NAFLD & NASH: Screening, Diagnosis, and Current Treatment Options

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Dr. Mantzoros: Let's move on now to diagnosis and risk stratification. What is up today in terms of diagnosis and risk stratification? We published two papers, this consortium of representatives of the professional societies. Two papers; one is a call to action and you can find it in Gastroenterology and Metabolism, Obesity, Diabetes Care, late summer or the new guidelines were published in November of 2021.

In summary, we need to take a history and medical review, obesity, Type 2 diabetes, metabolic syndrome, no known preexisting liver disease, rule out alcohol, up to two drinks in women, up to three drinks per week for men. Irrespective of what drink we are talking about with standard glasses for each drink, strongest alcohol containing beverages, we take them in in smaller glasses, in smaller portions so we talk about drinks per week.

We need to think about laboratory tests, ALT, AST. We need to rule out hepatitis B and C, we need to rule out autoimmune liver problems. We need to rule out iron as a cause of the liver problem.

Then we need to move to risk stratification. The liver ultrasound, as I told you earlier, is very sensitive and very specific. If fat in the liver is very high, but it has suboptimal sensitivity for mild steatosis, we do not order. We need to risk stratify with noninvasive fibrosis scores, and the one that we use today is FIB-4, there are several others the FDA is wondering and studying like ELF or PROP III or others that are not part of the recommendations today, but I will talk about this later.

FIB-4 is not perfect. I will show you the data in a few minutes, and if we have suspicion that something is not going well, we may need to do elastography, FibroScan or referred to hematology clinic.

As I told you there are other tests, ELF, VCTE, the PROP III that are evaluated as we speak for these four that are evaluated as we speak, by the FDA. MRE is MR elastography, is very promising and at this point almost pharmaceutical companies are using it to prescreen people instead of liver biopsies, but are not recommended for our clinical practices at this point.

At this point we use very, very simple set of tests, age, AST, ALT, platelet count, to create the FIB-4 score. If FIB-4 is very low, less than 1.3, 2.5 in older patients, it has a very, very good negative predictive value, so if it is very low, you can rule out fibrosis. Negative predictive value is higher than 90% but if it is high, it raises the suspicion but cannot prove fibrosis. Why is that? Because the positive predictive value is relatively low. We need to have cutoff points so with very low FIB-4, very low probability, you can rescreen the subject in two or three years. High cutoff point, unfortunately, we may have high probability, but the test is not ideal, so we need to supplement it with elastography or we need to send the patient to a liver specialist.

Vibration-controlled transient elastography easy to do, relatively inexpensive, you can have it in your office. It's compensated in most places by most insurances, look it up, has high specificity, and you can rule out cases. MR elastography, I don't use it in the clinical practice. It's not widely available, it's more costly, it identifies intermediate stages of fibrosis, it's primarily used for clinical trials by pharmaceutical companies. It may become the standard in the future, but the verdict is not out.

We start with serum biomarkers, FIB-4 is the one that most people use today. Others, as I told you, are out there and are being studied. We confirm the diagnosis or reject the diagnosis with elastography and MRE or MR PDFF is available, but mostly for clinical drug trials.

Dr. MANTZOROS: What are the emerging noninvasive diagnostic algorithms. I told you that this is what is recommended today for general practitioners or endocrinologists. If FIB-4 or NFS is low, we rescreen in two to three years. If the risk is higher, FIB-4 more than 1.3, more than 2.6 in older people, we need to do elastography. If elastography is low, low risk. Elastography is high, then we consider liver biopsy referral to a liver specialist. Very simple algorithm.

This is what the most recent guidelines recommend. Low risk, repeat in two to three years. Normal FIB-4, normal elastography, repeat in two or three years. High-risk, refer to a gastroenterologist or hepatologist for liver biopsy. We cannot do liver biopsy in 80, 85 million Americans who have fat in their liver. It's impossible. We don't have enough liver centers and even if we did, we would have about 10,000 excess deaths and thousands of hospitalizations every year because of side effects, so we cannot do it.

