about liver fibrosis that changes systemic physiology.

And when you think about it, it's probably not surprising since the liver is such an important organ for systemic energy balance, as well as lipid and carbohydrate metabolism. So in one way, not surprising. We're just learning about it now. But certainly makes sense that those who have the highest degree of fibrosis will do most poorly.

So if you were in a clinic today, and you had a question about a patient-- whether they had advanced fibrosis or not-- you don't need any fancy equipment. You don't need a $1,000 test to tell the patient whether they're at high risk or low risk. You could start that process of risk stratification by using a bunch of very simple tests that are based on components that-- at least for some of these tests-- we measure every day in routine clinical practice-- demographic features, like age, morphological features, like BMI, as well as the presence of very commonly-measured serum biomarkers.

Those of you who have MedCalc and all these other medical calculations apps on your phones, which I'm sure most of you do, most of these are available there. So we also have the NAFLD Fibrosis Score as part of our EMR system automatically generating these scores, thanks to Dr. Dunne's efforts from a few years ago. And we use it all the time to risk stratify the patient.

So if you're seeing someone that has a NAFLD Fibrosis Score of below minus 1.45, that actually has a surprisingly high negative predictive value that they do not have advanced fibrosis. So they do not have F3 or F4 fibrosis. So that's a pretty easy poor man's way of deciding if someone has advanced fibrosis or not.

On the other hand, if someone has a score calculated based on that formula coming out to more than 0.66, then you will consider that patient to be at very high risk of having advanced fibrosis or cirrhosis. And the others, which kind of perform about the same. And of these, FibroSure is a commercial test that you send out through Quest labs, that will give you values which kind of perform all about the same. I'm not sure we need to spend $250 on FibroSure, because the others are about the same in terms of their diagnostic accuracy and performance.

And this was a simple way. So if you're seeing a young patient, with normal liver enzymes, that's asymptomatic, doesn't have diabetes, perhaps just doing a NAFLD Fibrosis Score, focusing on lifestyle measures might be the most appropriate for them. So I think we underuse these tests. And certainly, if you have access to them and feel comfortable, start using them. And you'll find that they are quite helpful in some cases.

But the real revolution in the last five years has been FDA approval for three imaging modalities, which are non-invasive, all based on the principle of liver stiffness. They are now available to us, at least here at Presby. I think they're slowly trickling out into the community, with just a few other centers having it at this point, but, hopefully, soon in a lot in a lot of hospitals.

But those are vibration-controlled transient elastography, or Fibroscan, which is the brand name for that technology, the ultrasound shear wave ultrasonography, or elastography, and MR, or magnetic resonance, elastography. All of them based on the principle that when you throw a pressure wave or a sound wave through the liver, it distorts the tissue very minutely. And then that is measured by the computer, and their proprietary algorithms then will tell you how stiff the liver is. And the stiffer the liver, the greater the risk of having fibrosis.

So they're not perfect. They do perform less well in the middle ranges. But they perform fairly well at the extreme ranges to tell someone that they have very low fibrosis, or they have advanced fibrosis and cirrhosis. It's a great risk stratification tool. And I know that all the hepatologists are now routinely using these-- one or more of them-- before sending a patient for liver biopsy.

In my NASH clinic, I estimate we've cut down our liver biopsies by about 80% by utilizing a combination of these approaches in our clinic. And we have all of them available at Presby right now.

So this is a Fibroscan. And I just wanted to point out two very interesting sets of results that we get with a Fibroscan. It takes me about three, four minutes to do a Fibroscan. The patients love it. We give them an answer in real time.

And you can make actual management decisions in a matter of minutes. It takes one month for us right now to get prior authorization. There are all kinds of absolutely unreasonable BMI cutoffs for our patients. So the whole clinical, financial aspects of it is a mess right now. But from a medical perspective, this is an absolutely amazing new piece of technology.

And it gives you the number in blue. That's called controlled attenuation parameter. We call it CAP for short. That gives you a sense of how steatotic the liver is. Now it's not a linear scale, but it's still pretty helpful to know whether the patient has very severe steatosis or just mild steatosis. Sometimes I'm seeing patients that have fatty liver that have no fat by Fibroscan, and they turn out to have other problems.

