NASH: Take Action! Podcast Series

EPISODE 2. NASH and Metabolic Syndrome

TRANSCRIPT

The NASH Take Action Podcast Series is a CME program brought to you by the American Gastroenterological Association. NASH is the most advanced form of nonalcoholic fatty liver disease. This six-episode podcast series is ACCME accredited. The series is sponsored by a medical education grant from Novo Nordisk. You can find all six episodes and collect your CME credits at NASH.Gastro.org.

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Kenneth Cusi [KC]: Welcome to the NASH Take Action Podcast. I am Dr. Kenneth Cusi, I'm the Chief of Diabetes and Endocrinologist at the University of Florida at Gainesville, North Florida. In this podcast my colleagues, Drs. Fasiha Kanwal and Jay Shubrook and I will talk to global leaders in gastroenterology, hepatology, endocrinology and primary care about the real-world practical implications of screening, diagnosing, and managing people with nonalcoholic fatty liver disease and its worst consequence, which is steatohepatitis and liver cirrhosis.

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In this episode we're talking about NASH and its relationship with metabolic syndrome. We're going to cover some key topics today, among them the relationship between NASH, obesity, and other comorbidities; how obesity, diabetes, and insulin

resistance influence the natural history and the pathogenesis of fatty liver disease and steatohepatitis; what are the major risk factors that are related to this progression from simple steatosis to steatohepatitis, and from there to advanced liver fibrosis and cirrhosis.

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We are also going to cover the association between cardiovascular disease and nonalcoholic fatty liver disease and the role of statin therapy, and what are the available diagnostic and treatment modalities for early intervention and prevention of cardiovascular disease and cirrhosis.

Let me introduce our guests. Fasiha?

Fasiha Kanwal [FK]: Hi. I'm Fasiha Kanwal. I'm a gastroenterologist/hepatologist, and I serve as the Chief of Gastroenterology and Hepatology at Baylor College of Medicine.

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KC: Jay?

JS: Hi Ken. Jay Shubrook, a family physician and primary care diabetologist at Touro University, California. Glad to be here.

KC: Well, we have an epidemic at hand, and we have two leaders, one from the gastroenterology field, I'm an endocrinologist, Jay is in family medicine. Let's start with our GI expert here. Fasiha, what is this relationship between NASH, obesity, and all these comorbidities? What do we tell our audience?

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FK: Yes, so I think the way to think about it, it's a part of the same spectrum, same syndrome, very closely linked together. So I way I tell my patients is that it's a family. It goes hand in hand, NASH, NAFLD, weight, obesity, diabetes, hypertension, dyslipidemia. It's just part of the same spectrum – which is a problem, because we know that we are in the middle of an epidemic with the metabolic conditions. And with that, it's no surprise that we're seeing rising numbers in terms of incidence and problems of NAFLD and NASH. So they are tightly linked with each other.

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KC: Yeah, so that's a very important point. And one thing that strikes me is its relationship with obesity and insulin resistance. So Jay, you see in a busy family medicine practice, and you're a leader in the diabetes field. What would you like the audience to know about diabetes and insulin resistance? I mean, what can they take home that will be useful for the next patient tomorrow?

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JS: Yeah, you know, I really feel like it's so important that in primary care specialties we see patients with many problems. And you know, we could very easily make this ten different problems for one person, but the reality is that obesity, metabolic syndrome, cardiometabolic health, fatty liver disease – they all come from a central pathway. And so we really don't have to treat ten problems; we just have to treat the underlying problems better.

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And so I think it's really important to recognize that fatty liver to NASH is a complication of insulin resistance and obesity, and so it is important that we recognize that this is something that we need to address and screen early for. And then this is yet another reason to double down on lifestyle interventions, targeted screening, and making sure we get people to the specialists that can help them if they're on the pathway to complications.

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KC: Yeah. So a lot of primary care doctors, even in endocrinology, are a little bit frustrated with our failures in managing obesity. But this is key, I think. Structured programs help. There's bariatric surgery. But Fasiha must see many patients progressing to NASH and to advanced fibrosis. So what should a gastroenterologist know to do about disease progression? I mean,

FK: Yeah.

KC: ...what are the big factors, and how do you handle this in your own practice?

