LISA GLASS: We're going to talk about the definition and epidemiology of NAFLD. We'll get into the pathophysiology of this disease and how we make the diagnosis. And then I'll end with some treatment and management of NAFLD. And it's nice that Lauren and also have detailed information on that, as well.

So first the definition. NAFLD is the presence of hepatic steatosis, so that's fatty liver infiltration, and the absence of secondary causes of fat accumulation. So patients, most importantly, cannot have a significant alcohol use history. In men, that's defined as anything greater than 21 drinks per week, and in women that's anything greater than 14 drinks per week.

So that actually was confusing to people, in the past, where they were looking at these liver biopsies, and seeing livers that looked almost identical to alcohol related steatohepatitis, but they were, in fact, in patients without significant alcohol use. Patients can't be on medications known to cause hepatic steatosis. So those are things like antiarrhythmics, like amiodarone, anti-seizure meds like valproic acid, or tamoxifen used to treat breast cancer.

And they can't have any other chronic liver diseases. So there are actually subtypes of chronic hep C that can lead to fatty liver. And some of the less common, hereditary forms of liver disease can have some fat deposition, as well. I think in the last several years, in particular, the liver world has become quite interested in this disease. And it's probably a couple different reasons at play. First of all, we have finally had the benefit of finding really effective and great hep C therapy.

So there is a lot of work going into that. over a long period of time. And now we're curing patients like we never thought possible. And so that's freed up a lot of time to pay attention to other liver diseases. And we've also realized just how many people are affected worldwide. Almost 25%, with of course regional variations, so relatively low prevalence areas are considered to be in Northern Africa. And actually the highest prevalence rates are found in South America and the Middle East.

I'm sure we're not surprised to hear that the US is also a very high prevalence area. So we think about 30% of Americans have NAFLD. And that's well over 95 million people that likely have this disease.

In the US, in particular, it's the second most common cause of end stage liver disease, or cirrhosis of the liver. And it's the second most common indication for liver transplant. That's behind chronic hep C, which is first in both of those categories. And so, as I've already mentioned, we're now curing hep C and we're still seeing a rise in NAFLD.

So over the next decade it will likely take first place. So NAFLD is actually one of two different disorders. The vast majority of patients with NAFLD will have simple steatosis, and that's when at least 5% of the liver cells, or hepatocytes, will have fat accumulating in them. But none of the other liver cells will be damaged and there's no inflammation, or fibrosis found. These patients don't have a whole lot of liver related morbidity and mortality. But we know there are cardiovascular risks are really increased.

It's less common that patients will actually have steatohepatitis, or NASH. And that's when we have that same fat deposition, but the liver cells are damaged and there's a lot of inflammation. Really the characteristic finding on biopsy are these ballooning hepatocytes, which are basically degenerating liver cells. That drives the inflammatory process. And we can start to see the development of fibrosis, or scar tissue in the liver.

It's actually important to figure out which category these patients fall into when we see evidence of steatosis. So again, 80% of people will have simple steatosis. So on the left panel, you see on the top, this liver that has these round fat droplets in it, which is atypical. A normal liver won't have any fat in it. But the remaining part of the liver has actual normal appearing liver cells, it's kind of a lighter pink color up there. Not a whole lot of inflammation or fibrosis.

On the right hand side, we see that 20% of patients will actually have NASH. That top panel has a darker appearance of purple and some blue. And that is inflammation of the liver cells, even without the fat deposition. So if a pathologist saw the top panel, it would see the steatohepatitis. It would rate the fibrosis stage as zero. So it give it an F0. But these patients can have progression of their fibrosis.

So the middle panel there, you start to see these blue channels through the liver cells and the fat cells. And that's the development of scar tissue or fibrosis. So that middle panel would probably be given an F2 score, or maybe early F3. And 20% of patients will actually go on to develop cirrhosis.

So the bottom panel has a much broader band of scar tissue, that's bridging bands of fibrosis

between portal tracks. Elsewhere on this slide you would probably see regenerative nodules, and that's our definition of cirrhosis. And we call that F4.

There are many risks associated with the progression. So as people age there are a higher risk if they have increasing weight and increasing BMI, as well as if they develop diabetes or glucose intolerance. So NAFLD is the hepatic manifestation of the metabolic syndrome.