And then the second one here-- the number in orange-- is called the liver stiffness measurement, measured in kilopascals scales, which is the unit of stiffness. And that tells you approximately how much scarring a patient may have. So if someone has 7 or less, as in this patient, I would not worry about them at all. This patient has a very low risk of having fibrosis.

On the other hand, if this number was 12 or 13, I would be very concerned about advanced fibrosis or even cirrhosis. So these two numbers, in about five minutes, makes it very easy for you to risk stratify your patient as a starting point. And there's a couple of different probes that you can use based on BMI and skin subcutaneous fat thickness, et cetera. So these are really nice. It's a very nice tool that we can use.

And a very similar tool, which is available through our radiology department right now, is called shear wave elastography-- exactly the same principle, and it's exactly the same scale. So 7 or below, your good. 12 or higher, probably not that great. And they have a region of interest. They measure the stiffness there. They have a scale here.

And I'm sorry, this slide is an older one, so these scales are not the ones we use right now in Presby. So don't go by that. But the principle is exactly the same. And they'll give you a color. Red is bad. Blue is great. That means there's no liver stiffness. And you can actually pull these images up on [INAUDIBLE] or Clinic View and look at them yourself if your patient has had a shear wave in Presby.

This is what an MRI looks like. Again, ignore these stiffness values. That has changed based on the algorithm. For us, we're using GE software, so it's a little different. And here, you can just tell blue-- great, no fibrosis. Whereas, red-- bad, cirrhosis. I make it a point to pull this up and show it to my patients. And if someone is, let's say, yellow and a little bit of red, I can tell you, they're so motivated to change their lifestyle once they see what that's doing to their liver. So these are all very nice tools that we have available to us and, again, available at Presby.

There's a new software that's available only for a few months, called proton density fat fraction, that measures with exquisite detail the degree of fat in the liver. And I know that Shweta and Dr. Humar and the live donor team have started using PDFF for risk stratification of live donors. Because you can tell them right off the bat how much hepatic fat they have in terms of percentage steatosis. So really remarkable new technologies that we have available.

And we have a paper currently under review, where we prospectively looked at these three technologies for NASH patients with biopsies. And we are finding that their diagnostic accuracy is about the same. Perhaps MRE is a little bit better. We didn't have PDFF at that time when we did the study. So we don't have data on that. But looks like you could get away with doing any of those as the first level of risk stratification.

So this is a strategy that I utilized not exactly but pretty close to this. And there is no absolute algorithm that has been proposed. And it's still a work in progress. But essentially, someone that comes in that has risk factors, and you've ruled out other causes for elevated liver enzymes or liver injury, and there is an echo bright or fatty liver on an ultrasound, then it's important to risk stratification. And I think it's absolutely acceptable to use NAFLD Fibrosis Score for someone that has a very low score to maybe not take them through a very extensive work-up process, other than focusing on lifestyle, and weight loss, and dietary interventions.

For those who are very high risk, I would manage them as cirrhosis. And it's the patients who are in the intermediate risk who may require additional risk stratification, including inappropriate cases of liver biopsy. And so by doing this, we've actually screened out 80% of our patients. So very, very few people are requiring a biopsy right now in my clinic. Because we utilize a combination of the non-invasive measures, Fibroscan, plus, minus shear wave and MRE based on their body habitus, BMI, et cetera.

So I'll give you some very quick examples to make it a little bit more clear about how you could utilize this. So here is a 55 year old female. All cases from my clinic. 55-year-old patient, had normal transaminases, very low liver, stiffness below 7. I do nothing except lifestyle and monitor. Annually, patient doesn't need a specialist at this point.

42-year-old male, normal transaminases, stiffness a little bit higher. But here is the NAFLD Fibrosis Score-- very low, again extremely low risk for fibrosis. No need to do a biopsy for these patients.

63-year-old, mild elevation of transaminases, had an indeterminate NAFLD Fibrosis Score, and had a liver stiffness greater than 9 via Fibroscan. This patient did get a biopsy, had F2 fibrosis, as you'd expect from that. And she's currently on vitamin E.

And a 49-year-old male with a stiffness score of 11.2, this patient is going to get a liver biopsy, because he's interested in a clinical trial. But I would expect the biopsy to show F3 fibrosis. So these are just examples of real cases of how you can use these strategies for risk stratification when you're first seeing these patients.