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FK: Yes. One thing that I think you referred to, before we talk about progression – just the knowledge that these risks are, these groups are high risk is important for screening. I think for individuals with diabetes, this should become an automatic step, to look for nonalcoholic fatty liver disease, to look for markers of fibrosis, assess for presence of clinically important fibrosis, because the risk is so high in the population.

Same thing goes with obesity, and that's something in the NASH Clinical Care Pathway that we all worked on, is highlighted repeatedly, those high-risk groups.

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In terms of progression, the same risk factors also contribute to progression, from steatosis or, I would say, more advanced fibrosis. Different studies have looked at demographic factors, but clinical factors and genetic factors. The clinical factors are important, and not just that they're important independently when they're present together, which they do occur in most of these individuals, actually the effect is additive.

So the presence of diabetes, presence of hypertension and dyslipidemia in a patient who is obese, the risk of progression is manyfold higher than in an individual with each factor or each risk factor separately. So of course, older individuals have a high risk.

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And as I mentioned, there is some genetic predisposition that we are just beginning to understand in progression from simple steatosis toward advanced and also more advanced cirrhosis and liver cancer.

KC: Let me ask you something. So you mentioned a lot of cardiovascular risk factors. So I know that the gastroenterologists have a unique relationship with statins, and love them or hate them. I see a lot of primary care doctors, even endocrinologists, stopping the statin, I mean. So tell me how you prevent cardiovascular disease. In addition to all the lifestyle, what are you recommending people to do with statins in the presence of elevated liver enzymes, which is what puzzles many people?

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FK: You're absolutely right. We've moved away – and I think we've know it for a long time – that statins are protective and they are needed in this population. In my practice, for example, it's still not very uncommon to get a patient who's referred to me because of elevated liver enzymes on statins. And my recommendation is to continue with statins. And there are very studies that show it –

KC: Important message, yes.

FK: ...very clear message, and with no nuances to it.

Jay, what are your thoughts, are family practice physicians and internists, they are feeling more comfortable with using statins? Or how do they deal with it in the presence of elevated liver enzymes?

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JS: Well, I think we've gotten used to seeing slightly elevated enzymes, and I think we're less afraid. I think that certainly statin therapy is becoming more and more aware in the primary care settings that it's something that we need to use continuously, even in the presence of fatty liver. But I also would say that there's a caveat that if your liver enzymes are more than 2-1/2 times the upper limit of normal, you probably need to take a look and make sure there's not something else going on.

So for those that have mild elevation and have some confirmation that they have something on the spectrum of fatty liver, you're probably going to continue the statin unless they're high risk. And I think that more and more are becoming comfortable with that.

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I guess I would highlight that we have pretty good evidence that the intensity of statin is also important, and that, you know, particularly for cardiovascular risk, let's make sure we use statins that really are useful to help reduce what people are at highest risk for, which is cardiovascular death.

FK: And that point is a very important one, Jay, because yes, the risk of progression of liver disease is a real one. The most important reason patients experience suboptimal outcomes is cardiovascular disease. So that is something that we need to recognize and underscore and highlight as much as possible.

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And the Clinical Care Pathway talks about that. Lots of focus is in preventing, improving outcomes would mean improving both liver and cardiovascular outcomes.

KC: Yeah, well, this is so interesting. So, we have two more minutes, and I would like to ask each one of you, in one minute, tell me what you're doing now. Because you know we don't have any FDA-approved drugs. We know lifestyle is important. Anything that helps lose weight, bariatric surgery. But how are you managing, what are your pharmacological options? What do you with somebody with diabetes who you find out they have NASH? Tell the audience what they can do today, because that really comes up all the time. So, we have about 60 seconds for each. So, go ahead. We'll start with ladies first. Fasiha, go ahead.

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FK: So the point here is, there is no treatment that's FDA-approved for NASH per se. But there are options, especially for individuals with diabetes, where most of the

patients that we see have diabetes, that have been tested in patients with NASH. So the Clinical Care Pathway highlights use of pioglitazone, for example, as an agent that is useful and beneficial in patients with NASH.

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My emphasis is still mostly on lifestyle changes, lifestyle modifications, because that is something that each individual, at least that I see, needs to implement – most of the patients that I see have clinically significant fibrosis – both with diet and exercise. And there are different studies that have looked at different types of diets and different exercise routines, which we cover in the NASH Clinical Care Pathway and our other documents. But the important aspect is that these changes have to be implemented, sustainable, and something that the patients feel committed to doing in the long term – because these changes are going to be needed in the long term.

