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Reviewing Cardiac Complications in Liver Disease

Announcer:

Welcome to *GI Insights* on ReachMD, and this episode is sponsored by Siemens Healthineers. Here's your host, Dr. Charles Turck.

Dr. Turck:

This is *GI Insights* on ReachMD. I'm Dr. Charles Turck and joining me to discuss the risk of cardiovascular disease in patients with liver disease are doctors Zobair Younossi and Dr. Allen Wu. Dr. Younossi is the Chair of the Global NASH Council and Professor of Medicine at the Inova Fairfax Medical Campus in Falls Church, Virginia.

Dr. Younossi, it's a pleasure to have you here.

Dr. Younossi:

Thank you very much for having me.

Dr. Turck:

Also joining me on today's program is Dr. Allen Wu. Dr. Wu is a Professor in Laboratory Medicine and is Chief of the Clinical Chemistry and Toxicology Laboratories at San Francisco General Hospital. Dr. Wu, thanks for being here today.

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Dr. Wu:

Well, thank you Charles, and thank you all, for joining in today.

Dr. Turck:

So to get us started, Dr. Younossi, we know that nonalcoholic fatty liver disease was recently renamed to metabolic dysfunction-associated steatotic liver disease, or MASLD for short. What are the most common cardiac complications associated with MASLD?

Dr. Younossi:

Well, when you look at some of the earliest studies that either—well, I think the earliest natural history that has been published for this disease, we published this about, almost 22 or 23 years ago, and this was a cohort from Cleveland Clinic that, at the time, I used to work there, that we followed for a very long time and looked at causes of mortality. And in this context, the number one cause of mortality was cardiovascular mortality. That study has been replicated more than two dozen times in other longitudinal studies, population-based studies, meta-analysis, so there is no doubt that for most patients with non-alcoholic fatty liver disease, cardiovascular mortality is the top cause of death. Now when you actually get into more advanced stages of liver disease, like those who have advanced fibrosis or cirrhosis of the liver, then liver mortality becomes dominant, but before that, it's cardiovascular mortality.

And when you look at the type of diagnosis that these people have at increased rate, it's everything from increased coronary artery disease to diastolic dysfunction to arrhythmia, especially atrial fibrillation, as well as actually strokes, cerebrovascular accident and strokes, have been reported to be higher in this group of patients.

Dr. Turck:

And as a follow-up to that, which patients with liver disease are most at risk of cardiovascular disease?

Dr. Younossi:

Now in general, I think that all patients with non-alcoholic fatty liver disease regardless of what severity of fatty liver, or NAFLD or MASLD, they have, they are at risk for cardiovascular mortality. And I think you could imagine that they have the same underlying risk

factors, which has to do with metabolic syndrome and its components, especially tied to diabetes. But there are some studies that suggest that those patients that have increased fibrosis in the liver are also at increased risk for mortality from cardiovascular diseases. To me that may indicate a more aggressive inflammatory milieu in these patients that not only affect the liver causing more advanced fibrosis, but also other organs including different components of cardiovascular system.

Dr. Turck:

I was wondering if you would speak a little bit about what the literature has to say about the incidence of major adverse cardiovascular events, or MACE, in patients with MASLD.

Dr. Younossi:

Yeah, there are meta-analyses both from Europe, from South Korea, as well as even the United States that suggest that MACE actually increased. The different component of MACE, when you look, is probably the hazard ratio is somewhere between 1.6 to 1.7. So there is certainly an increased risk of MACE in general, but also different components that make MACE. There is in my view no doubt that these patients are at increased risk for MACE or component of cardiovascular diseases.

Dr. Turck:

For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Zobair Younossi about cardiac complications associated with liver disease.

So, Dr. Younossi, now that we have some more information about the prevalence of MACE in patients with MASLD, would you explain how these contribute to the overall health burden patients experience?

