NASH: Take Action! Podcast Series

EPISODE 5. Managing NAFLD and NASH

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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Ken Cusi [KC]: Welcome to the NASH Take Action Podcast. I am Kenneth Cusi, I am the Chief of Diabetes and Endocrinology 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'll talk about managing nonalcoholic fatty liver disease and nonalcoholic steatohepatitis and the importance of managing comorbidities, what are the current and emerging treatment for both nonalcoholic fatty liver disease and

nonalcoholic steatohepatitis, and what are the limitations of the current data for the management of these complex patients.

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I'm here with my co-hosts, Dr. Fasiha Kanwal. Hi Fasiha.

Fasiha Kanwal [FK]: Hi. Thanks for having me here. I'm Fasiha Kanwal. I'm a gastroenterologist/hepatologist at Baylor College of Medicine in Houston, Texas.

KC: And Dr. Jay Shubrook, family medicine doctor. Jay?

Jay Shubrook [JS]: Hi. Jay Shubrook, family physician and primary care diabetologist. Professor at Touro University of California, and glad to be here.

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KC: Thank you for having both of you. I know you have very busy schedules, but this is an exciting time for NASH. We have a lot of new information coming out. We have work done by a group of experts that has been published in several journals. We'll talk about that. And both of you have been critical in this effort.

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Now, why is NASH so important, and why are the comorbidities associated with NASH something that should be faced by a multidisciplinary team? Fasiha?

FK: NASH is important in and of itself, given the consequences that patients face, both from liver as well as cardiovascular disease endpoints. It's also important because there are lots of patients with NASH that we're seeing in our clinical practice, and the trend is not changing. I think this is something that we'll continue to face over the next few decades to come.

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In terms of the comorbidities, I think they are important for multiple different reasons. There are actually two reasons – the way I think about it is a bidirectional relationship between these comorbidities and NASH/NAFLD. And we have to manage them together.

Managing comorbidities can reduce the risk of progression of NASH to advanced liver disease. It also will help reduce the likelihood of having suboptimal cardiovascular endpoints. So managing comorbidities is the cornerstone, the base, the foundation of managing individuals with NASH. I don't think we can separate these things out in this patient population.

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KC: Oh no, that's excellent. Now Jay, help the audience understand which are the comorbidities that you more frequently see, and a couple of pearls on what to do and what is their relationship with fatty liver.

JS: Sure. So I think the first thing is, rather than being a splitter, we should be a lumper, because this is a place where we know that cardiovascular, insulin resistance, cardio renal, and really cardio hepatic are all inter tied together. So these are all having similar underlying pathways.

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And so when you think about fatty liver to NASH, of course we're worried about two very specific liver-focused complications such as hepatocellular carcinoma or cirrhosis. And those are horrible, and largely preventable, outcomes. But most people

with nonalcoholic fatty liver disease and NASH are going to die from cardiovascular disease, and we should take that as a serious marker of yet another indication of the inflammatory conditions associated with insulin resistance, metabolic syndrome, and now NASH.

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So in the primary care setting, it should just give us further emphasis to find out who is really at highest risk, and to double-down on those patients to really make sure they get the right information so they could do lifestyle change, and that those who are at higher risk, we make sure that we give a timely referral to a team-based care.

KC: Wow, those are great points, Jay and Fasiha. And for the audience that may not be aware, we discussed this with a group of experts, and we got together in July 2020, and we've published, with the support of the American Gastroenterological Association, who published a white paper recently in their journal *Gastroenterology*, with simultaneous publication in *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 in *Metabolism*, and followed by a clinical care pathway. Because I think that this really very very important.

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And I know that there are a number of emerging treatments that we can do, although, again, no FDA-approved drug yet. Many in development. But Fasiha, what would you tell today – and I think that all fields, I think some of the frustration that endocrinologists express to me is that many times we send the patients to the

hepatologist, but then there's not a treatment or a follow-up. So, if you had to speak to your peers, tell them what they can do today until we bridge this gap for the new drugs under development.

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FK: Ken, there are I think two points that you alluded to. One is the lack of agreement on what is the best pharmacological treatment for NASH and NAFLD, and I think that stems from lack of FDA approval for this treatment. I think that's needed before we can recommend something, or stress upon certain treatments.

And second is something that Jay mentioned before. This is really a team-based care that's needed for this patient population. It's a team sport, and into which specialties are not well-suited to manage it completely.