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JS: And then I would guess I just would add that in the primary care space, our first step is to be able to separate who's high risk and who's not high risk. I think that would be our most important thing. If you have someone that's not at high risk, or just make it even easier, at low risk for advancing to fibrosis, you need to double-down on cardiovascular risk reduction. Do all those things that you are already doing. Make sure you're working on healthy exercise. Making sure you're working on weight loss. Make sure that you continue your statin and other preventative treatments, and do optimal management of diabetes.

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And absolutely, we have some data and research that pioglitazone is useful in diabetes, but I think in family medicine and primary care, you don't have to go alone. You don't have to do it alone. Make sure that if you're not sure, bring your team in. And I think sometimes it could be as simple as, What medications should I use or should I not use for the patient who has multiple problems? And you can involve your endocrinologist, your gastroenterologist, so that they – again, we're doing a team-based approach. And patient care is improved when we're working together.

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KC: Wow, this is very good. This is dynamite, guys. So I would just have to say that this is all very well explained in the white paper that is being published in *Gastroenterology, Diabetes Care,* which is the official journal of the American Diabetes Association, and the *Obesity* journal, which is the official journal of the Obesity Society and metabolism. And, more importantly, there's a very simplified clinical care pathway available in gastroenterology. So go, find them – this is really something very current.

I talked to gastroenterologist, Dr. Lee Kaplan. He's the founding director of the Weight Center at Massachusetts General Hospital and Associate Professor of Medicine at Harvard Medical School. This is what he had to say.

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KC: Well, Lee, thank you, happy to have you today. I know you have a very busy schedule, but that you have a passion for NASH and metabolic syndrome and obesity. What can you tell us about this relationship between fatty liver disease and obesity?

How do you see it as an expert in obesity, and what do you think a primary care doctor should know?

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Lee Kaplan [LK]: Well, I think all of these diseases, whether they be diabetes or they be immune diseases, is a whole bunch of diseases that derive from the effect of obesity on normal biology. Obesity disrupts that. That's why it's associated with diabetes. It disrupts the normal signaling processes, endocrine signaling processes. That's why it's associated also with things like blood clotting abnormalities. And it's also associated with cardiovascular disease, renal disease, and liver disease. So, if you think of them as just different facets of a complex disruption of metabolic function, it's the easiest way to go. Then the question is, for any given patient, which ones do you have to focus on?

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KC: So, Lee, I've been fascinated by this relationship between obesity and diabetes over time, and then I stumbled onto fatty liver. And I was very impressed that 7 out of 10 people with type-2 diabetes have a fatty liver, particularly if they're obese. And, more importantly, I'm concerned about trying to prevent cirrhosis.

So, what do you think drives this inflammation in the liver, and why is obesity probably the target of treatment? I mean, you mentioned insulin signaling. What do you think about what's called this lipotoxicity – this energy-driven fat attack on the liver?

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LK: Yeah. I think we know far less about it than we'd like. What we know is that some people get fat in the liver – a lot of people get fat in the liver, if they have diabetes, if

they have obesity, even without diabetes. And yet only a minority, 20 percent or so, will go on to get NASH, will go on to get inflammation, fibrosis and cell death. And so the question is, what's the story there?

And we've talked about it in two different ways, historically. One is that you need two hits. You need to have the metabolic hit, the obesity, the diabetes, and the storage of fat in the liver; and then you need the inflammatory hit. Others have argued that it may be just that some people are more predisposed.

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But whatever it is, there's something that goes on to flip a switch that says fat in the liver is going to lead a patient down a pathway toward bad liver outcomes. Figuring that out is what we have to do. Right now, what we really need to do is find those patients, because those are the patients who are going to get into trouble, particularly with respect to liver disease.

KC: That's a great point. Primary care doctors always come to me and say, How do we do this? And there's other podcasts on the diagnosis. But what has been very perplexing to me is that we have two individuals who are overweight or obese, and one has severe steatohepatitis or cirrhosis, the other doesn't. and those individuals that are lean and have NASH, and some that just suggest that they still have insulin resistance and this adipose tissue that is releasing fatty acids.

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So, among – what would you tell a primary care doctor to look at, if they're trying to identify NASH and fibrosis early on in their patients?