So if we think of the stereotypical patient with NASH, they're going to be obese, which is a BMI greater than 30. They'll have central fat deposition, so they'll be that apple patient in the top corner. And that's really a marker of visceral adiposity, so intra-abdominal fat stores. That then can make them susceptible to insulin resistance. So we start to see patients with diabetes, or components of the metabolic syndrome. So hyperlipidemia, hypertension.

Patients with other obesity related diagnosis, like polycystic ovarian syndrome, are at risk of NAFLD. As patient's age they're more likely to develop this. And we actually see some ethnic disparity as well, particularly in the US, where the Asian and African-American populations actually have a lower likelihood of developing NAFLD with similar risk factors. Caucasians fall in the middle, and patients of Hispanic ethnicity actually have an increased risk. If we look at just the ethnic disparity part of this issue, we think that there are genetic components that drive a lot of this disparity.

I think this nicely outlines how the prevalence of NAFLD really has mirrored the increasing prevalence of obesity in the US. So starting on the left is NHANES-based data, which is a population based data that tracked obesity over about 25 to 30 years. Back in the late 80s, mid 90s, we saw that about just over 20% of Americans were obese. A few years ago that almost doubled to close to 40%. And those colored lines underneath show that it's really the all the stages of obesity that continues to rise.

The panel on the right is looking at the prevalence of NAFLD in veterans receiving care in the VA system. And they used a validated algorithm to find NAFLD, based on patients' risk factors and lab values. And they found that over the course of about seven years, the prevalence of NAFLD almost increased by over threefold, from 5% in the early 2000s, up to almost 20% at the end about 2011.

And I think they really underestimated the prevalence of NAFLD, in this case, because they were using labs to find them. So patients had to have elevated liver tests, and we know that people can have NAFLD and have completely normal liver tests. So if anything, this is an

underestimate of how many of the veterans are affected.

There are many high risk populations, and the prevalence really skyrockets from there. So over 90% of patients presenting to bariatric surgical centers have NAFLD. Almost 2/3 of patients with diabetes, half of patients with metabolic syndrome or dyslipidemia. We know that men are twice as likely to have NAFLD compared to women with similar risk factors. And then again, the ethnic disparity, where patients of Hispanic ethnicity have a 50% chance of developing NAFLD.

But not everyone who's obese, actually, has fatty liver and the reverse is true, as well. So not everyone who has fatty liver, actually, is obese. And people can actually have completely normal BMIs and still develop hepatic steatosis.

And so I think this brings up the importance of how fat gets distributed in our bodies. Again I referred to visceral adiposity-- that's fat that builds up in the abdomen or around the internal organs-- that leads to insulin resistance. It tends to be metabolically active fat. So some people are prone to developing that. And they can appear to have normal BMIs on the exterior, but in fact, they're accumulating this fat. Other people are actually more prone to developing subcutaneous fat, which almost may be somewhat protective, because it's kind of a depot for the excess calories, and it's not as metabolically active.

So this is, again, NHANES-based data, and they were able to look at ultrasound on patients, and saw that, even in people with normal BMIs-- so less than 25-- about 20% of them had evidence of steatosis. And if they expanded that BMI up to 30-- so that's considered non-obese-- the prevalence went up to 27%.

I think the Asian population is at particular risk for non-obese or lean NAFLD, because studies have shown that, for any given BMI, an Asian patient is going to have higher amounts of fat. So both subcutaneous and visceral. And so there are some people that have proposed coming up with a different BMI scale for this patient population, because ultimately we want to be able to prognosticate what their upcoming co-morbidities may be for any given weight. So while a Caucasian or non-asian population would have normal BMI up to 25, we'd proposed to drop that BMI down to 23 in the Asian population. And obesity, again, is defined as BMI above 30, but in the Asian population we should probably drop that down more to 25.

So we know that diets in patients with NAFLD tend to be different than patients without. And there tends to be an over-consumption or increased intake of industrial fructose or high-

fructose corn syrup in. The US, that's sugar sweetened beverages, most frequently. They tend to have higher amounts of red meat intake, and saturated fats, and cholesterol. And they're less likely to have more healthy diets, that are high in wholegrain fibers, lean proteins like fish or omega 3 fatty acids.