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So as a hepatologist, we look to our endocrinology colleagues to guide us in terms of managing a patient, especially with diabetes, because we really frankly are not very comfortable with managing diabetes. The field has moved so much, so fast. The treatments that have been tested for in patients with NASH are anti-diabetes medications and treatments.

So that's why, as a field, as a discipline, hepatology or hepatologists, they sort of shy away from recommending those treatments because they probably are best managed in endocrinology.

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So, part of the clinical care pathway is also to emphasize the importance of team-based approach, emphasize the importance of setting up these collaborations, setting up maybe even combined joined clinics, where all specialties are co-located to best meet the needs of this patient population. So I think that's one reason for the lack of clarity on what the right treatments are.

But I also want to emphasize what you just mentioned, that this might not be the case for much longer. There are some exciting data that are coming out. I am not so sure when exactly we will see those recommendations in our practice guidelines, or if and when the FDA approval will happen, but at least the field is very promising.

In terms of clinical management and clinical practical point is, we have to, and we need to, and we do stage ascertainment for patients with NASH. People who have clinically significant fibrosis, that's the group that we need to make sure we have a follow-up scheduled with them. Because yes, these treatments might not be available right now. It is going to change, hopefully soon.

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KC I like that. I'm going to ask Jay how he sees the future in management. But I want to take one comment you made, that hepatologists are a little bit out of the comfort zone. And I think we all have to get out of our comfort zone to grow and do things better in our personal and professional life.

Endocrinologists are beating the bushes with my friends because they have to get uncomfortable and begin ordering FIB-4s and imaging tests that they not used to, and they don't want to do it because they're very busy. But I think this is critical,

because you know that there's 10 or 15 percent of patients that have, in our clinics with diabetes, have advanced fibrosis.

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And I'm going to challenge the hepatologists to be a little bit of endocrinologists and start prescribing medication. So we have two that have been recently well tested. One very recently, semaglutide, that is also, that's approved for type-2 diabetes, and recently also approved for obesity. So again, it's simply a weekly formulation. The support staff typically teach the patients how to use it, or the pharmacist. So that is something that is critical because it promotes weight loss, and the weekly formulations are ranging from 12 to 16 percent over 4 to 6 months.

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The other is pioglitazone – very inexpensive. In our VA, costs 8 cents a tablet. And used at the lower dose of 15 mg, it doesn't cause weight gain, which is what the greatest issue is. And at the 30 mg as shown in PIVENS, can improve steatohepatitis.

So these are not very complex medications to use, but again, we all will have to stretch our comfort of practice. So Jay, what can you say from your other angle, which is primary care?

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JS: Yeah. So I think that we really have some guidance now, that we triage people at the risk. And I think that if we have patients who are at low risk by FIB-4 score for progression, don't be afraid to treat them for the cardiovascular conditions that they have, including NAFLD. So I think you want to work on weight loss, you want to use the

right medications for your diabetes – don't shy away from them. You also want to make sure that you use statins. So you can be very comfortable doing the right thing for those patients.

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Now, if they're intermediate or they're at higher risk, that's when you need help. And you want to make sure that you give your patients every aspect and have a chance to get treatments that are specific to their condition. And so you can do the patient a favor by triaging them early, and then triaging and sending the person to endocrine or gastroenterology so that they can get care if they need it, if they're higher risk.

And again, I don't expect primary care to know all the new treatments, but there are established treatments that we can keep using. And so I think that's really the most important thing is, don't be afraid to use these treatments in those who are lower risk. Continue to treat them for their cardiovascular risks that they have. And then identify those who are higher risk. And use your team.

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KC: Those are key points. So, a very important one is that to remember, none of these drugs that we have are FDA-approved. But the point to be made in the diabetes field, now we choose drugs based on comorbidity. So if you have heart failure or chronic kidney disease, SGL2 inhibitors are the drug of choice.

But we want to get the message across that if you have diabetes and NASH, choose drugs like semaglutide or pioglitazone, or even their combination, that can be helpful – although we need more data about that.

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Fasiha, two things. Number one, will you briefly explain our nonhepatologists what the FIB-4 is, and briefly the elastography, and a step forward – what are the limitations in our current management of patients? I mean, where do you think that the field is going to go, or how do you see this in two or three years?

FK: So, FIB-4 and elastography are two noninvasive tests that are readily available, relatively cheap to do, and would help risk stratify patients with NAFLD that are seen in routine practice in primary care, endocrinology, and even in gastroenterology clinics. FIB-4 is a combination of a few blood tests, so people would need two combined with age. Calculators are available online, very easy to do.

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Listography is something which also can be ordered and could help risk stratify individuals with NAFLD based upon the risk of fibrosis.

