[MUSIC PLAYING]

KAPIL CHOPRA: Thank you, Dr. [INAUDIBLE], for the kind introduction. It's a pretty neat way of introducing myself, is before and after a liver transplantation. So the topic that I've been given today is fatty liver disease, both alcohol and nonalcoholic.

Now, how do patients come to light? I think each of you may see patients in different clinical scenarios. People have liver tests done as part of a comprehensive metabolic panel, annual physical exam, health insurance, disability insurance, et cetera.

Another common way that we are seeing patients, abdominal imaging is being done for God knows what reason. Patients show up in the ER. CT scans are done of the abdomen, CT scans of the chest. The upper abdomen is in that image, and you have a fatty liver. And that's how the patient shows up in practice.

Now, this slide kind of summarizes what fatty liver is. It's either alcohol or nonalcoholic fatty liver disease. Everything else is actually very, very rare. Just for completion, I mean, I have a list over here-- different conditions associated with extra fat in the liver.

There's a large group of genetic liver diseases, and among them, truly, for a liver doctor, it's Wilson's disease which is, again, a very rare liver disease that can cause-- it looks like nonalcoholic fatty liver. Again, the rest of the diseases are too rare. Nutritional, in this group, would be rapid weight loss-- this can happen either surgically or otherwise-- and other malnutrition states, like inflammatory bowel disease, et cetera.

The third group, actually, is more common in clinical practice. It's medications. Now, look at the drugs listed there. I mean, many of these medications are used commonly in clinical practice-- an antiarrhythmic drug, amiodarone, methotrexate, which, you know, liver toxicity is pretty unforgiving when it occurs, tamoxifen--

I see a referral probably once every six weeks in the liver clinic, usually from the oncologist, when these medications have been started. High dose glucocorticoid therapy, and then some of the HIV medications. So don't forget medications.

Alcoholic liver disease-- having practiced as a GI doctor, as a liver doctor, for almost 20 years, I still think this is the most difficult liver disease to diagnose. Why? It's the first line, you know? Many a time in your initial encounter, you really don't have enough time, or you don't spend enough time, taking a history. You can develop any kind of questionnaire in your practice. I mean, having done this for many years, I'm not sure it truly helps.

The usual clue is the lab test, so the AST to ALT ratio. And these tests are picked up in a comprehensive metabolic panel. They're pretty useful. So if the ratio of AST to ALT-- because the ALT is usually normal or low-- if it's 2 to 1, it's 90% likely. If it's 3 to 1, even more likely. Now remember, these abnormal ratios can also be seen in nonalcoholic fatty liver disease, and again, hepatitis C, when you already have advanced disease, i.e. cirrhosis.

Another blood test that you could add is the GGT. Usually this is not done in the first encounter, but if you suspect that this patient may have alcoholism as a cause, check a GGT. You can always call the lab, and add that to the lab that was drawn earlier that day, yesterday, et cetera.

Now the liver enzymes are not that high. It's fair to say the AST and the ALT are going to be somewhere in the three to four times normal. So normal for upper lab is about 40, 50, so you know 120, 150. If the AST/ALT are higher than that, it could be NASH, it could be alcohol, but there's something else going on. The something else is usually a medication, it could be autoimmune disease.

As the disease advances, these enzyme elevation levels become lower and lower. And I'm sure you see this all the time, you see patients with established end-stage disease, or cirrhosis, and the ALT and AST are now normal. So they're useful in the beginning, clearly that may normalize as the disease advances.

Now the key to the diagnosis of distinguishing fatty liver from alcohol and non-alcohol is history. And this question, I'm sure, comes up in a primary care clinic, in a liver clinic, in a cardiology clinic, how much alcohol is safe for me, Doctor? And, boy, I think in the liver clinic, it's very difficult to answer the question. Actually my answer is very easy-- no alcohol at all.

But let's look at the data. Clearly this was alluded to earlier today, women are more susceptible to alcohol, as compared to men. And I still remember, when I was a medical student, and I read my first textbook of liver disease, up to eight drinks a day was OK. Look where we've lowered the bar. This is the latest kind of definition.

So for women, more than one a day. And for men, more than two a day may be excess, when taken daily for a period of five years or more. The other thing that you need to quantify is, what is a drink?

So this is again, the definitions of a standard drink, so 12 ounces of beer is equivalent to a five ounce glass of wine and listed over there, are other types of alcohols. and this all basically equates to the amount of alcohol, which you quantify in grams, is equivalent to each of these drinks.