So we know that there are multiple risks associated with intake of fructose. It drives pathways that end up creating fat in the liver. So the liver can take that fructose or carbohydrate and make it into a free fatty acid. It promotes dyslipidemia, and increased visceral adiposity, and it increases the risk of developing insulin resistance.

There's also changes to the gut microbiota, which can lead to increased intestinal permeability, and that's delivering increased inflammation into the liver. We know that, looking at patients with steatosis, if they drink more than six sugar containing sodas per day, in general, they not only have a risk of having NASH-- so the inflammatory type of liver disease-- but also NASH with fibrosis.

Patients are also more likely to be inactive. So this was a survey-based study of over 800 patients with biopsy-proven NAFLD. They asked them about what their physical activity tended to be like. Greater than 50% of these patients were inactive or sedentary. And less than 20% of them actually met the recommended daily physical activity guidelines set forth by the US Department of Health and Human Services.

And there's detrimental effects of being inactive, so there's all the weight related things we think about. So patients will gain weight, gain central adiposity, develop insulin resistance. But we also see differences in systemic inflammation-- inflammation in adipose tissue-- and this can drive patients' cancer risk and the development of coronary artery disease.

So I have two slides on the pathogenesis of how the fat actually gets into the liver in fatty liver disease. So this first panel is looking at just the steatosis. And so what normally happens is fat is delivered to the liver as a free fatty acid. It's then converted into triglycerides, where it's more metabolically stable. And then it can get exported to the systemic circulation through the assembly of VLDLs. So in the setting of steatosis, we have an increase in the inflow, and also a decrease in the outflow. And that, overall, leads to this fat deposition.

And, really, the primary inciting event, even for the simple steatosis, is the existence of insulin resistance. It can drive that de novo lipogenesis we talked about, we have increased delivery

from diet. And also the visceral adipose tissue is sending free fatty acids to the liver, and that's all regulated in insulin resistance.

We also have less export, so there's a down regulation of triglycerides leaving, because there's less VLDL being made. And then there's also less beta oxidation happening, and so free fatty acids are accumulating, as well as the triglycerides.

So this is the subset of patients that develop this steatohepatitis, so patients with NASH. I think a lot of it boils down to just the volume of the influx of the fatty acids. The systems get overwhelmed. So mitochondria start to dysfunction, there's the production of lipotoxic toxic species, and a lot of oxidative stress that then drives the inflammation. Then there's also those changes in the gut microbiota we talked about. There's delivery of inflammatory substances, which ultimately will lead to damage to the cells, increased scar tissue, potentially cirrhosis and hepatocellular carcinoma.

So overall, we think that patients with NAFLD-- so thinking about more of this simple steatosis-- have an overall increased risk of mortality. It's actually a bit hard to make these determinations without patients all having liver biopsies to prove that they have just the steatosis and not NASH. And a lot of these large population natural history studies don't have histology.

But a recent meta-analysis came out and saw a small, but significant, increase in overall mortality, and they were separating out NAFLD from NASH. And so we do think there is a small overall risk. And, of course, without a doubt it's cardiovascular disease and cardiovascular events that we worry about. That's what these people will die from. Second place is their increased risk of malignancy, and then further down it's actually more liver related death.

It's more clear that Nash is associated with both all-cause, and then look at the increase in liver related mortality. So that's clear. And there's actually a few studies that wanted to look at the histologic features of NASH, to see which thing would greatest predict this increase in mortality. So, is it the extent of steatosis? Is it the extent of inflammation or damage to the liver? Or is it the scarring? And all of them have really pointed towards fibrosis as being the driving factor of increasing this mortality.

So they used NASH patients with no fibrosis as their reference range, and saw that people with moderate stages have almost double the mortality. And that increases to over six-fold in

patients who have F4 or cirrhosis. So really when we're thinking about how to effectively manage these people, or what our outcomes should be when we're trying to come up with treatment, we need to keep this in mind. That it seems to boil down to fibrosis.

