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Navigating Non-Alcoholic Fatty Liver Disease: Top Management Strategies to Know

Dr. Buch:
According to recent estimates, non-alcoholic fatty liver disease affects between 80 and 100 million Americans. Non-alcoholic fatty liver disease can lead to cirrhosis and even liver cancer. So how can we better manage this illness?

This is *GI Insights* on ReachMD. I'm your host Dr. Peter Buch. Here to help us better understand non-alcoholic fatty liver disease is Dr. Colin Swales, a hepatologist who is the Assistant Medical Director of Transplant Services at Harvard Hospital. Dr. Swales, thanks very much for joining us here today.

Dr. Swales:
Thanks Peter, good to be with you.

Dr. Buch:
Let's get right into it. What are the risk factors for developing non-alcoholic fatty liver disease?

Dr. Swales:
OK. So the most important risk factor is overweight and obesity. And I think of fatty liver generally and now we're talking about in the first world, so the United States, western Europe, that kind of thing as being an analog to diabetes. And so overweight and obesity and the other signs and symptoms of the so-called metabolic syndrome tend to be the flags that helped us to identify this problem.

But we're now starting to better understand that much of the disease, at least the morbidity and the mortality of disease is driven by genetic predisposition. And diabetes is like that too, so there have been a number of genes that have been identified as risk factors for progression and the most important one is probably a phospholipase called PLP83 and so like diabetes, it's a situation where the genes sort of set the stage and the environmental risk factors or lifestyle risk factors as you will they pull the trigger. They get the disease going and cause the problems of the liver.

Dr. Buch:
And how do you treat non-alcoholic fatty liver and non-alcoholic steatohepatitis?

Dr. Swales:
Well, the treatments right now are basically lifestyle interventions. And so what we recommend is that people try to get closer to their healthy body weight and how they do that is largely up to them and the way I leave it with my patients to say do whatever works for you. And so what I need you to do is to get closer to your healthy body weight and however you decide to do that in terms of diet and exercise is really what works bests. What I mean by that is that the macronutrient composition, in other words, the carbohydrates, fats, and proteins of your diet, they can be adjusted any way you see fit in order to lose weight through caloric restriction. You'll see or hear mentioned out there that fructose may be problematic. That's an interesting hypothesis that fructose consumption in, especially in American diets, might be driving some of this. I think there are some data in animal models and some observational data in humans that might buttress that, but it's really not clear if that is critical per se, and so I basically tell my patients it's really up to them how they choose to lose the weight.

I used to less focus on exercise, but increasingly, there are data out there supporting that exercise is beneficial for non-alcoholic fatty liver, especially for the outcome we care the most about, which is mortality. And so I have been spending a little bit more time focusing on that with my patients as I do think it's helpful.

Pharmacologic interventions for fatty liver are wanting and a little bit controversial, and we can certainly talk about that in more detail, but right now, we don't have prescriptions that are a sure-fire bet at this point.

Dr. Buch:
Do you use vitamin E for non-alcoholic steatohepatitis?

Dr. Swales:
So that's one of the ones that does get bandied about. Where are the data from that? They come from probably the best trial that's been done on alcoholic fatty liver, it's called the PIVENS trial. It was a multi-centered NIH-sponsored trial that compared pioglitazone to vitamin E and was placebo-controlled. And the vitamin E group did show improvements in some of the surrogate endpoints. So what would those be? That would be the ALT levels, for example, and they did do biopsies. They biopsied people at enrollment and then again at the two-year mark I believe. And the biopsies did look better, but biopsies, number one, they're a surrogate marker for the outcomes we care about. So the things we wanna know is, did they get cirrhosis, do they need a liver transplant, did they die from fatty liver disease, did they get liver cancer? And those data are not available. We don't know if vitamin E-exposed patients are being benefited in that way. And, you know, as much as we love liver biopsy in hepatology, using it as a surrogate endpoint for those outcomes is not perfect. I mean, there are other disease states where that has been done and have been disappointing, like, I'm thinking specifically about a primary sclerosing cholangitis, for example. And so it's a widespread recommend vitamin E as a treatment. I think it's gonna require more outcomes data.

Now, people would argue, well, it's vitamin E, you know, it's a safe thing to give, right? Well, we're not sure about that because you may know that vitamin E was studied relatively extensively, especially in the 90s, as a treatment for heart disease. And the cardiologists, they will enroll thousands of patients in their trials which is not, we don't generally do that in GI and liver, we don't have huge trials say with the exception of hepatitis C and IBD. And so the cardiologist have meta-analyzed all of their vitamin E data and that meta-analysis is about 20 years old now, but it did show that there was a higher mortality in high-dose vitamin E-exposed patients. And I believe it was because of the increased risk of prostate cancer in men. And so I think it's a noble question as to whether or not vitamin E is helping people and it is concerning to see that, you know, long term vitamin E use might be associated with increased mortality.

Dr. Buch:
And can you please discuss how statins should be used for non-alcoholic fatty liver disease?

Dr. Swales:
Sure. So, I would divide my comments into two sections here. One is to say: do statins impact the liver disease per se in a positive way? And that's an interesting idea. And the second, which is easier is to say if somebody has a compelling indication for a statin otherwise, can they safely take it with fatty liver disease? And I think that answer is "yes." We know that because it has been studied in a controlled way in many trials over the past couple of decades and we know that statins can be safely taken, even by cirrhotic patients, if they're needed. And I think if a cardiologist were in the room, he would argue that statins have made a major impact in terms of reducing cardiovascular morbidity/mortality. And so if the patients need 'em, they should take 'em, and we shouldn't fear drug-induced liver injury from statins. The estimates for those kinds of injuries are very low and large, large trials, something on the order of maybe 1 or 2 in a million that would develop a severe drug-induced liver injury. That said, I take issue with some of the national advice from the HCC about not needing to follow a liver functions with statin use because, in particular, atorvastatin has been associated with a not common but not unheard of liver injury that's more autoimmune-like, and my worry is that even though that's rare that that is an opportunity to pick that up. And that can be obviously treated, and we would hate to miss an opportunity to do that.