So in general, this helps you to stratify these patients into early intermediate and late stage NASH. And the vast majority of patients, you will find, will be in this early stage NASH. They'll have very minimal fibrosis. They may have a lot of steatosis, but these are patients who would benefit from lifestyle modification and weight loss. And they probably-- at least as of 2019-- may or may not need any specific liver-directed pharmacotherapy. So that's the group of patients that I really focus on in terms of lifestyle and weight modification.

So the question, then, is, if that's what you decide to do for a particular patient who's in that part of the spectrum, then what exactly do you tell them about weight loss, other than just telling them to go home and lose weight? Can we be more specific than that? So that's what I'm going to talk about for the second part of the talk?

And the first question, of course, is, is that sufficient? And the answer is clearly, yes. So now, I think, in 2019, there's no doubt that weight loss and lifestyle modification does improve NASH. We're doing clinical trials where the patients lost 55 pounds, had complete resolution of fibrosis and steatosis. We congratulated ourselves on successful clinical trials, and it turned out the patient was on the placebo arm of the study.

So it's really quite remarkable for those patients who make those changes how dramatically the liver responds. So this is a older study showing that, and this was one of the first studies to show that there was a very dramatic histologic improvement.

But the situation is a little bit more complex than that. And that is that you have to lose 5% of your body weight to have improvement in steatosis. So that's the NASH resolution. You have to lose a little bit more-- perhaps 7% to 10%-- to start seeing some fibrosis regression. But you need much more than that to go to the area where there is no longer any NASH, and there is no longer any fibrosis or at least an improvement in your fibrosis. But by 10% or more, there's complete steatosis improvement.

So we have a study going on currently, where we're using exquisitely sensitive MR spectroscopy. And I can tell you, this number is right on target. Every patient that has lost 10% of their body weight from baseline, no matter what you're starting body weight is, has had complete resolution of steatosis. So it's really remarkable. I don't know why that is the case, but that's what we are seeing.

The problem, of course, is that the number of people who are able to achieve these milestones is relatively small. And I suspect it's because we simply haven't figured out how to treat the obesity part of the equation. And so it's less to do with biology than it has to do with medicine catching up with keeping that a top priority in our clinical settings. So I highly recommend using this Canadian Obesity Network model in talking about obesity management with our patients.

Always ask for permission before discussing weight, assess for risk factors, advise the patient on how to get the best care. Agree on specific and realistic weight loss goals, and do whatever you can to help them along in their journey. We try to follow this as closely as we can. Ramone talked about alcohol. Show a lot of sensitivity, a lot of cultural sensitivity and personal preferences, and try to help people along that weight loss pathway.

There's a bunch of medicines that can cause weight gain. It's very difficult to get people off. So if you are prescribing meds, always try to choose meds which are weight-neutral or which promote weight. So here's something that we can do everyday, even if you don't directly deal with NAFLD patients. You can make a difference.

We are seeing more and more patients who are on Neurontin, which is an absolutely horrendous drug for weight gain. Keep in mind that people who do lose weight initially will gain weight back because of physiologic changes. That's inherent to human physiology. Doesn't matter who you look at, which part of the world you look at, this is a very common problem. So this is a problem you need to follow with your patients long term.

So to summarize, what specific goals and recommendations? I think everyone should try to lose 5%. We certainly have protocols in my clinic to try to make people lose 5%. And we certainly have help in the form of pharmacotherapy and dietary intervention designed to take them up to 10%. But that's a work in progress. I think we certainly need ways to scale that up to the hundreds and thousands of patients who need our help.

The most common question, believe it or not, I get in my clinic is, which is the best diet? And the answer may disappoint some of you. The answer is, none. They're all the same. And this is a beautiful study from 2009, *New England Journal of Medicine.* They varied the composition of macronutrients and found the results were identical. So pick your favorite diet, just stick with it, and you'll probably have a benefit. There's no benefit of low fat versus low carb, et cetera.

However, there's some data now also supporting that, for people who are on low carb-- and that's a very popular option these days-- or a Mediterranean diet that seems to perform as well as low fat. So certainly, there is no hesitation in my recommending any of these to our patients.