We know that patients with NASH have increased risk of developing cancer of the liver, hepatocellular carcinoma. It's now the third most common cause in the US, and that's behind chronic hep C and chronic hep B. And compared to these viral forms of liver disease, NASH actually has a pretty low annual incidence. So patients have about 0.5% risk of developing HCC in any given year. And that's compared to people with chronic hep C having 3% per year.

But because we're dealing with such high numbers of patients, we're seeing that this prevalence is really increasing, and it's just going to continue to grow. And then, we also have found that patients without cirrhosis and NASH are actually at risk of developing HCC, as well. So it's another scary factor.

So we make the diagnosis of NAFLD usually incidentally. So we usually pick this up when patients are getting imaging for other reasons. And certainly ultrasound is a common way that people are usually initially diagnosed. The ultrasound report typically says increase echogenicity, or increase echo texture. And that's usually consistent with fatty deposition.

So I have two examples. On the left, we have a dark normal appearing liver and you can see that it lights up really brightly when it has fat infiltration. It's actually a pretty good way of finding fat, but with the caveat that greater than 30% of the liver needs to be involved in order for ultrasound to be able to detect it. So there's much better ways of finding it, if people have less than 30%. It's found on MRI and non-contrast CT, as well.

And oftentimes I'll find people in my clinic with elevated liver tests, and that's really what prompts the work up. But it is important to keep in mind, as I referenced, before that over half of patients who have even NASH or steatohepatitis will have completely normal liver tests. So we can't always rely on the labs to help us out.

Usually patients don't have any symptoms in the early stages. Sometimes people will remark on having some right upper quadrant fullness or discomfort. And sometimes that's actually a response to the degree of fatty infiltration. We can have the liver swell against its capsule and that can sometimes cause some discomfort. And fatigue is common among patients with NAFLD.

If we actually want to get into and quantify the amount of fat in the liver we have to use other modalities. So, by far, the most sensitive and accurate would be an MR-based imaging test, like spectroscopy. It's very expensive, it's not widely available. It's usually at research centers. But it can detect as little as 5% of steatosis in the liver, with 100% accuracy. So this would be beneficial in trials, looking for differences in fat in response to treatment. Or if you needed to figure out what was driving some elevated liver tests, and the ultrasounds were just not picking it up.

FibroScan is more widely available and becoming more popular. It also has some software on it called controlled attenuation parameter. And it makes use of that fact that the amplitude of the ultrasound wave will actually decline if it comes across fat in the liver. And so it can measure the amount of that decrement, and then give us an estimate of how much fat's in the liver. It's not nearly as accurate as the MR spec, but it's better than straightforward ultrasound.

But I think a much more important question we need to ask is, really, how much fibrosis is in the liver. Because that's what's going to predict the morbidity and mortality in patients. So there's actually a ton of noninvasive ways that we can try to get at this answer, without subjecting everyone to a liver biopsy, if we can avoid it. So there are some tests where you send the lab sample out, and you pay for them to look at the sample, look at a lot of atypical tests, or newer tests, and send back a score. I actually like to use the scoring systems that use just straightforward clinical labs that I'm collecting, anyway, and patient characteristics that's easy to determine in the office.

So I typically will start with NAFLD fibrosis score, that was developed and validated just for NAFLD. And it can also predict outcomes in patients. So you input age, BMI, presence of pre-diabetes or diabetes, platelet count, albumin, and liver enzymes. And it will divide patients into one of three categories. So if patients fall below the low cut off, they are very unlikely to have advanced fibrosis. And the negative predictive value of this test is its real strength. The greater than 90%, we can confidently tell patients that they don't fall in the higher risk category.

So these are patients that should be counseled for lifestyle changes, and perhaps managed mostly by their primary care. Patients who score higher than the high cut-off are much more likely to have advanced fibrosis-- with a positive predictive value of just over 80%. So they'll need additional testing to confirm the findings. And then we still do get a number of patients who fall in between those two cut-offs, so the indeterminate patients. So we do additional testing with them, as well.

Usually the second test is the image-based, and that's the transient elastography, or FibroScan. It's basically an ultrasound probe that has transducer on the end. And the technician will place it on the chest cavity, in between the ribs, at our standardized place. and send a mechanical shear wave through the liver.