But the second part is whether or not the statins impact fatty liver disease positively and I do think that's an interesting idea and there are some small trials that suggest that that may be the case because you'll see things like the ALT is improved on statins or the liver appears to contain less fat on imaging and those, I think, are an interesting hypothesis. There are no outcomes data that I am aware of that looks at things that we care about, in other words, so that progress to cirrhosis need a transplant and that thing. So, I personally would not recommend a statin for the treatment of NAFL, but if people have a compelling indication, I don't hesitate to "clear" them to use that.

Dr. Buch:
That's great. For those just joining us, this is *GI Insights* on ReachMD. I'm Dr. Peter Buch and today, I'm speaking with Dr. Colin Swales about non-alcoholic fatty liver disease.

So, Dr. Swales, do you recommend the use of non-alcoholic fatty liver disease fibrosis score, or NFS, to assess the level of fibrosis?

Dr. Swales:
So the answer is yes, I do. That is what is recommended by the AASLD, the multi-society guideline on the treatment of fatty liver disease

and the way that it is helpful is, number one, it's very easy to crunch that number. I think it's a six-variable calculation that is based on clinical data that is easy to get your fingers on. And the way it helps you is it helps to figure out if people are at risk for fibrosis. Now, it's a very broad brush and it heavily depends on the age of the patient, and so if you and you can do this yourself, if you crunch the numbers on anybody over the age of 40, even if all the numbers are in the normal range, it will spit out a sort of indeterminate, we're not sure, risk score for the presence of advanced fibrosis. And so that limits its utility, I think. But if you have a young person and you want to reassure them that they're not at risk for advanced fibrosis it can be easy and useful to do that.

I think if you use it regularly, you'll find that many people are coming up indeterminate or potentially at risk and can you use it as a stand-alone way to stage people? The answer is "no." You're gonna have to move to a more specific staging test and I think we're gonna talk about the FibroScan, in particular, coming up.

Dr. Buch:
That's a perfect segue. That's exactly right. So how do you use elastography and FibroTest in your practice?

Dr. Swales:
So I use elastography pretty much exclusively because I have access to it. The FibroScan is the FDA-approved elastography device in the United States. We're also seeing elastography done by other ultrasound, you know, in imaging centers and also MR elastography. They have less data to support them, but they're certainly better than using the sort of the gross imaging results to stage people, which is very problematic. But elastography is safe, it's easy, the patients tolerate it very well, and it's pretty good. It's really been well-validated in many different kinds of chronic liver diseases to try to get at the staging information that we would get from a liver biopsy, which is probably the most important part of the liver biopsy and was the part that was hardest for us to estimate in the absence of a biopsy. So it performs pretty well. It parses out the stages pretty well. Is it perfect? No. I have seen it be wrong on both ends of the spectrum where you get a result that suggests patients don't have advanced chronic liver disease and it turns out they do; that's unusual but I've seen that a couple of times. But more commonly, I'll see the machine telling me that the patients are at risk for cirrhosis and they are not. And so, you have to integrate the result of the FibroScan or the elastography with everything else you know about the patient. And in short, you just gotta use your clinical skills and evaluate the total set of the data. And what I do is when the results are discordant or discrepant, I usually would recommend a biopsy because biopsy is the gold standard test and gives us the most accurate results.

Dr. Buch:
Thank you. Let's move onto this question: is there a special approach to treat diabetic patients with non-alcoholic fatty liver disease?

Dr. Swales:
So this question is an interesting one, and if you read the guideline on the issue, this is where the pioglitazone are in the PIVENS trial might come in because pioglitazone is a treatment for diabetes, as approved by the FDA for treatment of type 2 diabetes. And so the guideline does report that pioglitazone might be a better option than vitamin E in diabetic patients. Again, that's based on surrogate outcomes. So whether, you know, the ALT and the biopsy changes in the PIVENS trial were positive in the pioglitazone arm, I think my knowledge about pioglitazone is that it is probably safe for patients with heart disease, heart failure. But again without the outcomes data to suggest that we're improving mortality for example, I believe it's an open question.

The rest of the diabetes treatment is a lot like the statin conversation we were having, which is, you know, whatever you would do to treat the diabetes in terms of A1C targets and organ targets that is all indicated and appropriate. And so my own approach to this is to attack the problems separately, the fatty liver and diabetes.

Dr. Buch:
Thank you. And lastly, Dr. Swales, is there anything else you want to share with our audience today?

Dr. Swales:
Well fatty liver is the emerging issue. There's more fatty liver than there's ever been in the United States. Hepatitis C is on the downswing for the most part. And so this is where the focus is gonna be in terms of the volume of patients that we're gonna be seeing for the next couple of decades, if not longer. I'm hopeful that we'll get a treatment approved by the FDA. There are many, many things in pipeline trials right now and some of them are looking very encouraging, so that's exciting, but we gotta get brushed up on this topic for sure and it's gonna be changing fast, so keep your ear to the ground.

Dr. Buch:
Thank you. That's all the time we have for today, but I want to thank you, Dr. Swales, for providing your wonderful insights.

Dr. Swales:
Thank you, Peter. It's been a pleasure.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this program, as well as others from our series, visit ReachMD.com/GIInsights, where you can Be Part of the Knowledge. Thanks for joining us today and see you soon.