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Addressing Alcohol-Associated Liver Disease and Sobriety Pathways

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and today, we're joined by Dr. Paul Kwo, who will be discussing alcohol-associated liver disease. Dr. Kwo is a Professor of Medicine and the Director of Hepatology at Stanford University. He's passionate about teaching, patient care, and medical research.

Dr. Kwo, welcome back to the program.

Dr. Kwo:
Thank you very much. Great to be with you.

Dr. Buch:
Let's dive right in, Dr. Kwo. Is there any safe amount of alcohol consumption for patients with chronic liver disease?

Dr. Kwo:
Yeah, that's an excellent question because as you know, Dr. Buch, we have a large prevalence of other liver diseases, including metabolic dysfunction-associated steatotic liver disease, formerly known as fatty liver, that we discussed previously. And we know that alcohol, even in amounts that seemingly were not harmful by previous assessments, actually can contribute not only to progressive liver damage but also, a variety of cancers.
So when it comes to those that have underlying liver disease, I approach patients in the following way, which is I tell them that they should really not drink alcohol regularly at all— sure, for special occasions or ceremonies; say you have a wedding; say you have an anniversary or a birthday, sure, but it should not be a regular occurrence for those who have underlying chronic liver disease.

There has been a very recent publication that looked at the National Health and Nutrition Examination Survey, which is a cohort that is followed, and allows us to make recommendations regarding general medical health, and it was very interesting in this analysis. They looked at the contribution in those who drank, and the risk of having a marker that suggested advanced fibrosis, and what they noted was that if you drank more than seven grams of alcohol per day, which is about half a drink, that you had a higher risk of developing more significant liver disease, and these were in individuals who had underlying metabolic dysfunction-associated steatotic liver disease, or what is formerly known as fatty liver. So if you have underlying chronic liver disease, I discourage regular alcohol use. Certainly, occasional use is fine.

Dr. Buch:
And based on your work, Dr. Kwo, why are only 3.8 percent of patients with alcohol use disorder referred at early stages for intervention compared to a much higher number for other liver diseases?

Dr. Kwo:
Yes. So the reason that we don't diagnose, if you will, those with early alcohol-associated liver disease is because we don't have great biomarkers to detect this yet. So for other diseases, we have appropriate screening tests. So for viral hepatitis, we can screen for hepatitis B; we can screen for hepatitis C. For metabolic dysfunction-associated steatotic liver disease, we know that there are risk factors that can include features of the metabolic syndrome, elevated body mass index, hyperlipidemia. Those who drink moderately may have completely normal liver tests, may have completely normal blood counts and analyses, and so what we lack is a set of good biomarkers that can help us when we see these individuals in primary care

settings assess whether or not a level of alcohol consumption that they are currently consuming is actually contributing to hepatocellular damage. When we see liver tests going up because of alcohol use, certainly we can intervene then, but that misses just such a substantial portion of those who have early alcohol-associated liver disease, and this is a major factor as to why we detect such a small percent of these individuals.

There are prospective studies going on right now to try to follow these cohorts and help identify biomarkers that would help us, and we hope in the future that these will be available to our patients and we will be able to detect these individuals and intervene at an earlier time point.

Dr. Buch:
So now when assessing a patient for alcohol-associated liver disease, what kind of testing do you perform?

Dr. Kwo:
Yes. So let's talk about alcoholic hepatitis because this has been something that we're seeing in much higher rates, particularly younger people ages 20 to 39, and particularly women, who are presenting with acute alcoholic hepatitis. We used to say this required a liver biopsy, but it doesn't. We've had some recent practice guidances, which have been very helpful here, so to diagnose alcoholic hepatitis, we like to look at the liver test, and we like to see that the bilirubin should be above three milligrams per deciliter. And if you look careful at these individuals, Dr. Buch, they should be jaundiced with that. You'll see evidence of hepatocellular inflammation with elevations of AST and ALT. And typically, the AST, which is typically always lower than the ALT in almost all other liver diseases except alcohol, the AST is going to be higher than the ALT, preferably again two times the upper limit of normal, but if it's higher, that's actually okay and helps us confirm that these individuals have the alcoholic hepatitis injury, typically a ratio greater than 1.5. Also, AST and ALT can't be too high as well.

We obviously talk to them about their alcohol use, and we clinically correlate this. We look for markers of hepatic decompensation. These individuals not only can present with abnormal liver tests, but they may have confusion, what we call hepatic encephalopathy; abdominal distension, where just fluid accumulates in the belly in cases of severe hepatitis; and they are also prone to what we call variceal bleeding, where the liver becomes stiff, blood can't go through the liver, and it backs up into blood vessels, which rupture. These all can be presentations that we look for also in the setting of acute alcoholic hepatitis.

You can do a liver biopsy, Dr. Buch, and we can certainly use this to make the diagnosis as well, but with our clinical tools that we have available to us, we usually don't require a liver biopsy. Not all patients are forthcoming initially about their alcohol use or may not recognize that alcohol use is what led them to their current clinical presentation, and there the biomarkers that can also be very helpful for us in confirming a diagnosis.

Dr. Buch:
With regard to that, on the AST-ALT ratio, can we hang our hat on that for all patients?