And we know that energy travels more quickly through a stiff, or fibrotic, liver, and much more slowly through normal kind of gel-like liver. So the machine will measure the velocity, give a slope of the velocity on the machine. So we know this the steeper the slope, the faster it's traveling. And the technician will collect at least 10 valid measurements. And we'll make sure that they all were within about 30% of each other to reassure us that we're getting accurate results.

So it gives us a median stiffness score measured in kilo pascals, as well as the interquartile range. So we know that it's important that patients prepare for this test correctly, and we know there's several circumstances that can lead to falsely elevated results. And one of those things is having significant steatosis. So we've had some concern and NAFLD patients, but I think that additional controlled attenuation parameter part of the FibroScan has helped us overcome that. And we've also had a larger transducer for our obese population that's helped reduce the failure rate.

So it's obviously important to make sure we're getting valid results in NAFLD patients when we're utilizing FibroScan so frequently. This study from last year looked at 170 patients, compared FibroScan results to liver biopsy results, and found that the optimal cut-off to predict advance fibrosis is a FibroScan result of 9.9 kilo pascals or above. And it detected that advanced fibrosis with 95% sensitivity, and pretty good specificity, as well.

This study last year was actually using the medium probe, which is what was developed in Europe. We now have the XL probe as part of the FibroScan being approved in the US. And so it's really reduce the failure rate in our obese patients.

Not everyone can avoid a liver biopsy, though, and a liver biopsy is the only way that we can definitively tell a patient if they have simple steatosis versus NASH. And our liver society recommends biopsy in patients who have a lot of risk factors for NASH, or findings of advanced fibrosis on our scoring system-- our non-invasive scoring tests. Or if we're ever concerned about an alternative liver disease, we want to make sure that we get a diagnostic biopsy.

When the pathologist look at the tissue under the microscope, they usually give a gray NAFLD activity score, which grades the extent of macro-inflammation. And it will give us a stage of fibrosis, like I referred to before, anywhere between F0 and F4. This was initially made for research trials, but I think the pathologists have now started using it more frequently just to characterize the biopsies of patients with NAFLD and NASH, to make it more standardized.

The biggest take home message that patients need to get when they have a diagnosis of NAFLD or NASH, is that this is both of these issues are completely reversible. They see people in clinic, and they are under the impression that they're stuck with what they have. And so I think it's an important message, that we start reinforcing immediately, is that this may not be easy yet, but these things are absolutely reversible.

So we want to screen them for co-morbidities, we want to make sure they're co-morbidities are being treated. If we make the diagnosis, it's really important for me as a hepatologist to reinforce that statins are completely safe and very indicated in this patient population at increased risk for cardiovascular disease. So I always wanted to make sure that their primary care knows that and doesn't stop a statin. When patients have simple steatosis there's really no liver directed therapies that we have to offer them, at this point. But everyone should get lifestyle modification recommendations, and I'll get into that in a little bit.

When we make the diagnosis of NASH, we do have a couple potential pharmacologic therapies that we can use at this time. And, of course, we hope there's more in the future. And we want to do the same sorts of things with patients-- protect them from their cardiovascular risks. Statins are absolutely safe to use in these patients, even with elevated liver tests. We should actually be using statins in people with compensated cirrhosis, there's really no issue with that, as well. So most of these patients should be on a statin, if it's otherwise indicated, and again we work on lifestyle modification, as well.

So the bottom line and the backbone of treatment for both categories of these patients NASH or NAFLD, is weight loss. That's the end game. We have lots of nice studies that have shown the degree of weight loss is really correlated with how much improvement we can see on a liver biopsy. If we're bypassing at baseline, and after some sort of intervention or some sort of weight loss.

So patients sometimes just need to lose as little as 3% of their total body weight to see an

improvement in the extent of steatosis. So that would be patients who don't have NASH-- have fatty liver-- they are they could lose as little as 3% to 5% and still have an improvement. If patients have NASH, they likely need to lose more like 5% to 7%, and we have seen improvement in both the fat and inflammation, with this degree of weight loss.