In terms of the future, there are many things that are going to change. I think we would have a more granular, or finer tools and techniques to risk stratify patients. There are several studies and techniques that are being developed, so I think that is going to change.

And as has been mentioned, many new treatments are in the pipeline. Both treatments, repurposing treatments that are being used for managing metabolic conditions, but also treatments that could potentially directly work on the liver.

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So lots of, I think, exciting advancements that are happening in the field which I'm sure we will get another chance to bring to the audience, hopefully in the next few years to come. But in the meanwhile, between now and then, the NASH clinical care pathway is a comprehensive, yet simple to follow, document, with clear steps that individuals could follow who are managing patients with NAFLD and NASH in their clinical practices.

KC: Fasiha, this is really great. I mean, the clinical care pathway is available in *Gastroenterology* journal, the official journal of AGA. And two things that I think are important for our audience. People ask, "Well, what if you don't have diabetes, what do I do today?"

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In addition to lifestyle and weight loss, there was a well-done study called PIVENS that showed vitamin E at 800 units a day can improve steatohepatitis. Again, there's been debate. And there's studies also in patients with cirrhosis that improve with it – again, not in randomized controlled trials. But this is important information to have. There's been controversy about increased risk of cardiovascular disease or prostate cancer, so that's an unsettled debate. And also the diabetes medication we mentioned have shown efficacy in people without diabetes and NASH.

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And there are many drugs in the pipeline. We don't want to approach that because it would be an entire new podcast, but they involved duo GLP-1 or, and

glucagon agonist, thyroid hormone-receptor agonis, FGF-21 agonist, new PPARs. So it's a big, big field.

Now, I'm just going to finish with a 30-second commend. Jay, what is your take-home message in terms of management of patients with NASH?

JS: I think the message I would give to primary care is that we no longer just have to sit and watch and wonder about people and their liver. I think that we now can identify those who have fatty liver, we can identify those who are at high risk, and there is emerging treatments so we can do something for our patients.

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You can do something for everyone to work on those lifestyle modifications, but know for those that are at higher risk there's new treatments coming.

KC: Thank you, that was great, Jay. And again, I love your primary care angle, because you guys are the ones who are going to really make a difference, as you made a difference in the management and the outcomes today of people with diabetes.

What about the hepatology angle, Fasiha?

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From hepatology, this is an exciting time. Finally we will have treatments that we can offer to patients with NASH who are at risk for advanced fibrosis. All the treatment that you mentioned are being tested in individuals with clinically important fibrosis.

One treatment that we didn't talk about is obeticholic acid. There is data on that as well, so let's add that to our pipeline as well.

But optimistic that in addition to lifestyle changes, where we are getting more and more data about the specific types of recommendations that we can make to our patients, we will have pharmacological treatments for our patients as well, hopefully in the next few years to come.

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Thank you for helping me here. Yeah, the FDA is still reviewing obeticholic acid, and we hope that it will be successful. It's a big, there are many additional – epicsauros(?) is the class that are being tested, so that's a big field.

And I'm going to move on and just thank both of you for your very very important clinical practice points. And again, I will remind the audience to check the clinical care pathway and journal *Gastroenterology.*

And now I'm going to move to our guest. I wanted to ask all these issues to somebody who's very relevant in the field of diabetes. I talked to endocrinologist Dr. Bob Eckel, immediate past president of medicine and science for the American Diabetes Association – a true leader in public health and diabetes care. This is what he had to say.

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KC: Thank you, Bob. Thanks for your time, and I couldn't think about somebody more proper to discuss management today, because before we dive into the things we can do to improve the liver, frequently – and I think this is why it's so compelling for primary care and our peer endocrinologists, and anybody who is taking care of people with

chronic conditions like obesity or diabetes, is the overall management that well exceeds liver care.

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So, you've devoted your career to improving cardiometabolic health, understand very well the pathophysiology of dyslipidemia and diabetes. How would you start managing, what would you tell a primary care doctor that asks you what to do with patients that they identify with fatty liver disease?

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Bob Eckel [BE]: Well, first of all I think it's important for the primary care physician to recognize the relationship of nonalcoholic fatty liver disease to metabolic disorders, such as obesity, such as metabolic syndrome, such as type-2 diabetes. And in those kinds of patients, we need at least a baseline set of liver function tests. It may not need to stop there, but screening and assessment of abnormalities needs to be a stepwise process going forward, Ken.

KC: So, would you in a nutshell tell me who people with fatty liver disease are particularly prone to dyslipidemia, the typical theragenic dyslipidemia that's so common today?