What do the guidelines recommend today? Someone comes to your clinic, Type 2 diabetes, obesity, two or more metabolic risk factors, steatosis that someone might have found serendipitously by doing a test out there think about NAFLD and NASH. Think about tests that we talked about CBC, platelets, liver tests. Rule out excessive alcohol intake, more than 2 drinks per day in women, 14 drinks per week, or more than 21 drinks per week in men. Rule out hepatitis C, with antibodies and reflex type testing for hepatitis C RNA, consider hepatitis B, consider and rule out autoimmune liver problems with ANA, AMA, immunoglobulins. Check for clinical signs of advanced liver disease. If you rule all these out, then you move down this screening algorithm. If of course, something comes back positive here, then we diagnose and treat these conditions. If everything is negative, FIB-4 is the number one test we need to think about. If it is less than 1.3 or less than 2.6 in older people, then low-risk just follow this person, repeat it in two to three years.

If it is intermediate, then do or refer for elastography, liver stiffness measurement, and again, if it is low-risk, two three years and then high-risk refer to a hepatologist.

What do we do in terms of the approach? This is another, we'll go over it in a few minutes in more detail. Low-risk we would manage by PCP, in our endocrinology clinics as we would need to manage for obesity and diabetes with a metabolic risk. Also, lifestyle intervention, weight loss, but there is no reason to prescribe pharmacotherapy for NASH. Of course, we would focus on cardiovascular risk reduction, diabetes care, and obesity care.

However, if we move now to indeterminate or high-risk for NAFLD and NASH, we need to have more structured weight loss programs, anti-obesity medications, think about bariatric surgery and think about medications for NASH. This is where we are going to go over in the next section; how to treat people with indeterminate or high-risk.

Before we do that, let's review again the algorithm. If you suspect it, evaluate alcohol, evaluate other causes, confirm NAFLD, do the blood tests, do the elastography, and then proceed.

Again, liver biopsy has a lot of pros. It's the gold standard to differentiate between NAFLD and NASH. It can tell you a lot about fibrosis stage and define disease activity. It has to be used for clinical trials or when we are in doubt; we don't know what we have.

What are the problems? Costly, very invasive, not only discomfort, but there is morbidity and mortality related to it, very rare, but if you think about the large number of people who need it, it is

significant. It is also limited because the liver is a big organ. We don't know whether with a biopsy we are sampling the right area. There is intra- and inter-observer variability and we are now working as a scientific community on this trying to minimize it using artificial intelligence or other methods and it is not available out there, only 55 liver centers in the USA exist last time I counted. It's not available. We should - - but we have a diagnostic gap.

Liver biopsy is invasive and costly. Ultrasound cannot be used. MRIs can be used, but again, in the context of clinical trials. FibroScan, FIB-4, there is a gap. There are about 20 to 30% of people that we cannot diagnose with current tests, and a significant effort is underway in order to develop FIB-4. This is a top-down approach adding one or two tests to the number of tests that we have to try to improve positive and negative predictive value or what we have proposed is the top-down approach.

Noninvasive liquid biopsy starting with everything that we can measure, clinical information, hormones, glycomics, multiomics and then let artificial intelligence and neural networks pick what is the best algorithm.

We, and others, have shown that several hormones for example, leptin, I told you about earlier is a pretty good predictor with very good sensitivity and specificity but alone, cannot do the trick.

Adiponectin I mentioned earlier is an endogenous insulin sensitizer. It has good sensitivity, good specificity, alone cannot make a difference. What if we put together IGF1, adiponectin, and leptin and all the clinical information and multiomics we have developed on the basis of artificial intelligence and neural networks, a new test that depends on this and we need to refine it and advance it. The two areas, progress is being made today, is better liquid biopsies, blood tests, with multiomic technology and artificial intelligence so we can have better blood tests or already all multiomics are advancing the MR technology so we have MR elastography or MR PDFF, one of these techniques, if it becomes less expensive may be the solution for the diagnosis predictions. This is work in progress, and we'll wait for another couple of years to see what is the recommended approach.

A 51-year-old man comes to your office. He has NAFLD risk factors, past medical history makes me think about. How do you proceed with the diagnosis?

Which of the following is correct? The degree of elevation of liver enzymes, you look at ALT, AST does not correlate with severity of the disease. In many cases ALT, AST can be normal at all stages, including fibrosis. B, liver fibrosis has been linked to morbidity and reduced overall survival. NAFLD and fibrosis are reversible with weight loss or building muscle - - . Differentiate alcoholic versus nonalcoholic fatty liver, AST/ALT can be used which is more than two in alcohol induced fatty liver disease. Or all of the above?