And it's amazing when you take a history-- Doc, I have these three solid drinks a day. And then you go further and further, and it may be actually six or eight drinks a day, by this definition. I use this to talk to my patients to say, if you stop at the right time, the disease is reversible.

And these are the stages of, basically, fatty liver due to alcohol or nonalcoholic fatty liver disease. You have a normal liver, you have fat, you have fat, plus inflammation, so steatohepatitis. Up to here, if the individual stops alcohol, or loses the weight, the disease is fully reversible.

It's very gratifying, actually, to talk to patients. You pick up this, you counsel them you see them a year later, you image them a year later, two years later, liver tests are normal, ultrasounds normal, the fat goes away. But beyond the stage, so beyond steatohepatitis, and this becomes now a histological definition, you start having scarring, you have fibrosis. And by definition, scarring anywhere in the body, fibrosis is irreversible.

And then you have cirrhosis, and clearly cirrhosis, by the conventional definition-- I use conventional because this definition is going to change over the years-- cirrhosis is irreversible. Cirrhosis leads to complications, which you will see a little later.

Let's move on to nonalcoholic fatty liver disease. This entity has gained a lot of publicity, a lot of material has been written about it. It's not a new disease. This goes back to 1980. This is a pathologic definition, this is a very eminent pathologist from the Mayo Clinic, who described this disease. That there's fat in the liver, and it's basically, it mimics alcoholic liver disease, and it can progress to cirrhosis.

For which, currently-- and this is 1980-- we know of no effective therapy. I could just change the date over here, 2015, and this is true even now. I hope this changes in the next few years because it's clearly become a very common problem for us in clinical practice, and so do you.

So basically, NASH, or nonalcoholic fatty liver disease, is alcohol-like liver disease in individuals who do not consume excessive alcohol. So see, the definition is all in the history, because there's no other way to distinguish these two entities. Now, there's a spectrum, which I showed you earlier, it's similar. You have fat alone, or nonalcoholic fatty liver, this can progress to NASH. And NASH is really a subset of nonalcoholic fatty liver disease. NASH basically means nonalcoholic steatohepatitis, which is inflammation. And, clearly, this progresses to cirrhosis.

Remember, this is a diagnosis of exclusion, there's no specific blood test, there's no specific imaging, clearly, a biopsy will help. So when you see a patient like this, you have to rule out all the other causes of liver disease. So viral, autoimmune, et cetera, et cetera. And then when you've done everything, you say this is most likely nonalcoholic fatty liver disease.

We talked about the enzyme elevations. They are not that high, so less than three or four times normal. It's more common in women. As in then the patients have classic metabolic syndrome risk factors, so type 2 diabetes, obesity, hyperlipidemia. We talked about the ASLT and the ALT ratio. We'll come to imaging, because you can use any imaging modality in a simple ultrasound, CT/MR.

And then I'll talk a little bit about liver biopsy, because I don't think you need this. And there's some new tools now coming out, in clinical practice, that may be able to avoid liver biopsy. So again, a useful picture to talk to your patients, fat, inflammation, cirrhosis, and once you have cirrhosis it'll lead to other complications like liver cancer. And ultimately, some of these patients will require a liver transplantation.

So, why such a big deal? I still remember sitting in the clinic, maybe 10, or maybe 15 years ago, and telling patients, you know you have a fatty liver, there's nothing to worry, go home, or follow up with your primary care doctor. We were wrong. We were clearly wrong. Why? Because this disease will progress-- not in everybody-- and when it progresses, it will cause liver-related morbidity and mortality.

What's the data for progression? And again, a very nice bit of information to talk to your patients. If you're fat alone, it's a pretty benign disease. So even 10 years later, hardly 3% will progress to cirrhosis. Now remember, to say this, you can't do this at the bedside. You need a biopsy to differentiate fat from fat plus inflammation and fibrosis. But I'll show you how you can do this noninvasively, without a biopsy.

But let's say for now, to differentiate this versus this, you need a biopsy. So if you have NASH, which is inflammation plus fibrosis, these patients are going to progress faster. So within 10 years, one out of three will now develop cirrhosis. And clearly, once it develops cirrhosis, it's not reversible.

So let's go forward. What causes NASH? We really don't know, there are some theories. And that's why some of the therapies are really not that great right now. We'll touch a little bit about different treatment options, and clearly, if you have end stage liver disease, these patients will require liver transplantation. It's fair to say today that every week, in our transplant selection conference at Presby, we present 10 to 15 patients every week. 30% are now coming with this diagnosis, so it's going to become the most common cause for liver transplantation, in the United States and probably most parts of the world.