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BE: Well, it's not only the dyslipidemia, it's the relationship to other cardiometabolic risk factors. But, the lipid disorders relates to an increased production of triglycerides in the liver. Now, fatty liver disease is when there's too much fat stored in the liver, but often associated with the increased production of triglycerides. In the liver, there's a

secretion of triglycerides in the form of a lipoprotein, and that's specifically the very low-density lipoprotein.

So one of the most common lipid abnormalities in patients with fatty liver disease is a high triglyceride level and a low HDL cholesterol. By the way, these are good bedfellows. Whenever triglycerides go up, HDL cholesterol tends to fall. So that adds to the risk for cardiovascular disease that occurs in patients with nonalcoholic fatty liver disease.

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KC: So knowing that cardiovascular disease and dyslipidemia are so common, I'm sometimes puzzled by primary care doctors not putting them on our typical lipid-lowering agent, and particularly statins. So, what would the message be for primary care regarding statin use?

RE: Well, many patients with nonalcoholic fatty liver disease need to be statin treated. Some of these patients have already had an atherosclerotic event such as a stroke, or have peripheral vascular disease or have had a coronary event. But more of a primary prevention really is very important in patients at high risk for cardiovascular disease, including nonalcoholic fatty liver disease, and therefore statin therapies are a very important strategy going forward.

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Liver tests being elevated should not be a reason to stop statin therapy, under almost all circumstances. If the liver tests were extremely elevated, I think that's one thing you might do to see ultimately whether there is any relationship between the

statins and the liver test elevation – but that's an incredibly unusual scenario clinically. Keep the statins going in high-risk patients.

KC: I'm glad that you make it so clear, you know. Guidelines have said that statins are overall safe. Even I've learned from hepatologists that there's a lot of beneficial effects of statins on hepatocyte metabolism.

So, we also did small prospective studies that followed people for three years –

BE: Yeah, right.

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KC: ...published in JCNM, and it was safe. So, I always say, if you're uncertain, just start low and slow, but keep them on a statin, because many studies have shown that they have about a two- to threefold higher risk of cardiovascular disease. So this is something really, really key.

Now, within this context, I mean, lifestyle can also help quite a bit. So, why don't you give us some pointers about how do you see lifestyle in the context of fatty liver disease, or patients that have NASH and, and advanced fibrosis?

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BE: Well, Ken, you've rung an important bell for us to be listening to. You know, lifestyle is a critical strategy for management of all cardiometabolic risk, including nonalcoholic fatty liver disease. And here it's not so much the quality of the diet, in other words the balance between carbohydrate, lipid, and protein – although we would prefer the patient not eat a high level of simple sugars if they have insulin resistance and/or

diabetes or metabolic syndrome – but ultimately it's the quantity of the caloric intake, and the physical activity to follow.

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So we really want our patients with nonalcoholic fatty liver disease to lose some weight. And whether this is simply a lifestyle intervention with a restriction of calories and some increase in physical activity, or whether there are steps going beyond that, but we'd like to see at least a 5 percent weight reduction, Ken, and perhaps 10 percent would be better, to reduce the presence of lipid in the liver.

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KC: Yeah, and as you know, Bob, I mean people have tried different diets. And I think the take nowadays of many societies is just, give a diet that they can stick with and lose weight. And you know, the Mediterranean diet has proven time again and again to work. Now, in your clinic, when do you decide to send people to bariatric surgery? Is there any, anything that sticks in your mind that we would like the audience to hear about?

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BE: Well, Ken, this is an evolving platform of intervention, I think. Bariatric surgery used to be restricted to people with BMIs above 40 or 35 with additional risk factors, but now we're seeing even in early onset type-2 diabetes that bariatric or metabolic surgery may be very effective in people with BMIs between 30 and 35. This may not be reimbursed, but I think we need to be more zealous in considering when a patient should be seen by a metabolic surgeon.

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And by the way, when we send our patients to surgery, that doesn't mean they're in the operating room. We're getting the advice, hopefully from an experienced bariatric surgeon who can help the patient going forward. But as primary care physicians, we need to be more animated in terms of that referral pattern going forward.

KC: Yeah. So that's exactly what we do here. We have a big bariatric surgery program, and we combine it with an obesity management program in which we combine, you know, structured behavioral modification programs, and weight-loss medications. And as we put in our clinical care pathway, Bob, with your help, to offer weight loss to everybody, but more, even more aggressively if you identify, identify advanced fibrosis. So, having advanced fibrosis puts you on a path to cirrhosis, so we have to be more aggressive.