It's all of the above. ALT/AST by themselves can fluctuate, can be normal in later stages of the disease are not reliable. Fibrosis, we need to know; the stage of fibrosis has been linked to morbidity and mortality. It is reversible. Regresses if we intervene controlling diabetes and controlling body weight. Alcohol needs to be ruled out.

What is the next step after FIB-4 if NFS calculation of intermediate risk is high? What is the next step?

Repeat in two or three years, repeat in one year, elastography, or refer to gastroenterologist?

It's elastography. If it is high, next step elastography. If it is normal, you can repeat it in two or three years.

Which of the following could be most probably useful in differentiating between NAFLD and NASH? Ultrasonography, MRI, elastography, or biopsy.

The gold standard is biopsy. In the future we may have other methods, but the gold standard is biopsy.

This review of the diagnostics, I would like to thank you for attending, and we are ready now to move to the next level.

DR. MANTZOROS: In the next few minutes I'm planning to talk to you about the management of NASH. We have discussed that this condition is a dis-metabolism or a metabolism associated condition. That's why, although in the past, hepatologists or other experts could view this as another hepatitis C or hepatitis B story, this is a metabolism condition. Similar to each and every cardiometabolic condition, we need to start with lifestyle modifications. This is the basis on which each and every other intervention should happen.

Review of what I told you earlier, again, it's accumulation of free fatty acids in the liver, which causes lipotoxicity, inflammation, and fibrosis. This is due in a small number of people, to genes, mutations of genes, but in the vast majority it's because of obesity, exceeding storage space, or sarcopenia that lead to insulin resistance and accumulation of fat. If this is the problem, then we should focus on earlier stages of the disease and address insulin resistance, diet, and exercise similar to what we do in each and every cardiometabolic condition.

What do we know from observational or interventional studies? We know that if we induced weight loss through exercise, diet, bariatric - - , if we keep weight loss weight down for at least one year, we keep it down by at least 10%. One hundred percent of people who have improvement in steatosis, 80% would have improvement with weight loss, it's 90% would have resolution of NASH. Seven percent or more significant, 76% improvement in steatosis, 50% improvement in fibrosis, 64% improvement in NASH. What is the problem? Until recently without bariatric surgery, only 10% of people would be able to keep their bodyweight down by at least 10% for one year.

Now we are making progress, and we'll have better medications that in addition to behavioral modification, can help people keep their body weight down by more than 10%, but until recently, this is difficult to achieve. This is what we can achieve in terms of NAFLD and NASH if we can control body weight.

What about bariatric surgery, which is the most weight loss we can achieve now with any means. This is a recent study from Cleveland Clinic, a retrospective study 1,158 patients with biopsy-proven NASH. Six hundred fifty went through bariatric surgery, 500 were nonsurgical controls. We see the nonsurgical controls have 12% cumulative incidence with liver outcomes and 16% are cumulative incidence to develop MACE. If you do surgery, you cut this risk severalfold. You see here nonsurgical controls, liver outcomes, and bariatric surgery very significant decrease going down from 12 to 2% and cardiovascular outcomes from 15% down to 8%. Very significant decrease by bariatric surgery.

What about lifestyle modification? Bariatric surgery is the target of - - . Can we achieve weight loss up to the level of bariatric surgery? This is the benchmark. With diet and exercise, we can achieve very, very small amounts of weight loss. Lifestyle modification is not as good, but still, with weight loss, in several studies, we and others have shown that we can improve NASH and NAFLD.

What is the best diet to recommend out there in addition to weight loss? We have studied the Mediterranean diet in large observational studies and we are not the only ones.

We followed 2,500 subjects for 10 years and we found that those who follow this Mediterranean type of diet consistently, they did not develop NAFLD and they have much less risk to develop cardiovascular disease. In contrast, the lowest 50% of people, lowest adherence to Mediterranean diet, they had more than twofold risk to develop NAFLD and cardiovascular disease. Strong associations.

What is the Mediterranean diet and why is it recommended? In contrast to western diet that we consume in western populations, which is high in processed food, red meats, sugared beverages, high in energy intake, high in saturated fat, so this is a diet that promotes NAFLD and NASH and cardiovascular disease.