LK: Yeah. So I think that you've hit it on the head. What we really need to do, particularly in the clinical arena, is to worry less about the mechanisms. You know, who needs to worry about mechanisms is people who are developing therapies and developing markers for progression, and the like.

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But in clinical practice, what we need to do is find the patients who could be in trouble, whether they could be in trouble because of heart outcomes, meaning that they have cardiovascular adverse outcomes, or they have progression of the liver disease itself. And figuring that out is most important.

Unfortunately, only 40 percent of people or so have elevated liver tests, if they have any stage of fatty liver disease, whether they have cirrhosis or they have just fat alone. And so we have to do other things. We have to look at scoring systems, like the FIB-4 scoring system. We have to look for evidence of stiffness of the liver that suggests that there's fibrosis by doing elastography or FibroScan, is one of the techniques that's used.

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And so, those are the kinds of things, and fortunately new algorithms are being developed to allow a primary care physician to navigate this pathway – know what to do first, then when to refer to a hepatologist.

KC: Hey, Lee, This is really very good, and I want to thank you for all your contributions for our, a paper that came out in *Gastroenterology* and these clinical care pathways that just do that, ask you to use a FIB-4, that for our audience that may not be

familiar, it's a formula that you can get on any website combining age – big factor for disease progression – liver enzymes, and platelets that obviously go down as you develop cirrhosis. And that could be incorporated into an electronic medical system and help screen that way.

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And Lee, about the elastography – that's a key point that you made. Because you're not really looking for fat, right? We're looking for fibrosis. Would you expand on that?

LK: So, having a lot of fat in the liver does reduce elasticity, or make the liver a little bit stiffer, but not nearly so much as fibrosis does. As we all know, fibrosis makes things, makes all organs much stiffer.

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What you're really wanting to do is balance the ability to intervene early. Because the first step in this process is a metabolic step. It's the deposition of excess fat in the liver. At the other end of the spectrum, though, you have severe fibrosis, cirrhosis, liver disfunction. And so what you want to do is figure out, where can we intervene?

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We know that the people who are late in the game, that we can detect fairly easily by elastography or FibroScan, those people need to have intervention. The problem is that we don't have a lot of great interventions at that late stage of the disease. We have better interventions at the early stage of the disease. So what we recognize is that when

you have just steatosis, if we knew which steatosis was going to progress to fibrosis and NASH, then we could selectively intervene there.

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So what we're left with, then, is we can intervene in a lot of patients early, by weight loss, by fixing the obesity, by decreasing fat deposition – which is a necessity but not a sufficiency to progress – or we intervene late. If you want to know when you 've got a patient who has the patient for future trouble, the FibroScan is your best method for doing so right now.

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KC: Yeah, that's a great point, Lee, because it's a relatively inexpensive test, our friends, our hepatologists know this very well. In the clinic they take it as a vital sign, almost. And it really helps guide therapy.

And, again for those who are not hepatologists, a cutoff of 8 in the liver stiffness is a red flag to seek care by the specialist, and again, a value of 14 or higher is talking probably of cirrhosis. But again, the techniques that we have are good, not perfect, so they do require the hepatologist to look into this more carefully.

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LK: Can I just add and expand on what you're saying, because I think that it's critical. I think that from a point of view of any clinician – you mentioned primary care, but it could be a cardiologist, it could be an obesity medicine expert, it could be a kidney doctor who has patients, a disproportionate number of patients with obesity. So many people take

care of patients with obesity that I think we all need to be knowledgeable about the early stages of how to evaluate these patients.

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So, if you've got somebody with fat in the liver – and that can be detected in a number of different ways – what you want to do is you want to think that this a potentially serious complication, just as diabetes is a potentially serious complication, and think about addressing the obesity.

When you, through whatever mechanisms you do, and we've talked about a couple of ways of testing and evaluating patients already, when you start to go down the evaluation process, you want to know what is the simple things to do that will allow you to determine, do I send the patient to a hepatologist, or do I observe the patient on my own?

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KC: That's a good point.

LK: When you get used to doing that, when you put it into your reflexes, clinical reflexes, that you can manage patients on their own by focusing on managing the obesity effectively – and there are a lot of ways of doing that now – or you need to get serious about the liver disease, then that bifurcation of thinking – getting serious about the liver disease because it's progressing, there's evidence of progression – will eventually bring you to a hepatologist, or bring the patient to a hepatologist.