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So, the key concept that we have discussed before is for people screening for fatty liver, we're not so concerned about just a fatty liver; we're really concerned from a liver perspective in preventing cirrhosis.

So, there are few treatments that have worked for people with steatohepatitis with NASH and fibrosis. So, how do you think we should, recently with the approval of semaglutide for obesity and the study that was published in November in *New England* on NASH, where do you think that we're going to be placing our diabetes medications in the management of these patients?

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BE: Well, that's a great question, Ken. You've worked exclusively in this space for many years, and I think that really one of the important issues to bring up here is that the FDA currently has no drugs approved for the treatment of nonalcoholic fatty liver disease or NASH. So we've really got to attend ourselves to when we're using drugs, we're using them kind of outside the FDA approval.

Now, in terms of the treatment of patients with diabetes, or may be at high risk for diabetes and metabolic syndrome, pioglitazone is something that you've used – we've all used to some extent, and modified liver fat in terms of content. Now, NASH is fibrosis, and fibrosis leads to cirrhosis, and ultimately in some patients, to hepatocellular carcinomas.

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So, now, what are the other options? Well, I think one of the exciting new players in this game is semaglutide, which creates tremendous amount of weight loss. Now, the question comes up – and Ken, you maybe can address this yourself. Is the benefit of semaglutide simply on the weight reduction, or in fact does it go beyond that by other mechanisms? What are your thoughts about that?

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KC: Great question. So, we have been debating this quite a bit. As you know, before a number of studies showed with liraglutide, reductions in liver fat, and a small pilot study had some histological benefit. I have to say, also, there's a study with other, with dulaglutide, little pilot studies with exenatide.

So, the take of these studies, plus the semaglutide that I, our center, and I'm a coauthor, that November paper in the *New England*, showed is that the vast majority of the benefit, at least in the semaglutide trial that showed that up to 60 percent of people had resolution of NASH, it's largely from weight loss. So we are presenting an abstract at the liver meeting in November that looked at this data in more depth, and the majority is from weight loss.

So, it's a little bit puzzling, I would say.

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BE: You know, Ken, I grew up in medical school, and that's a long time ago now, really to be taught that fibrosis was irreversible. And I know the liver's an organ that can regenerate and do all kinds of fancy things almost every other organ doesn't, except the gut and the bone marrow, but nevertheless, all that aside, the liver's very special, and you're privileged and we're benefitting from that privilege to work in that space.

But anyway, why can we change fibrosis in the liver, but we can't change it in other tissues where scar has developed? What are your thoughts about that?

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KC: Wow, that's a tough one. So, that talks to what is, talk about plasticity. Well, I think, to be honest – and again, this could all be a matter of debate and controversy – but I think there's a threshold where you still have this ability to reverse fibrosis.

So, even people, pathologists observed that when you have early cirrhosis, that can reverse to less severe stages overall. For example, in hepatitis C, with the new drugs, cirrhosis tends to reverse or hold, or not advance further, definitely. So it can

reverse. And when you are in moderate stages of fibrosis that we call F2, or even F3, these can reverse. And we have observed that with pioglitazone, and it's being observed with some new drugs that are in early stages of development. The only frustrating thing is Semaglutide did not reverse fibrosis as we would have expected. And then there's debate whether it's the pathology reading or not.

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However, for the audience, there's an important concept to keep in mind. Even if you halt fibrosis and it doesn't progress any further, you have done a great service to the patient, because the vast majority are going to die of cardiovascular disease.

BE: Yeah, absolutely.

CS: And lifestyle, pioglitazone, semaglutide, all reduce cardiovascular disease. So it is critical that you identify patients with fibrosis to treat this with drugs that will have all these cardiometabolic benefits. How do you see this, Bob?

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BE: Well, I think that's a mistaken, or at least an ignorant aspect of primary care. I'm not being critical here, I'm just saying that the independent relationship of fatty liver disease, NASH, and fibrosis to cardiovascular disease is really not apparent to many primary care physicians. And I think that's a message we need to continue to promote, and that's why we keep the statins going, that's why semaglutide, pioglitazone are agents that make a lot of sense, based on what we know about their benefit, and people with high risk or with atherosclerotic cardiovascular disease. So, Ken, that's an important point for us to make here today, for sure.