And then there's mounting evidence that, even if patients have fibrosis, which we used to think is kind of a permanent change, we can actually have improvement in the degree of fibrosis and scarring if people are able to lose greater than 10% of their body weight. So that's pretty important to reinforce.

This is a recent trial looking at over 290 patients who had biopsy-proven NASH, and they underwent a lifestyle modification. So they had a calorie deficit diet of, I believe, 750 kcals per day, or might have been 500 kcals per day. And they were put on a physical activity regimen. And they had a biopsy of baseline-- a liver biopsy-- after their intervention. And they had found that 30% of their cohort was able to lose at least 5% of their body weight, 60% of them had complete resolution of their NASH, and 82% of them had at least a two point reduction in that NAFLD activity score that I was referring to.

Now, there is 10% of the patients that actually could lose greater than 10% of their body weight. And the exciting finding there was, of course, the NASH improved significantly, but almost half of them actually had improvement in their fibrosis. And that is, as we've talked about a much more important end point in patients with NASH.

So the downside to lifestyle intervention or weight loss is just how difficult it is. In only 10% of the previous cohort was able to lose 10% of their body weight. If we took all the weight loss trials in NAFLD, we'd see well under 50% of the enrollees are able to attain 5% to 7% total body weight loss. And these are the people who are motivated. They join the trial, they're getting supervised, they have extra kind of resources, in all likelihood. And we're seeing less than 50% of them being able to lose greater than 7%.

And then there's the question of how long this weight loss can actually be sustained. And I'm sometimes talking to people in their 30s about having NASH, and already developing scar tissue. And so I'm trying to find ways that they're going to stay healthy over the next four decades.

Weight loss related trials really show that, in general, people tend to regain at least half of their lost weight within the first three years. And it doesn't seem to make a whole lot of difference if

people are doing things in a kind of a step wise fashion-- making healthy choices and losing weight over a relatively long period of time. Versus people who are going on more exaggerated diets and losing weight really quickly. They both tend to regain, which is somewhat disappointing.

In looking at the components of lifestyle modification, there are some trials looking at diet in particular. And not a whole lot of data is available, but it seems the most important thing is that patients are recommended to have a calorie deficit. The bottom line is they need to take in less calories, with a goal of about 500 to 750 kcals per day.

Some trials have looked into low carb diets versus low fat, and at least in the NAFLD literature, it seems that it's resulted in very similar amounts of hepatic fat reduction, when we use that MR spec to measure. And there seems to be similar reductions in ALT and insulin resistance.

So I think, really, the bottom line is patients just need to be taking in less calories. But there's some interesting more recent data on Mediterranean diet. First of all, I think there's a lot better information out there and how beneficial it is for metabolic diseases. And so we can kind of extrapolate that NAFLD patients would benefit from this, as well.

But there's also some recent pilot study in NAFLD in particular, randomizing patients to either Mediterranean versus low fat diet. They found similar weight reduction in both groups, but the people on the Mediterranean diet had a better improvement in hepatic fat. And had a better insulin sensitivity profile at the end. So that's pretty promising, but we have it's a very minimal amount of data so far.

Regarding the physical activity, we know that there's many benefits, related to the liver in particular, actually, with increased exercise. So it will improve insulin sensitivity, which decreases that pathway of the hepatic lipogenesis. There is a reduction in visceral fat stores, and so we can reduce that lipid delivery to the liver, through the pathway we talked about before. And then we can see and improve VLDL clearance with physical activity. And then, some suggest that the increase in activity can actually help maintain that weight loss, that's been driven by the diet modification.

So this is a trial, again, looking at biopsy-proven NAFLD patients, and looking at what predicts NASH and fibrosis. And asking patients about their activity levels. They found that patients who engaged in vigorous activity-- which they defined as patients using like the elliptical machine or jogging on the treadmill for over an hour and 15 minutes per week-- had a reduced risk of

having NASH. They were more likely to have the simple steatosis than the inflammatory NASH. If patients actually did this for over 2 and 1/2 hours per week, they had a lower risk of having advanced fibrosis.

We don't know for sure if there's any particular exercise that's more or less beneficial. So aerobic exercise and anaerobic weight training have both been shown to reduce hepatic fat by almost 30%, independent of weight loss. So that's important when talking to people with a lot of issues with joint pain or limited mobility. So they can benefit from doing more stationary resistance training, perhaps, and not needing to go out and take a jog.