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But there's a lot you can do before you ever have to make that decision. One of the most important things I think you have to do when you do that is to recognize that the number one cause of adverse outcomes, at all of the early stages and even some of the later stages of fatty liver disease, is cardiovascular outcomes.

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So you want to, at the same time you're addressing the obesity to try to prevent progression, reverse progression, what have you, you also want to be addressing the cardiovascular issues. Just like diabetes, you want to be focusing on cardiovascular outcomes as a major cause of disability and death.

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KC: You made a number of great points, Lee, so I'm going to break this down a little bit. So, we're going to talk about the cardiovascular disease in a couple of minutes. Before that, the FIB-4 numbers to remember are, if it's below 1.3, probably little chance of having advanced liver cirrhosis or advanced liver disease and cirrhosis. If it's above 2.67, probably you're already fairly advanced. And unfortunately, a large number of people fall in between that 1.3 and 2.6. So, in that group, you need to do additional tests. There are some commercial assays, there are other imaging techniques available like magnetic resonance, elastography. But that should be left to the hepatologist.

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So, Lee, you mentioned high-risk patients. Which are the top patients that you think should be at risk of progressing two advanced fibrosis and cirrhosis?

LK: Yeah, and I think you've mentioned some of the criteria. Obviously, the one criterion that alone is not as helpful as we'd like it to be, are the simple height of the transaminase elevations, the ALT and AST elevations.

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However, as part of the FIB – they contribute to the FIB-4, and most importantly the ratio of AST to ALT contributes to the FIB-4. So FIB-4, if it's above 2.67, as you've mentioned, we ought to be thinking about this patient as likely to be progressing. And I would say it's 'be progressing'. We may not know from there how much it's progressed, but it's a progressive form of fatty liver disease.

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And so for any clinician, particularly those who are not hepatologists, I would focus on, is this a patient who looks like they're progressing, or is this a patient who doesn't, at least currently, look like they're progressing? FIB-4 is one.

A second one is elastography. Elastography, or again, the trade name FibroScan, you're looking at the stiffness of the liver. Anything above 12 is clearly progressing; probably above 8 is clearly progressing. And so you want to be thinking about that as another criteria, independent criteria. Any kind of liver dysfunction is an evidence of clear progression of disease. You want to be – you obviously want to be handling that.

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So the most important thing is, again, a bifurcating decision. Do I take care of this patient focusing primarily on the metabolic disease and the obesity, or do I send them off to the hepatologist so that they can have focused attention on the liver disease

itself? And when you get comfortable making that decision, and making that decision over and over again, because a patient can progress over time, then I think you're ready to truly handle the burden of this disease – which is enormous across a primary care or cardiology practice.

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KC: Those are excellent points, Lee. I mean, I'm so glad to have you here. We couldn't get a better voice for summarizing this. One question I have is, again, I get asked a lot about type-2 diabetes and NASH. As an endocrinologist, I've been, for the past 10 years, suggesting that we should do some early screening in the same way we do for nephropathy or retinopathy, because type-2 diabetes is a risk factor not only for steatosis but fibrosis.

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We've found that roughly 21 percent of people with type-2 diabetes just going for their routine check in general medicine clinics and endocrine clinics have fibrosis. But it seems to be still overlooked. And how do you see that relationship between type-2 diabetes and risk of cirrhosis?

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LK: So, all of these diseases are both fellow travelers, and probably are related mechanistically. And in some cases they're more related mechanistically, and in other cases they're just fellow travelers. And we don't really know in every patient, because patients are different. Their genetic backgrounds are different, they're likely that complications are different.

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So I think what we have to do is we have to look at all of these things. I don't think that a nephrologist should be ignorant of the concerns about cardiac disease. I don't think a cardiologist should be unconcerned about the possibility of diabetes, fatty liver, and the like. All of these sub-specialists that have been defined by organs have to now start thinking across sub-specialty lines when it comes to these metabolic diseases, because they're all related and travel together.

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Having said that, the relationship amongst diabetes, heart disease, and liver disease is a very strong relationship. And once you see any one of those diseases, appreciate any one of those diseases in a patient, particularly a patient who has obesity – although even patients without obesity can have this constellation of problems – you have to think of the full spectrum.

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When we look at obesity, we know that there are more than 225 comorbid diseases, diseases that obesity is either causing or exacerbating. And so, as a result, we have to think very broadly about these relationships. But the big ones are liver disease, kidney disease, diabetes, and cardiovascular disease. And if you think about that group as a group, no matter which entry point you get to, you should look at all the others.