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KC: Yeah, Bob, that's important. So many times I get this point, "Well, we don't have any drugs for fatty liver. Why should I worry about this?" That is true, but number one, when you have somebody with diabetes and you have to choose the diabetes medication, if you know that they have NASH and fibrosis, you would choose drugs that have benefit. For example, there are now five studies of pioglitazone that have all shown that about two-thirds have improvement in the inflammation, and fibrosis improves, has improved in some studies. And it also reduces cardiovascular disease.

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So, if you have somebody with diabetes, and you know that they have NASH with fibrosis, you would choose drugs like semaglutide or pioglitazone. And again, when we use pioglitazone, we used a max dose in these trials to see a max effect. But I currently started with 15 mg that basically doesn't induce weight gain, and then if the patient is doing well, you bump it up to 30 and see. And by the way, you can also combine it with semaglutide and lifestyle, which will anyway promote weight loss.

But again, in your view, Bob, how can we get primary care doctors – and I would say endocrinologists – to think more about NASH, and to treat it?

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BE: Well, I think we need to have a low threshold for screening for NASH to begin with. So that – people need to be aware of this. And I think for every patient being seen in an endocrine clinic who has type-2 diabetes, ultimately liver tests should be part of that, you know, comprehensive metabolic panel up front. And of course if the liver tests

are normal, I'm sure other podcasts have indicated that that may not mean that the patient doesn't have fatty liver disease.

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KC: Yeah, regarding that, I hope the ADA will be a little bit more aggressive, because the ADA current guidelines for our audience is that you would screen for steatohepatitis or fibrosis if you have fatty liver in an imaging study which may not be strictly related to your visit, but you identified it in your electronic medical record. Or, liver enzymes are elevated.

However, we published this year in *Diabetes Care* that the vast majority have liver enzymes that are below 40. So, normal ALT is 19 in women and 30 in men. So, I think that ADA should say, "Well, you have to have a FIB 4," which is free, comes out of age, liver enzymes and platelets. You know, it can be free, and you go to a web browser and it will give you a number that can tell you if the patient has fibrosis or not. And if it's less than 1.3, you're good. Greater than 1.3, worry. And then you can do some imaging, like elastography or FibroScan.

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And this is important that we get this training, because I think there are a lot of new drugs coming down the pipeline. What do you think, Bob?

BE: Well, you know, the other point I want to make about pioglitazone is, you really indicated the lower dose may be effective. And you know, one thing that even that the lower dose does, you see some body fat redistribution. So the fat in the liver does become less, but not only that, but maybe the visceral depot tends to change a bit. The

liver may see less inflammatory, pro-inflammatory cytokines and that may reduce the inflammation. And moreover, there's not much systemic weight gain, not much edema, and the bones are protected at low dose.

So, I think that's another message we really need to get across –

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KC: Yeah.

BE: Is that low dose may not be in any way harmful, but be beneficial for a plethora of downstream effects that patients with fatty liver disease can ultimately have accomplished in their care.

KC: You know that that – I'm laughing a little bit, because we just are about to have an acceptance on a paper looking at visceral fat with pioglitazone in patients with NASH, and guess what? Visceral fat goes down, histology improvement is directly related to this reduction in visceral fat. And again, the 15 mg, all the side effects on bone, all the debate that has happened with bladder cancer, are all dose-dependent. And 18 out of 23 studies have been negative about bladder cancer. And gain, these are things you have to look at, maybe do a bone density at baseline, do a urinalysis. But again, the 15 mg dose is very safe, and it does lower the A1C by .6 to .8 percent. So, it has benefits, it's safe, and it helps you become familiar with a drug that has, you know, got the backlash of rosiglitazone.

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BE: Well, you know, Ken, we're almost sounding like Ralph DeFranzo here right now. [Laughter].

KC: I know, I know. But you'll be so funny that it's just, it just had a stigma that is almost impossible to reverse. What I would invite the speakers is try the 15 mg. I mean, this, you won't get any acute – in fact, these are things you can control over time. And more surprisingly, I get people say, "Oh, you're going to cause heart failure." But if you don't have preexisting heart disease, you'll improve that particular function. I mean, you know, Bob, all this. What do you think?

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BE: Oh, for sure, yes. I mean, the pioglitazone at low dose, maybe a little less effective than modifying biomarkers of cardiovascular disease, but it does modify them in the right direction. So, no question it's an important strategy to utilize.

But now, with the new GLP-1 receptor agonist, particular at high dose with more weight reduction as your study indicated, ultimately that's another thing to seriously consider.

And finally, what about the SGLT2 inhibitors? Are they potentially useful here? The amount of weight loss with SGLT2 inhibitors is clearly not as high, but the benefits for hospitalization for heart failure and progression of renal disease have been clearly documented now with that class of drug. So your thoughts about that class, Ken.