So again, lifestyle intervention. I think the bottom line here is that people need to lose weight. The more weight they lose the better their liver's going to look under the microscope. We think, likely, it boils down to a calorie deficit, more than anything else. Maybe the Mediterranean diet, we'll be able to get better data with that. I think it's reasonable to recommend that they should really focus on reducing high-fructose corn syrup and industrial fructose as a good way to prevent all the other negative impacts of that.

And patient should have moderate exercise for hopefully up to 2 and 1/2 hours per week. If they can build that up, that would be great. Of course, that's easier said than done. It's not always successful. Which brings up the topic of bariatric surgery.

So both the amount of weight reduction and the sustainability of weight reduction is remarkable, even at 10 years after surgery. There's a mean weight loss of about 14 to 25% of total body weight, which is a lot more promising than some of the lifestyle modification groups. At two years post-op, 75% of patients can actually resolve their diabetes. At a year, 80% will no longer have high blood pressure. 60% to 100% of patients won't need their lipid medications anymore. And there's a clear cardiovascular and overall mortality benefit in patients who received bariatric surgery overall.

So there's some trials looking at bariatric surgery in NAFLD patients, in particular. The first large prospective trial came out in 2009. A large number of patients undergoing various bariatric procedures. They looked at baseline biopsies-- one at one year, and one at five years. They saw a lot of improvement in steatosis and inflammation in patients. But they did notice this significant, but very small, increase in fibrosis.

It's important to recognize that 96% of the cohort actually had less than F1 fibrosis. So they

didn't have much to start with, and they developed a very small amount. But it was statistically significant. So that brought some questions up. The other important point to make is that there was no progression of fibrosis after that one year mark. So it tended to develop at one year out, and it was stable from one to five years.

More recent studies have looked at NASH in particular, in over 100 patients, prospectively, paired biopsies-- one at baseline, one a year later. They actually found NASH resolution in close to 90% of patients. And they actually saw fibrosis regression, so that's a very important finding. 34% of these patients actually had improved fibrosis. So that's good. So everyone in the second trial had NASH, or the inflammatory type of NAFLD. People had NAFLD or NASH in that original study.

There's been a meta-analysis looking at very heterogeneous bariatric surgery trials. That's the downfall, we don't have many great big, prospective trials. The meta-analysis does feel like there's an improvement, both in inflammation and fibrosis, overall. But it's still premature for us to recommend bariatric surgery as primary therapy for NAFLD. Many of our patients would benefit for many other co-morbidities, and so we encourage them to be evaluated, if that's something that they qualify for, or they're eligible for, and something they're interested in. But we wouldn't be able to recommend it if that was their primary indication-- was their liver disease.

I'm going to end with a couple pharmacologic therapies that we can use to treat biopsy-proven NASH. I never start medications unless I do have that biopsy result in front of me, because of some potential side effects of being on medication.

So vitamin E is the first, it's an antioxidant, and it is thought to benefit that oxidative stress we talked about, in the setting of NASH. The largest trial to date is from 2010, it's the PIVENS trial. It looked at all non-diabetics receiving either vitamin E or placebo in the first group. Their primary outcome was an improvement in the activity score by at least two points, without worsening in fibrosis.

And they did see a significant improvement in the patients receiving vitamin E, compared to placebo. So 42%, versus 19 in the placebo group. They saw greater numbers of patients with resolution of NASH in the treatment group versus placebo. But this didn't quite meet statistical significance, and they did not see any difference in fibrosis.

The treatment took place over the course of two years. So the biopsies were two years apart.

Vitamin E does have some potential adverse side effects. At first, we were concerned about an increase in overall mortality, but I think that's been debunked when we've looked at the quality of the data suggesting that. But men have an increased risk of developing prostate cancer, and that's important to talk about. And there is an association with a potential increased risk of hemorrhagic stroke.