Dr. Younossi:

I look at three different components or burdens. There is clinical burden, which has to do with development of adverse clinical outcomes, like cirrhosis and liver cancer, those are hepatic component of this clinical burden. But there is a variety of extrahepatic diseases that these patients are at risk for; cardiovascular disease

we talk about. These patients are also at risk for extrahepatic malignancies, gastric cancer, that type of cancer. They're at high risk of a disease called sarcopenia. The prevalence of sarcopenia, which is related to muscle abnormality is higher with patients with NAFLD, and sarcopenia is an independent predictor of mortality amongst patients with NAFLD. Additionally, there is significant evidence suggesting that renal disease is higher in these patients. So there are a number of other non-cardiac or non-liver extrahepatic manifestations that lead to these adverse clinical outcomes. Therefore, there is higher overall mortality in patients with non-alcoholic fatty liver disease.

The second type of outcome that I actually pay attention to is what we call, outcomes related to patient experience, and these are patient-reported outcomes, health-related quality of life. We've done a lot of research here ourselves and shown that without a doubt, that patients with non-alcoholic fatty liver disease are at risk for more impairment of their PROs, patient-reported outcome, and quality of life. In fact, the worse the disease becomes in terms of severity, the more advanced the disease becomes, the more impairment of quality of life you see in these patients, and of course, that will have additional impact on these patients. Of course, besides that type of impact, there is also impact on caregivers, there's increased risk of disability. In fact, when you look at DALYs, or disability-adjusted life years, for patients with fatty liver disease, that is pretty huge when you look at it globally, or even regionally, in different regions of the world.

The last type of outcome I look at is the economic impact of non-alcoholic fatty liver disease, and we have done a few of these studies ourselves, more in terms of modeling, as well as actually looking in our databases. The impact of NAFLD direct cost associated with non-alcoholic fatty liver disease is probably, in the United States, is probably about 100 billion dollars. Now when you add indirect cost of things, like reduced work productivity, then the cost associated with this disease could be enormous. And then unfortunately, the way things are going, things are not getting better, things are getting worse because the problems of NAFLD has increased. Currently, NAFLD is the second indication for liver transplantation in general and is the number one indication for liver transplantation in the United States for those who get listed for liver cancer. It's also the most common indication in women and in also in those who are over age 45. So it is rapidly becoming one of the two top causes, or it already is one of the two causes, of liver transplantation and may become the most common cause of liver transplantation in the United States. And finally, it is probably in the United States and in the western world, it is the most common reason for liver cancer.

Dr. Turck:

And how might a multidisciplinary team approach impact patient outcomes?

Dr. Younossi:

Well, I believe that that's the only way to actually manage these patients—meaning that the core of this multidisciplinary team you have

to have your primary care physicians because most patients with non-alcoholic fatty liver disease are seen there and a lot of them are not recognized. Then, of course, you have to have a nutrition expert and exercise expert because lifestyle and their micronutrients, macronutrients, and the way that the activity is actually being maintained are going to be important in terms of at least addressing some of the root causes of this disease. Of course, this has to be done in a way that is sustainable, so that's why you need to have a behavioral expert there to help these patients; endocrinologists just because they have a lot of patients with type 2 diabetes and the prevalence of nonalcoholic fatty liver disease there is about 70 percent, so you have very high number of these patients, and in fact, type 2 diabetes is also a predictor of progressive disease, liver disease in these patients, so you have to have endocrinology involved. And of course, gastroenterology and hepatology should be a part of that, and it should be specifically with those patients that have more progressive and advanced disease. The multidisciplinary team can be delivered under the same roof, obviously, or virtually, because there are challenges for bringing all of these folks together in the one clinic. But certainly, without having multidisciplinary team and approaching this disease as a care pathway, we're not going to really get anywhere.

Dr. Turck:

Now, Dr. Younossi, from your vantage point, what further research needs to be done so that we can best care for these patients?