0:37:21

KS: Yeah, well, that's a great, great point. I think, you know, we, chronic kidney disease is much more common in people with fatty liver, and fatty liver and diabetes, than those without. So, it's a great fit. Fatty liver is associated with subclinical what used

to be called diastolic dysfunction, or now heart failure with preserved, yeah, ejection fraction. So you're treating that.

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And specifically for the liver, we have done a study with Canagliflozin, but this had been shown with empa and dapagliflozin. There's about a 20 percent placebo-subtracted reduction in liver fat in imaging. And it's likely to have other benefit. We don't have any biopsies, but you know, studies combining for example pio with empa have shown a net weight loss over time. There was an additive weight loss if you use it with a GLP-1. I think they're going to be added as a great benefit to these people. I mean, I use it all the time with a lot of benefit.

0:38:28

BE: You know, another point that I think is worth making is that, you know, if you think of the drugs out there that we treat diabetes with, ultimately there's really only one major insulin sensitizer. Yes, metformin has some insulin sensitization, but it does nothing to the natural history of non-alcoholic fatty liver disease.

But pioglitazone represents the thiazolidinedione class, and that's really the only drug approved that modifies insulin resistance favorably, meaning makes the patient more insulin sensitive. And if you think about it, fatty liver disease, in addition to a lot of other metabolic complications of type-2 diabetes, relate to the insulin resistance. So that's another rationale to give pioglitazone more frequently to these patients. And I've use it for years in my clinic to treat patients with insulin resistance and type-2 diabetes.

0:39:15

KC: Well, as I like to explain to Fellows and young endocrinologists in our university at the University of Florida, it makes you metabolically healthy, in the sense that by keeping fat in the proper stores, subcutaneous tissues, it prevents ectopic fat accumulation that causes the typical dyslipidemia, triglycerides go down, ACL can go up. The heart works better.

And I think we need to begin reassessing it, and using it in combination, as you said, with GLP-1 or with SGLT2s to reach this goal. Now, for the audience, again, none of these drugs is FDA approved for fatty liver, but you can use it into the context of diabetes.

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The other question, again, what do we do with those without diabetes? Well, pioglitazone has shown to work equally well, but again, not approved for people without diabetes. Semaglutide, with its obesity indication, would be a nice approach. And just from an educational perspective, vitamin E, 800 units a day, has showed benefit in a large, well-done study called PIVENS, published in the *New England* in 2010. There's still always a doubt about whether it can worsen cardiovascular disease, or there's a debate about prostate cancer. Bob, what do you think about the cardiovascular disease and vitamin E?

0:40:36

BE: Well, I think that story is still out, but not very convincing at this point in time. I would not recommend high-dose vitamin E for anything but non-alcoholic fatty liver disease, and that would be in people without diabetes, not people with diabetes.

KC: Well, vitamin E, we tested it with pioglitazone or alone, and it had mixed results. It had modest benefits and not any greater than just using pioglitazone. So that's why in people with diabetes I don't use it.

0:41:03

Now, to close, I mean, I would like the audience to know that the other reason why you have to develop a routine of screening for fatty liver in the same way you do for retinopathy or nephropathy is because there are a number of new drugs. And I don't want to bore the audience with the number of new agents, but there are agents, for example, dual agonists that can promote weight loss. Bob, is there any of the new agents that, in your mind, you think might be more promising?

0:41:37

BE: Well, kind the twins, so they're called, of GLP-1 and also the GLP-1 receptor agonist in GIP is a combination therapy we're going to hear a lot about in upcoming scientific sessions this week and the weekend at the American Diabetes Association. So, that's a new combination that seems to show potentially additional promise for various aspects of metabolic diseases including not only glycemic control, but perhaps even non-alcoholic fatty liver disease. So that's certainly something we should be thinking about.

0:42:08

The important aspect of non-alcoholic fatty liver disease relates to the ultimate fibrotic development that occurs in the liver. And I think, you know, drugs that modify the fat content but may not modify the existence of fibrosis or the progression of fibrosis are

drugs that we're going to be a little less likely to use ultimately, once we know more about the natural history of non-alcoholic fatty liver disease and NASH.

0:42:36

KC: Yeah, that's a great point. So, the FDA asks you to modify either dramatically inflammation, or reverse fibrosis. And again, in that sense, some big classes of drugs like FXRs have been considered anti-fibrotics, but they're falling a little bit short of their target. There's NTF 21s (?) of different classes. Again, they've shown effects on fat, but we're still learning about their, if they can meet the FDA target.