So that's why we want to save vitamin E just for patients who have biopsy-proven NASH, because those are the patients that would stand to benefit from it. We don't want to subject others to the potential side effects. Usually if I start vitamin E, I'll watch liver enzymes periodically over the course of six to 12 months, to see if I see an improvement. I think if liver tests don't really budge, it's unlikely to be working very well. So probably would be encouraged to stop the medication. Sometimes getting a repeat FibroScan, or something like that, a year or two after starting can help figure out if we're seeing any improvement.

The second treatment we have to offer patients is called pioglitazone. It's a PPAR agonist that can reverse adipose tissue dysfunction, insulin resistance. It's used to treat diabetes and obesity. The PIVENS trial I just referenced actually had pioglitazone arm, so it's been looked at in non-diabetics with NASH.

And it narrowly missed significance, where their primary outcome of that decrease in NAFLD activity score. So 34% of patients in the treatment group versus 19 in placebo. They had an a priori p-value of less than 0.025 going into it, because it was a triple arm study. So it's under 0.05, but it didn't quite meet their significance.

But more significantly, higher numbers of patients actually had a resolution of their NASH. At 47% versus 21. Again, no significant improvement in fibrosis. Since then, last year, this very interesting study came out, looking at pioglitazone in pre-diabetics and diabetics. Everyone in the trial was on a calorie-restricted diet-- about 500 kcals per day-- in addition to receiving pioglitazone or a placebo.

And they did find a significant improvement in the activity score, resolution of NASH, and, in this case, they actually did see improvement in fibrosis, which is pretty exciting. So 40% of patients had improvement in the treatment group, versus 25% in placebo. Now the improvement that we saw in placebo is likely a reflection of everyone being on a calorie restricted diet. Then the biopsies in this study occurred 36 months apart. After 36 months of treatment.

So I think the outcome of this trial, last year, prompted this group, this year, to conduct another meta-analysis, because I think pioglitazone is building popularity right now, as some of these trials are coming out. So they wanted to see if these high-risk NASH patients with F3 to F4 fibrosis could have improvement on pioglitazone, and conducted this meta-analysis. So their primary outcome was someone going from a very high-risk, advanced fibrosis stage, down into a less advanced lower risk stage-- from F3 to F4, to F0 to F2.

And patients who were on pioglitazone had three times the likelihood for improved fibrosis, and three times the likelihood of resolution, compared to people on the placebo arms. So that's all exciting.

I have been hesitant to use pioglitazone I may use it more frequently, now, with that data, because it is associated with weight gain. So that's discouraging to everyone, right? So you're treating their NASH, but they're gaining up to five kilos. So what do you do with that?

But the studies actually show that some of this weight gain is related to water retention, and there have been some studies looking at fat distribution. And so there tends to be a decrease in visceral fat, and an increase in subcutaneous fat. So it kind of gets redistributed. And our end game is to decrease visceral adiposity. That would be a benefit of pioglitazone. There are some concerns for cardiac risk and bone loss in women. So it's also important to have those conversations with your patient.

So to wrap it up, NAFLD is the most common cause of chronic liver disease worldwide, and unfortunately, it continues to climb. It's slated to be the primary indication for liver transplantation in the next decade. It's associated with an increase overall mortality, and primarily we're concerned about cardiovascular risk in these patients. But in the NASH population, it's really fibrosis that predicts their adverse overall and liver related mortality.

The bottom line, right now, is patients need to lose weight. That's really the safest and most effective things we can do for them. As difficult as it is, it would be great if people could lose 10% of their body weight, because we need to get the maximum benefit in their liver. It looks like calorie restriction is probably the best way to go about that, rather than necessarily recommending a particular diet. And it's worthwhile to talk about the decreasing intake of high-fructose corn syrup. Encouraging people to be physically active is an important thing, as well.

We can't yet use bariatric surgery as primary treatment for NAFLD, but if patients are

otherwise eligible, the data actually looks quite promising. And for biopsy-proven NASH patients, we can consider using vitamin E. Right now, it's only recommended for non-diabetics, based on the PIVENS trial. There's some growing evidence that it's beneficial in diabetics, as well. We just don't quite have enough data the AASLD, our liver society, just updated their guidelines, and they can't yet recommend it in diabetics. But they are noticing that we're getting more data in that patient population. And we can consider pioglitazone in patients with or without diabetes.

Thank you very much.