A Mediterranean diet and DASH are the healthy diets. DASH is high in fruits and vegetables, low in total fat, and low in salt, and Mediterranean diet is rich in fat, but not animal fat. It's rich in liquid fat and extra virgin olive oil is the best out there. It's rich in antioxidants and polyphenols and also in mono and polyunsaturated fatty acids that create an anti-inflammatory milieu that helps us in terms of cardiovascular risk and NAFLD. It's primarily a plant-based diet. Even within plant-based diets avoiding animal fat and meat, even within plant-based diets not everything is created equal.

There is more and less healthy plant foods and I have summarized here the plant foods to avoid, which foods to avoid. This is about to be published and this is from our studies but other studies have shown similar results. You can get the pictorial impression of what I want to show you. Exactly the same food items that are bad for diabetes and cardiovascular outcomes do not help our livers.

To summarize, refined sugars found in sugared beverages, increase hepatic synthesis of triglycerides, increase gut permeability and endotoxins and promote uric acid production which causes oxidated stress, insulin resistance and there is a dose response association between soft drinks and fatty liver disease in the Framingham Heart Study. I told you about our study; this is the Framingham Heart Study; this is the same. It's the same.

This is what we need to minimize. If we maximize Mediterranean diet or low-fat diets, we can decrease significantly hepatic steatosis in randomized trials. We have a limited number, relatively small studies. We need more studies, but consistently, these studies have shown that Mediterranean type or DASH type diets help.

What about leptin? I told you that leptin is approved for lipodystrophy and fatty liver disease in extreme congenital complete leptin deficiency. This is a hormone that is low in lipodystrophy. The question is, is it good only for complete leptin deficiency or for partial leptin deficiency. This is an open-label study showing that we have shown in this paper that even with relative leptin deficiency, if we give it back, we improve metabolic disease and fatty liver disease. This remains to be shown in randomized placebo-controlled large trials in the future whether this can work on top of lifestyle modification.

Let's go back now to the Mediterranean diet. Very small trials as I told you. If you meta-analyze them, very small number of trials, but meta-analysis shows that they decrease percent fat by about 5%. Are the other diets, low-carb, low-fat diets any better?

Low carb diets out there decrease in the short term, fat in the liver, much more than the Mediterranean diet, but the effect does not last. It's not recommended. Mediterranean or DASH diet is what is recommended today and we'll come back in a few minutes.

It is negative energy balance, restricting calories, causing weight loss, which decreases fat in the liver or the quality of the diet, which is the Mediterranean diet.

The same diet and the same physical activity that is recommended for cardiovascular disease, also helps liver. What is recommended today in the guidelines is the same exercise that's recommended for cardiovascular disease. It improves peripheral insulin sensitivity and de novo lipogenesis in the liver, decreases visceral fat, and increases the LDL clearance and decreases lipid storage and has several positive outcomes, not only in terms of the liver, but also in terms of heart and the muscle and the fat. This is why it is recommended.

What is recommended today in the guidelines? Earlier stage hepatic steatosis, weight loss at least 5%, Mediterranean diet, regular meal pattern, avoid alcohol, avoid fructose, refined sugars. Exercise, increase daily physical activity, aim for 10,000 steps per day or 150 minutes per week, 30 minutes per day, at least, of moderate intensity exercise.

If you have NASH or fibrosis, more weight loss, 7, 10% weight loss. Again, Mediterranean/DASH diet, avoid snacking, avoid alcohol intake, avoid processed, refined foods. If cirrhosis has developed, then we modify the weight loss target. Modest caloric restriction, 5 to 800 kilo/cal per day, increase weight loss targets in well compensated obese patients. You need to be careful here. Protein intake 1.2 to 1.5 grams per kilogram per day and again, no alcohol, fructose. Exercise is recommended for all. This is lifestyle modification on which everything else is going to work.

Now, we realize by saying this that treating NASH is not the work of one person. It takes a village. It takes a family care doctor, an endocrinologist, a dietician, maybe behavioral modification by psychologist to increase body weight loss. Then we need to think about the new medications for weight loss or the medications to improve NAFLD and NASH. We need behavioral modification, and we need to work together with the patient and the family. They don't have symptoms, so we need to work with them to provide information, educate them, create a group of dieticians, behavioral psychologists, and physical activity supervisors to work with the person on weight loss and lifestyle modification, which is the basis for any medication that we may want to use.