There's a very nice study published just last year from Stanford. It's called a DIETFITS Study. And the bottom line for that study is very important to take home. And that is, it doesn't matter whether you're on a low fat or a low carb diet. What matters is the quality of food. So this is Berkeley, California. This is where they recruited their patients.

Everyone is going to farmer's market, eating a very healthy diet with fresh vegetables, and lean meats, et cetera. But what they found was that there was no absolute difference between low carb and low fat diets. But everyone that ate a very healthy diet had their weight go down, as well as metabolic markers improve. So that seems to be very important.

The second very hopeful message from the DIETFITS Study is that they did lots of genetic testing to see whether genes affect your response to a healthy diet. And the very hopeful and positive message, in my opinion, even though the results were negative, was it seems to be independent of genes. So no matter-- don't blame your genes. Improve your diet. That seems to be a very important message here.

A bunch of studies here that the only reason I put this here is to make the point that the Mediterranean diet seems to be quite beneficial. And for those people who stick to the Mediterranean diet-- this is from the Framingham Heart Study using a very, very large number of patients, over 1,500-- they found that those people who had the best adherence-- so the way this graph is set up here, liver fat increases in the bottom direction and decreases in the upper direction-- those who were in the highest quartile of sticking to a Mediterranean diet had the least risk of developing a fatty liver over the next five, six years. So that's a very hopeful message there.

An important message to take home is that there's some very strong data emerging on the role of fructose. And this is a great study from UCSF showing that those who were on an isocaloric fructose diet had dramatic decrease in their hepatic steatosis. So remember, the number of calories are the same, but they've just cut down on their fructose intake, mainly in the form of sugar-sweetened beverages.

And this has also resulted in decreased in fat production, which is called hepatic de novo lipogenesis, all within nine days. This is remarkably short amount of time to see these effects. Always spend a couple of minutes to tell your patients about the new nutrition labels. The number to look at is down there, which is included added sugars. And you'll be shocked at how much there is.

Here's an example of your favorite sugar-sweetened beverage. This is directly taken from their website. I left out the brand name. It doesn't matter what it is. Just to point out that a 20-ounce bottle of America's favorite sugar-sweetened beverage has 65 grams of added sugar. So you're essentially consuming a pound of Domino's sugar every five or six days, and that's 130% of your daily allowance.

Coffee consumption has been associated with lower risk of fibrosis. So for those individuals who drink coffee, I think it's great. They can continue. I think it's a little premature to make people drink coffee. I actually don't know if there's any clinical trials on that, but it's something that's easy enough to do. And those who drink regular caffeinated coffee seem to have a lower risk of fibrosis.

So these are easy guidelines. And really, Mediterranean diet seems to be a key part of it. There is nothing comparable in the ASLD NAFLD guidelines as yet, except that they also support Mediterranean diet. Again, we talked about the weight reduction issue.

And I think, wherever you are in this stage of the process, dietary intervention is very important. And we are now seeing some patients with high-- not super-high MELD scores, but medium MELD scores-- 10 to 15-- who seem to have an improvement when they make a concerted effort to improve their diet.

So we use this in my clinic. It's a very nice, colorful image from the Harvard School of Public Health and their nutrition program. And this is very similar to a Mediterranean diet. And so then I don't have to argue with people who say, but, doc, I'm Italian. You can't make me change my particular diet, or I'm Indian, and you can't make me give up whatever food that's their favorite.

So this, I think, gives you plenty of flexibility. And I really like all of their recommendations, which are very simple and straightforward, that anyone can download and use from their website. So we have color copies of this in our clinic that we hand out to every patient and certainly something that I would highly recommend.

Moving on very quickly, the last few slides talk about some specific interventions in terms of pharmacotherapy. And the thing to keep in mind is that there is no FDA-approved medicine. And I also would focus on this stage where pharmacotherapy might be beneficial, which are people who have some degree of fibrosis. And I'm currently focusing in my clinic on stage 2 and 3.

So F2, F3 fibrosis, we usually try to do F0 and F1, which is very mild fibrosis, into lifestyle and weight loss. And then cirrhosis, currently, we do not have anything for them specifically. So this is the population in the middle that we like to think about pharmacotherapy, because they're at the highest risk of progressing to cirrhosis. And the goal is to avoid progression to cirrhosis and hepatic decompensation.