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And then there's, there's a new drug, lanifibranor, that is a PPAR alpha delta gamma, that had very promising results in 2020 presented at the liver meeting. It's supposed to be like an upgraded version of pioglitazone, and it has shown to be pretty impressive.

So, there are a number of other drugs. There's a A and B kinase activator called PXL770. But I think that for the audience, if they focus on choosing the diabetes medications we have plus lifestyle, there's a key thing that you can do today.

0:43:46

So, Bob, we're going to try to close here. What would be your last message for our audience that has to take care of these patients tomorrow?

BE: Well, my message for the primary care physician, actually even endocrine people and cardiologists too need to be in this space. They need to screen for non-alcoholic fatty liver disease, and if that ALT is elevated, we may need to make sure that we rule

out other causes of liver disease. We didn't mention that, but that's really an important step.

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But once other causes are eliminated, then ultimately I think we need to progress to understand how much fat is in the liver, and ultimately use the FIB-4 to discern whether the patient's at low risk, intermediate risk, or high risk, and move on from the algorithm we're going to be publishing – in fact, I think the article is in press now, isn't it Ken, for people to turn to. The Figure 3 there is an incredibly important figure for primary care physicians to have in their offices and on their walls or on their desk.

0:44:43

KC: Yeah, Bob. So, there's a call to action that summarizes the state of knowledge that is simultaneously being published in *Gastroenterology, Diabetes Care, Obesity, General Metabolism.* And all of these are going to try to convey the message that we need multidisciplinary teams. Screening is here to stay, particularly those at the highest risk, people with obesity and diabetes. And the clinical care pathway that Bob is mentioning, they're going to come out in *Gastroenterology* very soon, summarize in three simple figures what we have to do.

0:45:19

BE: Well, you know, Ken, what, one thing I've promoted for a number of years now, working with my colleague Mike Blahous, a preventive cardiologist at Johns Hopkins, is the development of a new medical sub-specialty called cardiometabolic medicine. Now,

that name has been changed by my renal colleagues to cardio-renal metabolic medicine, but I think we could change it to cardio-hepatology metabolic renal medicine.

So whatever, I think this type of comprehensive clinic should probably include someone with expertise in liver disease that also complements nephrology, cardiology, and endocrinology.

0:45:56

KC: That is a great point. To be – when I teach, I say there's a triangle of care: heart, kidney, and the liver. The liver is still a little bit behind, but hopefully will catch up. I've been, many times people kid me saying that I'm a gastroendocrinologist, but in reality, care is becoming more complex, but the good thing is that the medicine we have for diabetes are the more promising to treat these three targets.

0:46:22

So, Bob, I've really enjoyed it. Keep doing the great job that you're doing. Thank you for all – I have to say to the audience, Bob was instrumental in getting our white paper in all these journals, and in the clinical care pathways, and hopefully this has helped the audience manage or understand better why fatty liver is important, and we hope to hear from you soon. And Bob, any final thoughts for us?

0:46:52

BE: Well, nothing other than more aggressive and zealous screening in the clinic. And hopefully once the disorder's been identified, excess liver fat, perhaps with NASH – and you know, there you're not quite sure without a biopsy - anyway, all that aside, we need

to get these people to lose weight. That's probably the most critical and important thing for the primary care physician to do.

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So I'll leave that with a take-home message: get some weight down for a multiplicity of reasons, but for non-alcoholic fatty liver disease, for lipids, for glucose tolerance, inflammation and everything else it relates to. Good luck. This is tough, but good luck. We've got a lot of helps to bring you along the path of success in that area.

KC: Thank you, Bob. We can't give up now on our patients. And I think we have better tools. As I like to say, we've never had better tools to take care of our patients as we have today from our understanding of the disease and the pharmacological options. So, thank you Bob. Thank you all, you on the other side. And let's get back to work.

0:47:59

FK: Thank you, Fasiha, Jay, and special thanks to my guest, Bob Eckel. Thank you all for joining us for this episode on managing nonalcoholic fatty liver disease and NASH. You can find the other five episodes in this series, the NASH Clinical Care Pathway, and more resources at the program's website, NASH.Gastro.Org.

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Announcer: Thank you for listening today. Visit NASH.Gastro.org to get your CME credits, and find clinical pearls and a full transcript of this episode. Be sure to listen to the other five podcasts in this series on NAFLD and NASH, covering important topics like diagnosis, management, and team-based care.

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