What are the barriers? The higher the BMI, we all know, the more difficult it is to decrease body weight by lifestyle modification. We may want to refer to surgery. New medications are more effective. The higher the number of metabolic components, the longer the duration, the less likely individuals are going to successful in losing weight or having regression. We need to be more vigilant. We need to think about neurohormonal mechanisms that are defending the original body weight. We can't make people lose weight. There are mechanisms that make them keep their weight the same. We need to think about it and address them with new medications.

We also need to think about genetic predisposition. We don't have all these tests at our disposal, but they are coming, and there is a panel of tests that is going to be available for us but especially the - - polymorphisms that are associated with a threefold greater reduction in triglycerides in response to lifestyle intervention. These will be the targets for personalized medicine, specific medications that will be addressing these genetic components. Genetic components, one bucket, degree of obesity, duration of the abnormalities are the challenges.

Management of NASH: Overview of Guidelines, Current and Select Emerging Treatment Options

DR. MANTZOROS: In the next 20 minutes I'm planning to very quickly go over the basics, an overview of guidelines and the current and select emerging therapies for NAFLD and NASH. This is an introduction. The next speaker is going to go deeper and broader in terms of medications available to us today or in the future.

My presentation is an overview; quick introduction to what is available to us today and what is coming down the road and I will pave the way for the next speaker.

Again, going over pathophysiology, I told you that in a very small percentage of people we have genetically associated fatty liver disease. Here, personalized medicine detecting these mutations and specific RNA technologies most of the time, that will be addressing these specific polymorphisms is coming down the road. It is in clinical trials today, hopefully will be in the clinic in a few years. This is work in progress.

What about metabolism associated fatty liver disease? Central obesity, fatty diet, sarcopenia that I told you about earlier? Do we have any drugs that can act here? We talked about diet modification, lifestyle modification, about insulin sensitizers. What about medications that would decrease lipotoxicity and fatty acid accumulation? Are there medications that decrease inflammation or fibrosis? I can tell you that we already have some of these medications. More are coming that are addressing each one of these factors; central obesity, sarcopenia, insulin resistance, lipotoxicity, inflammation, fibrosis, one by one.

Activins/follistatins these are from our studies; these are hormones that are peptides that are muscle related peptides. They respond to exercise. They have metabolic outcomes. They improve muscle mass, so if you increase follistatin, you block myostatin and increase muscle mass. These are very promising medications for weight loss and for improvement of NAFLD or NASH. Physiology guides us here.

There are other medications that are now in development for weight loss. The GLP-1 receptor agonists, medications that are based on gastrointestinal - - that decrease - - . Pioglitazone is an insulin sensitizer that I told you about, so how do we put all of these together? If you have NAFLD earlier stage, lifestyle intervention that I told you about, is indicated. It's indicated irrespective of whether you have NAFLD, NASH, what stage of NASH, cirrhosis or not. In earlier stages NAFLD or NASH with fibrosis F1 or F0, there is no role for liver directed pharmacotherapy. For fibrosis in later stages 2 or 3 or cirrhosis, 4, yes, we need medications. For NAFLD or NASH, up to fibrosis stage 0 and 1, standard of care for diabetes, standard of care for cardiovascular risk reduction, lifestyle intervention or medications for obesity. Nothing else is needed. NASH, fibrosis 2 or 3, in addition to that, insulin sensitizer pioglitazone for diabetics, or GLP-1 receptor agonists maybe. Nothing is approved directly for NASH, but all these are in

trials. For diabetics, we use pioglitazone. Think about using it more if you have NASH. Only 8% of our diabetics use pioglitazone. For cirrhosis we need to individualize.

Management of NASH, think about the whole person. Think about NAFLD and liver conditions being part of a cardiometabolic risk where the heart, the kidneys, the pancreas and adipose tissue play a role. All these medications that we have now for insulin resistance thiazolidinediones, for weight loss. Are they good for NASH? It makes sense to try it.

We put together, as I told you about earlier, the current recommendations were published in Gastroenterology in November, you can find the details there. In brief, we recommend lifestyle modification according to the guidelines I told you about earlier. Weight loss surgery which is very effective for patients for whom bariatric surgery is indicated. For commonly prescribed medications nondiabetics vitamin E, several trials up to two years of duration, have shown that up to 800 units per day improves liver histology in nondiabetic adults. Not affecting diabetics probably because the burden of inflammation and the disease is higher but in nondiabetics it works. Vitamin E is not recommended for diabetic patients or NAFLD without liver biopsy, NASH, cirrhosis, or cryptogenic cirrhosis.