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KC: Lee, I love what you just said, because I think that this is something that is coming to the mainstream of care. So, with the type-2 diabetes meds, GLP-1 receptor agonists and SGL-2 inhibitors, that endocrinologists began thinking beyond glucose, and incorporating the cardiovascular disease and the kidney disease into the management.

And when I give talks now, I talk about a triangle of care. Just saying what you said, that when we make decisions about, beyond lifestyle changes but with pharmacotherapy, to think of drugs that can impact these three endpoints: the heart, the kidney, the liver.

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By the way, fatty liver disease, NASH, is strongly associated with more cardiovascular disease and more CKD. So, I think, many times I get specialists who say, "Oh no no no, I don't do" – if you're a cardiologist, "I don't look at the kidney much," or if I'm a hepatologist, "I don't do diabetes drugs." But I think that has to change. What would you tell that cardiologist nowadays, but an angle of non-alcoholic fatty liver disease? What should they be worrying about if they hear this podcast?

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LK: So, a cardiologist is looking at two things. They're looking at all of the cardiac risk factors that are promoting cardiac disease. And it's not just the metabolic risk factors; there are lifestyle risk factors and others.

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And the other side of it is, they're looking at the end state, frequently the end-of-life state of all of these diseases. And so, as they do that, they have a unique

vantage point. They should look back and say, “What are the contributors?” And fortunately, in many cases, some of the same therapies are affected at reducing cardiovascular risk. If you have diabetes, for example, SGLT-2 inhibitors and GLP-1 receptor agonists both decrease heart cardiovascular outcomes, and so they improve heart cardiovascular outcomes.

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And so, as a result, you should be thinking about, what are the different places, what are the different diseases where I might be able to use some of these? SGLT-2 inhibitors, modest inducers of weight loss. GLP-1 receptor agonists, better inducers of weight loss. So that takes care of, or at least helps to take care the obesity. Both of those drugs help with diabetes, substantially. Both of those drugs have the potential, particularly GLP-1s, to be helpful in renal disease. And, of course, we now know that it can be either independently or directly helpful in cardiovascular disease.

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Notice, I just mentioned two groups of drugs that work in all of these different things. It’s another way of reminding ourselves, if the same drugs are working to improve all of these different manifestations of metabolic disease, perhaps they’re more related than we give them credit for.

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KC: Right. And again, I mean, I think this is a very important thing. I discuss a lot with my cardiologists at the university, and I see that they’re beginning to update the use of SGLT-2 inhibitors, but slowly. Primary cares have been usually more at the forefront to

wanting to use this in a more comprehensive way. But I also the hepatologists that are also beginning to learn more about diabetes meds, and again, of those, pioglitazone has the greatest benefit for NASH, with some cardiovascular benefits.

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Now, my question to you is, we talked about the progression from steatosis to inflammation and fibrosis. And although the mechanisms are not clear, we can identify fibrosis early on. Now, what is the number one cause of death in our patients with NASH? Do you want to expand on the cardiovascular conundrum that we have, and how primary care doctors can play such a big role here?

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LK: Yeah, and it may be a surprise to some people who are listening to this podcast, that the number one cause of death is cardiovascular, in people with liver disease. It is clear that in early liver disease that's the case, again because liver disease travels, fatty liver disease travels with other precipitants of cardiovascular disease. There may be mechanistic relationships that we haven't yet discovered.

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Even in later stages of liver disease, you'll see that the primary cause of death is heart disease. So, as hepatologists, we can't be ignorant of the fact that a disease that is becoming the number one cause of liver transplantation is still causing most of its death through the cardiovascular pathway. And so, because of that, we have to remember that we have to pay attention to the cardiovascular outcomes as much as

diabetologists do, as endocrinologists do, as kidney doctors do, and of course, as cardiologists themselves do.

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So, in all cases we have to be focused on that adverse cardiovascular outcome, even as we address the liver disease, even as we address some of the other complications of obesity.

KC: That's really a very very important point and take-home message. Cardiovascular disease is perhaps the greatest reason to identify steatosis, and to treat people with fibrosis.

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So, liver disease, of course, overcomes mortality as you travel from compensated to decompensated cirrhosis. But we need to do more. So, in a nutshell maybe, which would be the best diet, and do you think we're underutilizing bariatric surgery in this population?