We talked about this. I think the key point here is once patients develop cirrhosis, they are likely to worsen, or decompensate. And this occurs roughly about 2% or 3% per year. So from cirrhosis to transplantation, patients it's roughly about 10 to 12 years. That's the average kind of natural history for cirrhosis.

Clearly, when we do liver biopsies in these patients, even they have no other features of cirrhosis, about 15% will have cirrhosis at the first time we do this liver biopsy. This slide basically highlights the magnitude of the problem today in the United States. And this is based on very solid data. So today, this is general population-- all comers. This is not a diabetes clinic. This is not an obesity clinic. This is not a bariatric surgery, because there, the incidence is going to be even higher.

So all comers, 30% of the US population has nonalcoholic fatty liver disease. So this is the number. Now if you take a subset, as we said, NASH is roughly about 10%, so this goes down to this nine million. And those that develop NASH, 25%, one out of four will progress to cirrhosis. So this is the number here, 2.25. And then roughly 2% to 3% per year will develop liver cancer. So this is the figure right now, potentially at risk in the United States.

And this is occurring all over the world. This is not a problem of the East, not a problem of the West, it's everywhere in the world. So if you look at different countries, Japan up to 30%, China 25%, South Korea, India, Indonesia, Malaysia, Singapore. There's some differences between the East and West. I think, clearly, the prevalence is the same. These are autopsy-based studies, so they're very solid.

But it's not it's not obesity everywhere. So clearly, in the East, it's much lower as compared to the West. Type 2 diabetes is higher in the East as compared to the West. And then, clearly, the natural history data is not available all over the world. So I think these maybe different diseases, but if you look at the US data, and these are studies done in-- there's a very large study at this Army base at San Antonio, and the Dallas Heart Study. Again, 30% NAFLD.

There is an ethnic distribution. So the Hispanic population has a much higher incidence of NAFLD, and this is clearly related to type 2 diabetes, insulin resistance, metabolic syndrome, et cetera. And then, clearly, these are some of the other subgroups, with the incidence. And again, this is another study for ethnic groups. Clearly, the Hispanic subgroup tends to stand out in the United States.

Now, this is not just a liver disease. And I find this interesting because-- and this, I've just learned over the years-- I see a patient in the liver clinic for the first time because they have abnormal LFTs, they have a fatty liver. And we follow them and follow them and five years later, they become diabetic and they have other complications.

So basically it's been touted that fatty liver, or nonalcoholic fatty liver, is just a liver manifestation of the metabolic syndrome, which means these patients are now at risk for other complications of the metabolic syndrome. It's fair to say that liver disease is not the only cause of morbidity and mortality. And clearly, we'll see, you have cardiovascular disease, you have pancreatic disease, chronic kidney disease, colorectal carcinoma, et cetera, which accounts for the higher morbidity and mortality in these patients.

So these are some studies, if you start doing the carotid artery thickness in these patients with fatty liver. Cardiovascular disease is a much more common cause of death in these patients as compared to liver disease. And this, I'm showing you this data because, ultimately, if you want, to treat a patient it will come down to the same thing-- how you manage a patient with metabolic syndrome, and addressing the risk factors for metabolic syndrome would basically also help that liver disease.

Looking at some other data, there's some data that these patients are more prone to vitamin D deficiency. So it's our standard approach in our liver clinic to check for vitamin D and provide supplementation if necessary. And as I mentioned earlier, NAFLD has been proposed as one of the components of the metabolic syndrome. So you're all familiar with this term, systemic hypertension, obesity, hyperlipidemia, diabetes, et cetera.

And I think as you can see the liver is missing in this list and, clearly, it's time that the liver is added on to this list of complication of metabolic syndrome. I think it's fair to say, whenever you see a cartoon like this, we really don't know what causes this. I think--

[LAUGHTER]

--the gut, there's lots of literature now emerging about bacterial flora, as a triggering factor. I'm not ready to commit in clinical practice that probiotics should be used, but there's lots of literature emerging, so stay tuned. But this is kind of gaining a lot of popularity right now, because these gut antigens trigger these lipopolysaccharides, which ultimately go and cause inflammation of fatty tissue. So adipose tissue, and then this contributes to the high free fatty acid load, et cetera, to the liver. So the liver is just like an innocent bystander.

How do you make the diagnosis? I mentioned before, you have to exclude all other causes of liver disease. And today, I've become a little skeptical. Why? Because when I see a patient in the liver clinic, there's a 30% chance, one out of three, that individual already has fatty liver.