In summary, what we and others have shown in animal studies is that medications that act as GLP-1 receptor agonists, liraglutide, semaglutide, you name it, not only decrease body weight, but also decrease inflammation in the liver and decrease hepatic stellate cell activation and regulate carbohydrate metabolism leading to improvement in hepatic outcomes.

Selective or nonselective PPAR gamma modulators like pioglitazone or CHS-131 decrease insulin resistance, decrease inflammation, fatty acid oxidation, and improve outcomes.

PPAR alpha delta agonists like elafibranor in mice work very well. In humans the trials were not positive.

Early data with SGLT2 agonists, empagliflozin is one of them, they excrete glucose in the urine, they decrease body weight, they improve inflammation, autophagy, they decrease SPMs, they also improve steatosis and liver inflammation.

Very quickly I'm going to go over what is now in development. We have at least 60 trials, many medications in Phase II clinical trials to the extent that we cannot perform as many biopsies as we need for these trials. We have four medications in Phase III clinical trials. Statistically, one or two of those will come to our clinic in a couple of years. How do we organize these medications? Normal liver or early steatosis, we need to use medications for weight loss. We need to use insulin sensitizers and these are in clinical trials. Pioglitazone, a PPAR gamma agonist or elafibranor. GLP-1 receptor agonists earlier stages, liraglutide or semaglutide. I told you about dapagliflozin or empagliflozin. There are medications that act by activating thyroid receptors specifically at the level of the liver and they decrease apoptosis and they gave good - - results. There is FGF21 analogs that have shown very good results in early-stage clinical trials and FGF19 analogs that are expected to progress to later stage trials.

As you can see, we have medications that act at the level of steatohepatitis. We have tried a medication in mice in this class of medications that they have very good results in animals and early stages in humans. Are we going to be able to address steatohepatitis by focusing on one or two of the molecules that cause inflammation? Remains to be seen. We see much less medications for fibrosis and cirrhosis.

The more advanced the disease is, the more years it took to get there, the more difficult it will be to cause reversal. My hope that remains to be seen whether I'm right is that the medications on the left of the curve will have much better outcomes in the future.

With that, I would like to remind you that the cornerstone of our approach and treatment is lifestyle modification, exercise, and a healthy diet. Medications will be available to us in the future to help us treat this epidemic, which is a metabolic epidemic of our century.

Thank you very much for your attention.

Now let's move on to quickly talk about the classes of medications that I told you about. Metformin causes a very small amount of weight loss, there is no real effect in NASH - - .

Statins have shown very good results and pioglitazone has shown very good results. I told you about GLP-1 agonists, SGLT2s, and Vitamin E.

Metformin, we meta-analyzed the data out there, very small weight loss, not major effect on NAFLD and NASH outcomes.

Move on to statins, again, we meta-analyzed all the data out there, no one is probably going to do another clinical trial with statins. Statins decrease fat in the liver by about 5%, they decrease NAFLD activity score, they don't influence fibrosis. Late stages of fibrosis are not as good, earlier stages don't stop them. Keep them if you are using them for your patients.

GLP-1 analogs and SGLT2s as well as pioglitazone for diabetics, pioglitazone expands the adipose tissue storage space, so it improves the metabolic outcome, improves inflammation and fibrosis in the liver, several medications in clinical trials, you will hear about it in the next session.

Selective PPAR gamma modulators may be the future. This is from one of our studies in animals, randomized control study improved like every PPAR gamma selected agonist increases mitochondrial function, browning, decreases inflammation, improves adiponectin, improves all the liver outcomes. You will hear more in the next minutes.

I told you about GI secreted hormones. This is from our physiology studies. These molecules increase in response to bariatric surgery. They are now being treated prototypes based on GLP-1 treated, used in the treatment for diabetes and obesity you see more and more duals and triples, duals with glucagon, possibly oxyntomodulin glicentin GIP, coming down the road.