LK: Yeah. These get to be stickier questions, because now we're getting into weighing the alternatives. And we're not there yet. We need more data, we need more understanding.

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But, what we know today is that all therapies for obesity, and by extension for metabolic disease, have an enormous patient-to-patient variability. You can swear by your favorite diet, you could swear by your favorite medication. You could even swear

by bariatric surgery. But when you treat hundreds or thousands of patients, you'll see a very broad distribution of outcomes.

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So, what's the best diet? The best diet is the diet that works for that patient. And truly effective diets, in terms of having a major impact over a long period of time, probably are beneficial for 10 to 20 percent of patients. You get to medications, you're going to see the same kind of thing, until we see the new generation of more powerful medications for treating metabolic disease start coming forward. You mentioned pioglitazone, we can talk about the GLP-1 receptor agonists, we can talk about a whole variety of different categories of medications that are emerging, but look to be far more effective.

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With respect to bariatric surgery, bariatric surgery has the unique benefit of being very effective for treating obesity, the most effective therapy we have today, even though there's a variation from patient to patient – and also appears to have weight-loss-independent effects on metabolic function, particular diabetes and perhaps kidney disease and liver disease as well.

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So I would say, we need to keep all of these things in our armamentarium. In our hands, when we use bariatric surgery – which is still a small minority of patients, overall – we frequently ending up combining it with more intensive lifestyle interventions and

medications, to get the greatest benefit for any given patient. If the disease looks progressive, we don't want to be bashful about treating.

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KC: Right, in progressive and chronic diseases like liver disease, heart disease, it's not really a destination –the journey is really the work. And it's a chronic effort that we do with our patients day in and day out.

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Now, one thing that is important to me in terms of talking about progression of cardiovascular disease is the role of statins. So, I get many patients where statins have been discontinued because of mild to moderate elevations in liver enzymes. What would say about the use of statins in NASH?

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LK: I think that NASH, or fatty liver disease, is the number one cause of liver disease right now. And so when you see elevated liver tests, although they're only elevated in a minority of people with fatty liver disease, fatty liver disease accounts for a very large portion of the people who have, I'd say, elevated liver enzymes.

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So, it stands to reason that if you've got elevated liver tests, you've got to evaluate them. Forty years ago we just let them pass; today we can't afford to let them pass. We've got to identify the autoimmune causes of elevated liver tests, we've got to identify the viral causes, the toxic and drug-induced liver disease causes – and we also have to identify fatty liver disease.

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When somebody has fat in the liver, therefore they have fatty liver disease, regardless of whatever else they might have, we have to keep in mind the cardiovascular outcomes to it. And we really should have a high threshold and demonstrated poor liver outcomes of statins before we discontinue them. That doesn't mean you never discontinued them, but it means the vast majority of the time, the elevated liver tests, and even the variation in the height of that elevation, which is normal in fatty liver disease, is not due to the statins. And if you don't demonstrate that it's due to the statins by repeated testing, then you should probably keep the statins onboard.

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KC: Exactly. So, I learned from my friends in the liver field that statins actually have a lot of beneficial effects on liver cells at different, at many steps. But from a practical point for clinicians, for the most part you can keep the patients on the statin at least if the liver enzymes are not higher than three or four or five times. And if you have any doubt, just keep them on the lowest dose. Or, if you think they're inducing harm, you can stop them for a brief period of time and reevaluate.

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For guidelines from the American Association study of the disease and all over the world have recommended to not discontinue statins because of the very high risk of cardiovascular disease.

LK: I think it's also important to re-emphasize what you said earlier, which is that we're looking at a chronic disease, and a chronic disease is a long path. And so you can make adjustments, you can test out whether the statins are associated with the elevated tests, you can go further if need be with biopsies if it's absolutely necessary. But the most important thing is to take a very long view – whether it's liver disease, obesity itself, diabetes, heart disease itself, or kidney disease, these diseases will evolve and progress or regress over time, depending upon how we handle them.

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What we do between today and next month is far less important than having a strategy for managing these patients and the diseases in all of their manifestations over a period of years and decades.

KC: So, Lee, I'm trying to wrap up here. And one aspect that you made a point over and over is not to rely just on elevated liver enzymes, and that's a great point. I mean, a minority of patients with fatty liver disease have liver enzymes above 40. That cutoff is saying as, "Let's diagnose diabetes with an A1C of 7.5. It's a high cutoff, and lower ones have been proposed. An easy number to remember is 30.