So I am going to diagnose fatty liver as my baseline, so it's fatty liver, plus hepatitis C. Fatty liver, plus autoimmune hepatitis. So just because the patient has features of fatty liver doesn't mean the patient could not have another disease. So you have to do due diligence and rule out or exclude all the causes of liver disease.

Once you've done that, the diagnosis is very easy. Any imaging, whether it's CT, ultrasound, MRI, are non-contrast. You don't have to do any contrast for the MR. Clearly, if you see the density of the liver, that's enough to call it a fatty liver. And then, of course, you can consider-- you probably won't to do a biopsy in your practice. That's restricted to probably a tertiary center or a liver clinic. But if you do biopsies, you can find fat, you can find fat plus inflammation.

And the biopsy really, more and more, is being used to do this part. To see, what's the stage of the disease? Meaning how far has it advanced? How much fibrosis has occurred? And clearly, this is a very rapidly evolving field. I think in most organs, if it's a lung and fibrosis, it's a pancreas and fibrosis, or liver disease and fibrosis, is a very rapidly advancing field. And I'll show you some of the advances in assessment of liver fibrosis.

I've shown you this, I think if you have fat alone, it's a very low risk for progression to cirrhosis. If you have fat plus inflammation-- so lots of blue stuff-- that's going to go quicker to cirrhosis. What's interesting is that sometimes we see patients right at this end of the spectrum, they already have cirrhosis, advanced disease, and for whatever reason a biopsy gets done, the fat is gone.

So as the disease advances, the amount of fat in the liver actually goes away. And sometimes it's very difficult to even say that this patient truly had a fatty liver on that. So just to reinforce, you go through your usual checklist-- it's history, history, history. So ASH, which is alcoholic steatohepatitis, and NASH cannot be distinguished by a liver biopsy. You go back to your basics, taking a good history is very, very important.

What's the new stuff out there? There's something called a FibroScan, or elastography. It's FDA approved in the United States. This was a technique that was developed in France to measure stiffness of cheese.

[LAUGHTER]

So good cheese, versus bad cheese, or they measure stiffness, and it's a very simple tool. It's a bedside tool, you put this probe, and it sends a certain signal, and when you get the signal back, you're able to measure stiffness of the liver. It's so simple, the physics. And this is what the technique is, it's elastography. Clearly, the stiffer the liver, the more the scarring, which means more the fibrosis.

OK, this is an outpatient procedure. This machine, or this tool, is available is available in our liver clinic right now, in the UPMC system. I think there are one or two clinics that have this machine, it's paid for by payers. And then this is a reading you get. And we actually have this report generated via Epic, so we will send it to you. I generally-- I sign this report out, when I see patients from outside the practice, and we stage fibrosis.

So from F0 to F4. F0 means no fibrosis, and then, clearly, as the fibrosis advances, F4 is the highest on the scale. And F4 is cirrhosis, and then, basically, the different stages. Clearly, from a clinical practice, F3 and F4 are important. As a primary care provider, you could do all your tests, rule out all causes of liver disease, get a FibroScan. If it's F0, F1, F2, keep the patient in your practice, repeat the FibroScan in one year, before you decide to send it to a tertiary care or a hepatology clinic.

We are happy to see these patients. I don't mind saying that we are getting inundated with these type of patients. And I think we're trying to partner with primary care as to how we can see these patients together, and what kind of patients truly need to get to the next level, or the next center. So very quickly, treatment, and this is just basically-- and I'll share some of the advances at our clinic, and because we're not doing very well, what to do with treatment right now.

And you've probably heard this many, many a time when-- so this is standard management of metabolic syndrome. I think the key is weight loss. I don't mind saying, if there's one thing that's been shown to reverse the syndrome, reverse the steatosis, the steatohepatitis, it's weight loss, whichever way this occurs. I think diet, exercise, and you can come up with different ways of prescribing exercise-- and I have some handouts, or this is probably in your handout, some very useful techniques or tips to tell your patients. But this is the key.

My starting discussion is, sir, or ma'am, you need to lose 10% of your current weight. That should be your starting discussion, 10% of whatever your weight may be at that time. This patient may be morbidly obese, et cetera, but I think your first discussion is, let's start with 10%, and let's keep that as our goal for the next 12 months. Because I think this helps a lot. Clearly, the other risk factors, which include diabetes management, is very, very critical, as well as management of hyperlipidemia. We'll talk a little bit about these, because I think all these therapies right now are not proven. I would put everything in the experimental group, which includes vitamin E, pioglitazone, and then some new therapies.