Dr. Kwo:
So there are two instances where the AST is higher than the ALT. So number one is the disorder that we're talking about. In alcohol-associated liver disease, particularly with alcoholic hepatitis, AST is higher, and this is because of some vitamin deficiencies. As it turns out, those with alcohol use disorder turn out to be deficient for a vitamin called pyridoxine, and pyridoxine deficiencies actually suppress the ALT level more than the AST, and that's one of the major reasons why the AST is higher. The other condition that we can see this in is cirrhosis of any etiology. And what I mean by that is, for instance, if it's viral hepatitis, if it's metabolic dysfunction-associated steatotic liver disease, any of these are diagnoses that can also lead to, in the setting of cirrhosis, an AST that's higher than the ALT, but the AST and ALT will not be as high. They typically, are not two times the upper limit of normal. And then when you see these individuals, you have to clinically correlate. For instance, are they more jaundiced? Are these individuals also someone who's presenting with what we call macrocytosis, large red cells? There are a variety of other factors. But in general, in the appropriate clinical context where there's a history of potential excess alcohol use or alcohol use disorder this AST-ALT ratio is very useful.

Dr. Buch:
Thank you. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Paul Kwo about alcohol-associated liver disease.

Let's zero in further with regard to severe alcoholic hepatitis. Are there any medications that might exacerbate that situation?

Dr. Kwo:
Yes. So let's talk about the medicines that can get you into trouble if you have alcohol use disorder and inflammation of the liver with alcoholic hepatitis. There are medicines that actually cause the same type of inflammatory injury as does alcoholic hepatitis. So there is a medicine we use

for breast cancer, called tamoxifen, that can cause the same kind of pattern and accelerate the injury. There is also a heart medicine we use for those with irregular heartbeats, called amiodarone, which also can contribute. and in fact, can lead to almost an identical-appearing type of hepatocellular injury. And then there's also a rheumatologic medicine, an antimetabolite, called methotrexate, which also can do this.

Now the vast majority of people with alcohol use disorder probably aren't taking these particular medicines, but I want to bring up one other medicine that gets people into trouble all the time, and that is acetaminophen. And so the acetaminophen, which is widely available, is a drug that doesn't necessarily, if you will, exacerbate the severe alcoholic hepatitis in the same manner, but as it turns out, when you drink in excess, you actually generate additional enzymes in the liver, which metabolize alcohol. So it's normally by an enzyme pathway, called alcohol dehydrogenase. But when you have excess alcohol, what happens is your liver makes another protein, called cytochrome P450 2E1. And just think of this as like recruiting an additional person when you have such a heavy workload. You need to bring in somebody to help take care of this excess alcohol and metabolize it.

As it turns out, this other enzyme, which is cytochrome P450 2E1, or CYP 2E1, is also the key enzyme that generates the toxic metabolite in those who take too much acetaminophen. And what we see with those with alcohol use disorder who take acetaminophen, seemingly at doses that aren't so high, is that they can get into trouble with severe alcohol—not only alcoholic hepatitis—but they get a severe acute hepatitis from, if you will, acetaminophen overdose.

So if you drink regularly, I advise my patients, in addition to avoiding those medicines that we discussed, which are pretty uncommon, that acetaminophen really should be something that you do not use regularly, particularly those who have heavier alcohol use because you can, indeed, get yourself into trouble.

Dr. Buch:
When treating patients with alcohol-associated liver disease who need a liver transplant, what do we still need to learn about utilizing a limited sobriety pathway?

Dr. Kwo:
Oh, yes. Thank you for bringing this up. So this limited sobriety pathway is something that is relatively new. Historically, when we had referred individuals with cirrhosis due to alcohol use for evaluation for transplant, they had to be sober for six months, and it was an attempt, if you will, for stewardship over our organs, and so people donate organs. We want people to make the best use of organs. For families who sign their loved ones or for people who wish to be organ donors, out of respect for the donors, we want them to have good sobriety skills. But as it turns out, particularly in the last 10, 15 years, we've had more and more young people present with acute alcoholic hepatitis, and many of these individuals who are younger were not considered appropriate transplant candidates, and we were seeing just a large number of deaths.

And so limited sobriety is a way for us to say, "Okay, you haven't been sober for six months. Do we have a pathway available for you so that we can bring you in and we can evaluate you for transplant, see if you can get sufficient skills to overcome your addiction?" And again, alcohol use disorder is an addiction. It can be medically treated, but we need to make sure in those who have limited sobriety pathways that you have sufficient support.

Most limited sobriety pathways also look for individuals who are generally presenting with an initial decompensation. These individuals didn't know that their drinking was, if you will, harmful to their liver. And so for instance, if you're somebody who has had a 30- or 40-year history of alcohol use disorder, you now present with alcoholic hepatitis but you failed multiple programs, most transplant centers aren't going to consider this person for a limited sobriety pathway. Rather, you would consider that person for transplant after six months of sobriety. But many of our younger people, particularly post pandemic in their 20s with severe alcoholic hepatitis with or without cirrhosis, and these individuals with good support can move forward and be transplanted, and we have to have a support plan afterwards to maintain sobriety. And in general, the preliminary reports actually look pretty good. The survivals actually are quite good.

Dr. Buch:
This has been a wonderful review of alcohol-associated liver disease, and I want to thank my guest, Dr. Paul Kwo, for sharing his insights. Dr. Kwo, it's always a pleasure to have you on the program.

Dr. Kwo:
And thanks so much for having me.

Dr. Buch:

For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on reachmd.com, where you can Be Part of the Knowledge. Thanks for listening.