So this is what it looks like-- simple steatosis, just fat. Here's a person with NASH, NASH with fibrosis. And that's a well-formed cirrhotic nodule. So the closer you are to this process, the greater your risk. So most of the clinical trials that are going on are here and maybe just little less than that. And that's also where I would focus pharmacotherapy for most of these populations.

There was a landmark study from 2010, the first study really showing a drug can improve NAFLD, and that's vitamin E. Back in 2010, I had a bunch of patients that started this right after the paper came out. 800 international units of alpha-tocopherol, or vitamin E. And now, eight, seven, eight years later, when we re-biopsy these patients because they are interested in clinical trials now, I've been shocked at the number of people who have had histologic responses.

So there's a couple of papers now coming out that vitamin E may be effective, even in people who have established cirrhosis but not quite decompensation. So I think it's an interesting drug that we severely under-utilize. And so this is something that, if you have appropriate patients, we should be utilizing it. Because it does seem to help some patients.

An important message is that those who lose weight-- as little as two kilograms of five pounds-- have a response with vitamin E. So whether you do vitamin E or not, if you lose weight, you seem to do better. I'm not sure of this is just a marker of improved diet and a lifestyle or there's something inherent about weight loss. I'm not sure. But the point is that weight loss with vitamin E appears to be a very effective strategy for some patients.

The other drug, which was utilized in that famous Bivens trial is Actos, or pioglitazone, which is a PPAR gamma agonist. So essentially, what it does is takes fat from all over the body and sends it to fat tissue, including taking it away from the liver and redirecting it to the adipose tissue. And so there was some benefit to it. Certainly, if you have a patient with diabetes, this would help.

The only problem is that it's associated with very significant weight gain of up to four kilograms or more, average. So that means some will exceed that. And that's a real problem with pioglitazone. I don't use it that much. But certainly, if you have a diabetes patient that needs help, and they're normal body weight, that might be helpful.

There's a bunch of clinical trials going on. We have a few phase 3 studies going on. Certainly, if you have patients that you think would be interested, please let me know. We'll be happy to screen them for our studies.

We had one of the highest enrollments for obeticholic acid that some of you may use for PBC that may possibly may get FDA approval later this year and certainly has shown some benefit. And I've had a couple of patients who've had a very dramatic improvement in their fibrosis scores. So we are hopeful that there'll be something available.

It has some side effects. I'm not sure how popular it might be with our patients. But at least we'll have some options. And there's over 200 clinical trials going on. So hopefully, we'll have something to offer our patients in the future.

Very quickly, in the last couple of minutes, I'm going to talk about what about those patients who are in the extreme stage of that spectrum-- cirrhosis, advanced fibrosis. What can we do about them? One thing to think about patients who do not have cirrhosis, but have very high degrees of obesity, is to consider bariatric surgery-- another lifesaving intervention we seriously under-utilize. And there are very good data emerging now that there is a regression of steatosis and fibrosis, provided there aren't other risk factors, like concurrent alcohol use, as Ramone had alluded to.

Some issues to consider-- the indications currently-- in the US, at least-- are BMI over 40 or BMI over 35, with obesity associated comorbidities. And if a patient has established cirrhosis, I think we have to pay very close attention to portal hypertension. Because if they have portal hypertension, I would not recommend, at least today, outside of a protocol to do weight loss surgery. Because the risk is pretty significant of decompensation. But short of that, I think it's not a bad option. I have about four or five patients who've undergone sleeve gastrectomies, not gastric bypass, with compensated cirrhosis with no portal hypertension and have done well.

And one final slide on outcomes after liver transplantation. No surprise to this audience that NASH patients, especially the carefully selected ones, actually have pretty good outcomes. So certainly, you've heard a lot about that today.

So finally, very quickly, please think beyond eat less, move more. Think about noninvasive assessment. Do help your patients achieve that 5% weight loss. I think it's doable for most people.

Here are some dietary modifications-- low sugar, Mediterranean-type diet. There are some treatment options. I think we are under-utilizing them, so please use them if you can. And think about weight loss surgery for appropriate patients.

And finally, just a quick plug for our clinic-- if you ever have any patients that are interested in either primary weight loss as an intervention for the NAFLD or are interested in pharmacotherapy clinical trials, we certainly have a very active clinic and area of research in this area. Thank you very much.

[APPLAUSE]