Good results today. How do they act? Do they act in the brain? This is from our studies. They worked in the reward centers of the brain and the prefrontal cortex to make us easier earlier rewarded by food, we don't eat as much, and they decrease hepatic fat significantly, they decrease levels of abnormal liver enzymes irrespective of whether we use dulaglutide as shown here or semaglutide, you decrease fat in the liver, you decrease NASH without worsening fibrosis, but they are not as good in terms of fibrosis for the duration and the dose studied today. There is more coming down the road as you will hear from the next speaker.

We wanted to see whether we could use combinations of these drugs and we have studied in animals one or the other and we have studied the metabolome in the liver. GLP-1 agonists in brief, I don't want to inundate you with details, but you can see the results here. GLP-1 agonists improve carbohydrate

metabolism, they cause moderate lipidomic alterations. PBR alpha deltas they act primarily by restoring the hepatic lipidome and inflammation and oxidative effects. Different mechanisms. In the future, we should be studying and seeing the effect of these medications in combination, I think for better outcomes.

Let's move on very quickly as an overview of SGLT2s. Again, they decrease body weight less than GLP-1s. They have very good results in terms of cardiometabolic profile. They decrease fat by about 2 to 5%, and they improve NASH score.

We have studied empagliflozin, I would say that probably dapagliflozin or it's a class effect is not related to a specific medication. We have studied this in diabetic mice and nondiabetic mice. Again, it improved body weight, cardiometabolic profile, inflammation, ER stress, in both studies. Diabetic and nondiabetic animal models. They improve autophagy, SPMs, and they decrease liver inflammation.

To summarize, there is a lot in terms of preclinical, early clinical studies going on to develop medications for the management of NASH. Late-stage clinical trials, more than 60 Phase II trials, 4 medications in Phase III clinical trials. There are several medications that are very promising, in my opinion, including medications that act specifically as I told you, to limit inflammation.

I will go very quickly over these because the next speaker is going to go over the medications. I mentioned bariatric surgery earlier. Bariatric surgery is a very effective way to cause NASH resolution similar to decreasing diabetes, improving hypertension. If a person qualifies for bariatric surgery and goes through bariatric surgery, we would expect NASH resolution in 85% of the cases after one year or five years. Fibrosis improvements, significant after one year, even more significant after five years. It's an effective therapy.

Several studies have shown that complete resolution of nonalcoholic fatty liver disease after bariatric surgery, a systematic review and meta-analysis here, resolution of steatosis, very significant percentage, inflammation, fibrosis, ballooning. The problem is we cannot do bariatric surgery for each and every person with NAFLD and NASH. In the extreme cases of very high body weight, it will work. Number two, we are learning from what is happening after bariatric surgery, which hormones are altered and will try to make medications out of these hormones. GLP-1 for example, is the hormone that goes up after bariatric surgery. Other GIAP, glucagon, duals or triples are now coming down the road, and we will try to replicate what happens with bariatric surgery with medications avoiding surgery.

What is the bariatric surgery down the road? I told you that several molecules are altered. What we have observed from a longitudinal study of patients that we have followed for at least ten years after bariatric surgery, is that several peptides are permanently restored after bariatric surgery. We observed, and I can show you here, decreases that are robust in BMI, fat mass, waist circumference over ten years.

Metabolic profile, liver function tests, renal outcomes, cardiac ultrasound is improved up to ten years after bariatric surgery. What we show here is that both gut peptides to a large extent, leptin adiponectin significantly improved and then molecules that are associated with building muscle mass are also significantly - - . All these hormones that are related to pathophysiology of NASH hormones that decrease body weight, improve muscle mass, leptin and adiponectin, will be used in the future in the context of making medications and giving it to people instead of doing surgery.

Next steps. We need to learn more about bariatric outcomes in patients with NASH. BRAVES study is one of them we are participating in. Can we make medications using these hormones alone or in combination or can we have a pill that will replicate the effects of surgery?

To summarize, we need to think about this disease. We need to diagnose it and treat it with what we have at our disposal today. The future is bright. Medications that act through the GI tract, treatments, brown adipose tissue, muscle, either as pharmacotherapy or gene therapy are being developed and will make a difference in the next few years. Several are in development. We just published this paper in Endocrine Reviews but it is coming. Until then we have certain tools in our therapeutic armamentarium and we should use them. We should make the diagnosis and use what is available to us and watch for what is coming down the way because down the road a lot is going to come in the next two or three years in terms of new treatments.

Thank you very much for your attention. I hope that this was very useful to you and your patients.