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If you have ALT above 30, it's likely you have a fatty liver, and probably inflammation. But more important, if the AST is going up in the mid-30s, the chances of fibrosis are higher. But go to your electronic medical records, try to see if there are prior studies showing fatty liver, or if you are a high-risk group, consider doing an ultrasound, ideally, and a elastography test. I think that the main point that I loved from all your

comments is, think that this is a condition that's serious, and that you can have a huge impact from an early diagnosis.

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So, we don't know what the mechanisms are, but as you said, Lee, cardiovascular disease is the thing that we want to prevent in these people. So if we were to look closely – I mean, what would be your key three thoughts for our audience in trying to change or improve what they're doing on a day-to-day basis?

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LK: I think first of all, be aware that fatty liver disease is a really entity that can, in a significant number of people, cause severe bad outcomes and death. It is not universally the case, but the denominator is so high, there are so many millions of people in the United States alone who have fatty liver disease that the numbers who are progressing, and who have adverse cardiovascular outcomes, is staggering. So pay attention to it.

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The second thing is that, get comfortable with that, what I call the bifurcating pathway. Do I manage it on my own and just follow it, and at what point do I need to refer to additional help – whether that help is in terms of worrying about the cardiovascular complications, by referring to a cardiologist or an endocrinologist, or by referring to a hepatologist because of concern about progression of the liver disease itself.

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And then the third thing is to recognize that over the next 10 years or so, we're going to be having new therapies that are going to be better and better at addressing different aspects of liver disease. We're going to be able to address the early aspects in terms of the deposition of fat in the liver, and although that is not necessarily the worst thing in and of itself, it still increases cardiovascular risks, and it still can lead to progression.

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We'll also be developing new therapies in terms of the inflammation, the fibrosis, and then the end-stage complications of all of these processes. So we're going to need things to prevent, new therapies to prevent the cirrhosis and try to reduce the necessity for liver transplantation. We're going to need therapies that are going to prevent hepatocellular carcinoma, and we're going to need therapies that have a demonstrated ability to reduce cardiovascular risk.

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But that's the third thing. I think for a primary care provider, take it seriously. Know when to refer. And know that help is coming.

KC: Nobody could have said it better, Lee. That's why I love having these conversations with you. So, there are a lot of new developments coming. Our mission now as clinicians is to think about it, and think about the screening in the same way we do for diabetic microcomplications.

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And finally, remember, as Lee said, there are things you can do now. Weight loss helps significantly, in proportion to the success in achieving that. The problem is there's variability in the response of fibrosis, so that's why some diabetes medications, as Lee mentioned, GLP-1 receptor agonists, particularly liraglutide and semaglutide tested more directly, and pioglitazone can help. Vitamin E has also shown benefit in people without diabetes. So there are things you can do today. And don't forget about bariatric surgery.

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So Lee, I don't want to abuse your time. If not, you're not going to come next time I invite you for a cup of tea. So, thank you for these really brilliant perspectives on the management of fatty liver and of fibrosis. Any final thought?

0:45:39

LK: No, I think that, first of all it's been a pleasure to participate, and I think that just as sleep apnea was something people didn't pay attention to 25 years ago and we're paying attention to it now, just as diabetes was something we didn't pay attention to 50 years ago, and now we pay a lot of attention to it, I think we're moving in that direction for fatty liver disease. I think that having programs like this are very very helpful.

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So, thank you for inviting me, and thanks for the opportunity to talk about it.

KC: Thanks, Lee, and for the audience, if you want to learn more, go to the proceedings of our work with Lee and a group of experts from primary care, endocrinology, and hepatology published in *Gastroenterology* and the Clinical Care

Pathways. And I'm sure there are going to be a lot of new developments that are going to rapidly change this field. But I think with what we've learned today from Lee, we've got our task ahead well defined.

Thank you, Lee. Take care.

LK: Bye bye.

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[music]

KC: Thank you Fasiha and Jay, and a special thanks to my guest, Lee Kaplan. Thank you all for joining us for this episode on NASH and metabolic syndrome. You can find the other five episodes in this series, the NASH Clinical Care Pathway, and more resources at the program's website at NASH.Gastro.org.

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