There's some very nice literature with surgical weight loss, also. I think this is useful when the disease has not advanced, because every month, we get a referral from the bariatric surgery clinic. They do an operation, they didn't know the patient had liver disease, they find out the patient has cirrhosis at the time of a planned bariatric operation. And clearly, the pre-op testing would have probably picked this up, but once they have cirrhosis, once they have portal hypertension, any surgery is very risky. But in the pre-cirrhosis, so F0, 1, 2, this may be a pretty good option. And then, obviously, transplantation.

So just to summarize, the key points about NAFLD, it's most commonly associated with obesity, diabetes, and the metabolic syndrome. Don't forget medications, because sometimes removing some of these medications could go a long way. You have to know the differences between fat alone, and fat plus inflammation, and, clearly, not all patients with fatty liver disease are going to progress to cirrhosis. It's the subset, NASH plus fibrosis, which has the highest progression risk.

How do you make the diagnosis? You suspect it when you have abnormal liver tests. Remember, these days, we are seeing patients with normal LFTs, but an abnormal ultrasound, so just because these ultrasounds are being done for reasons that may be abdominal pain in the ER visit, and a CT was done, et cetera. Usually, or at this time, a liver biopsy is necessary to diagnose NASH, but we have now noninvasive methods for assessment of hepatic fibrosis.

And then we address the treatment options. So now I'm going to go into some of-- these very busy slides, and I've got-- there's some very nice references in one of our liver journals, the *Seminars in Liver Disease.* I actually print these out, and I have copies in my clinic, which I actually share with my patients.

So it goes through some very-- because I really don't mind saying this, I don't do a good job of this kind of stuff, caloric restriction recommendations, and what's the level of evidence? Managing cholesterol, different types of fats-- I get this question a lot, which diet is the best diet? And you've heard this earlier today, it doesn't really matter what diet you choose. I think weight loss is extremely important.

There's good literature to say that high fructose corn syrup is not good. And these are some other components of the diet. We do tend to use vitamin E, it's 800 units. It's only like a two year follow up right now, so beyond two years, once I make the diagnosis, I usually will not continue vitamin E, because we already don't know what the long term vitamin E does.

Clearly, if there's reasons to use vitamin D, you should. This is a very interesting topic, you may have read about this-- coffee protects patients from progressing of liver disease. There's lots of literature on this, this is very interesting. Now, how much coffee? I have to admit, I have no relationship with Starbucks here.

[LAUGHTER]

But there's a lot of-- you know, stay tuned. And again, this is what was there in many studies, not ready to commit that probiotics are going to be useful, but again the bacterial gut flora very important, maybe in the pathogenesis, and so we may see therapeutic approaches. Exercise, I think this is probably a very important bit of information, what type of exercise advice you give. And then I have a nice summary. And I've talked about this earlier.

So I think this question I get a lot, which patient do I need to send to you, Doctor? Which patient do I need to send to the liver clinic, to the specialist? And as I said to you earlier, you can pretty much make the diagnosis. You can do your lab tests for causes of liver disease, you can do imaging, you can do transient elast-- you can do elastography. Remember, I talked about the FibroScan, at Presby, you can get elastography using an MRI, also. So, clearly you can classify the disease, F0 1, 2, 3 and cirrhosis, and then decide how you would make your referral.

I think you can hang on to F0, F1, you can hang onto F2. I think beyond F2, the patient should come to our clinic. This is the pioglitazone data, again, not that great. And truly, we do not use pioglitazone right now, I'm not ready to recommend this. Vitamin E, I said yes. And then there's a host of agents, so look at the list of clinical trials ongoing, stay tuned. I think this medication, obeticholic acid, may probably be the closest to getting FDA approval. But again, hopefully within the next one year.

And then lastly, this is a resource. These are my last two slides, we have a fatty liver clinic now. I think this was driven clearly by the volume of patients and request from our referring docs. It's housed at Presby, it's actually-- it's run by one of my colleagues, Dr. Behari. He's a hepatologist, along with an endocrinologist, and it's pretty much a multi-disciplinary clinic that offers different comprehensive evaluations, et cetera.

They do a lot of-- they have a lot of clinical protocols ongoing, and some of these which I shared with you earlier. So you clearly have this resource. I send patients to this clinic, but I tell the patient, I'm still going to be your doctor, I'll still be involved in your care. But if you want-- such patients have so many questions, I'm telling you, these days. So this is a very useful resource that we have in our health system. So on that note, thank you very much for your attention, and I'll be happy to take any questions.

[APPLAUSE]