Dr. Younossi:

I think our challenges are maybe in three different levels. I would say the most serious challenge we are facing is that despite the increase in the prevalence and the burden of this disease and the fact that it's associated with all kinds of adverse outcomes, as I explained, knowledge about this disease is pretty poor, specifically, in where it matters, like in the amount of primary care physicians, maybe a little better in the endocrinologist circles these days, and of course, that's almost negligible among patients themselves. So there has to be efforts and research in terms of how do we increase through education efforts knowledge gap that currently exists about this disease?

The second area that needs to be strengthened is finding non-invasive ways to identify patients who are at risk. Now historically, we have used a liver biopsy that would tell us if a patient is early stage or advanced stage. Liver biopsy is invasive, and a lot of people don't want to do it, and I would agree with that. So we are developing non-invasive tests to be used to identify those patients who are at risk.

The third challenge, of course, is to find drugs that could actually be used for patients that have more aggressive disease or some signs that they have more aggressive disease with NAFLD or MASLD. And this is the group of patients who have NASH, or now it's called MASH also, and there are some targeted drugs that are being used, and hopefully, in the next near future we'll have one of them approved.

Dr. Turck:

So, Dr. Wu, is there a connection between chronic liver disease and development of cardiac risk or onset of disease?

Dr. Wu:

Well, there certainly is. Liver disease plays a central role in the development of cardiometabolic syndrome. In particular, hepatic steatosis, lipid dysregulation, along with obesity, diabetes, hypertension, and renal disease will lead to myocardial fibrosis and diastolic dysfunction. We usually think of fibrosis as occurring after acute myocardial infarction, but in fact, coronary artery stiffness is a risk factor for AMI development that certainly occurs in patients with cardiometabolic syndrome.

Dr. Turck:

And would you tell us the different cardiac biomarkers for which we should be screening in patients with liver disease?

Dr. Wu:

There're really only two, the natriuretic peptides, which include a B-type natriuretic peptide, and the metabolite NT-proBNP are useful for screening diagnosis of heart failure, assessing the severity of heart failure, and stratification overt risk or disease progression, as well as predicting future major adverse cardiac events. Patients with cardiometabolic syndrome have a two-fold higher likelihood of developing CAD and a three-fold higher chance of suffering from AMI. Cardiac troponin is the standard for diagnosis and rule-out of AMI from the ED, but high-sensitivity assays are increasingly being used to assess cardiovascular disease risk and screening for active coronary artery disease.

Dr. Turck:

Now, Dr. Wu, once we screen patients for those biomarkers, what should our next steps be, and what kind of impact can they have on our patient's health and quality of care?

Dr. Wu:

Well, in the absence of acute symptoms, patients with increases in the natriuretic peptides or high-sensitivity cardiac troponin should enter a plan to mitigate risks for future adverse cardiac events, such as AMI and heart failure. At a minimum, there can be lifestyle

adjustments, like smoking cessation, changes in diet, and engaging in an appropriate exercise regimen. Therapeutic interventions may be warranted, including drugs to lower lipids, blood pressure, manage diabetes, and perhaps a statin to reduce inflammation and coronary artery disease risk. High-sensitivity troponin is emerging as a primary assessment of biomarker in conjunction with traditional tests, such as the lipids and lipoproteins. However, at this time, I'm not a big proponent of using natriuretic peptides to monitor the success of anti-heart failure medications. I think that we have other tests that are emerging that will fulfill that role.

Dr. Turck:

Well, those are great thoughts for us to consider as we come to the end of today's program. And I want to thank my guests, Dr. Zobair Younossi and Dr. Allen Wu, for joining me to discuss the risk and burden of cardiovascular disease in patients with liver disease.

Dr. Younossi and Dr. Wu, it was great having you both on the program.

Dr. Younossi:

Thanks very much, it was a pleasure.

Dr. Wu:

Well, thank you again, and I thank ReachMD for hosting this today.

Announcer:

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