ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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How to Identify and Treat MetALD

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G&H Why was new nomenclature created recently to describe metabolic dysfunction-associated steatotic liver disease and increased alcohol intake, or MetALD?

PK A multinational, multisociety consensus process recently created a new nomenclature to get a better handle on the terminology for steatotic liver disease, which is the dominant liver disease that hepatologists are seeing now, ensuring that metabolic dysfunction was a requirement for the diagnosis. Steatotic liver disease includes metabolic dysfunction-associated steatotic liver disease (MASLD), which used to be called nonalcoholic fatty liver disease. Similarly, alcoholic liver disease was renamed alcohol-associated liver disease to better reflect the causes of the liver disease while also mitigating some of the stigmatizing factors that might have been associated with the old terminology. MetALD is a new disease entity that involves both MASLD and increased alcohol intake. Patients with MASLD often consume alcohol and those with alcohol-associated liver disease often have components of metabolic syndrome. MetALD is defined as hepatic steatosis in patients with at least 1 cardiometabolic risk factor and alcohol consumption that exceeds MASLD thresholds but remains below alcohol-associated liver disease thresholds by the amount of alcohol consumed (ranging from 20 to 50 grams of daily intake for females and 30 to 60 grams of daily intake for males). Those with relatively low alcohol consumption levels with an intake of 20 to 30 grams are defined as MASLD-predominant. In contrast, those who have higher alcohol intake of 50 to 60 grams per day fall on the alcohol-associated liver disease spectrum of MetALD. This allows more precision in how these patient groups are defined, which will help clinicians tailor specific interventions for patients with MetALD. As more clinical data emerge about the contribution of alcohol consumption to liver-related outcomes in patients with MetALD, there will be further refinements of this relatively new disorder. Clinicians evaluate patients with MASLD regularly but do not always account for the contribution of alcohol to the morbidity, mortality, and liver-related outcomes of patients who have the disease entity MetALD. Establishing this disorder helps clinicians better crystallize their approach to addressing risk factors and appropriate interventions.

G&H Could you discuss the relationship between alcohol intake and metabolic dysfunction?

PK Alcohol can directly contribute to cardiometabolic risk factors, including hypertension, hypertriglyceridemia, hyperglycemia, and abdominal obesity, and these effects appear to be synergistic with existing metabolic disease. The more alcohol a patient consumes, the more likely they are to develop metabolic syndrome and its potential complications. If a patient has preexisting metabolic liver disease, they are more likely to develop significant liver-related outcomes such as hepatic fibrosis. As mentioned previously, these effects of alcohol consumption directly correlate with the amount of alcohol consumed. For instance, if a patient has MASLD and just 1 metabolic risk factor but very low alcohol consumption (eg, a few drinks per week), the contribution of that low level of alcohol to overall fibrosis is not very significant. However, if a patient has MASLD and is drinking heavily (eg, 30-40 drinks per week), it does not matter if the patient has a few metabolic risk factors or many; their risk of developing increased fibrosis is substantial. That is why an accurate alcohol consumption history is important in those with

MASLD. Individuals may present with alcohol consumption that has not yet disrupted their life; for example, no one at home is saying there is a problem, there are no work performance issues, and patients themselves may have concluded that their alcohol intake is just part of their normal lifestyle. There is interest in intervening in this group because alcohol consumption combined with metabolic syndrome is associated with significantly higher rates of liver-related outcomes. In fact, someone can have a relatively low body mass index, but if they are a heavy drinker, they have as high a risk as if they had 5 metabolic syndrome risk factors but did not drink as much. Thus, alcohol combined with metabolic syndrome leads to liver-related outcomes that clinicians are trying to mitigate and reduce the risk of subsequent advanced liver disease.

G&H How can hepatic steatosis be detected for diagnosing MetALD?

PK Multiple screening tests are available, and steatosis is often detected incidentally. The most common test to detect steatosis is a liver ultrasound. It is not particularly sensitive for mild steatosis but has good sensitivity and specificity in detecting moderate to severe hepatic steatosis. Patients have incidental computed tomography or magnetic resonance imaging, and significant steatosis is commented on, leading to a referral for evaluation of steatosis where a diagnosis of MetALD can subsequently be made. When patients are seen in the hepatology clinic, steatosis is typically quantified using a point-of-care test such as vibration-controlled transient elastography, which provides both a measure of hepatic steatosis (measured in decibels per meter) as well as an estimate of liver stiffness correlating with hepatic fibrosis in kilopascals. When steatosis and/or fibrosis is detected, and both are often detected together, it is then incumbent on the clinician to determine the level of alcohol consumption in addition to metabolic risk factors.

G&H What questionnaires can be used for quantifying alcohol consumption?

PK One of the most useful questionnaires for alcohol consumption is the Alcohol Use Disorders Identification Test (AUDIT), which consists of 10 questions. Because that questionnaire is not practical to deploy in busy clinics, there is an abbreviated version called the AUDIT-C, which is commonly used. The AUDIT-C asks just 3 questions (on a scale of 0 to 4): How often did you have a drink containing alcohol in the past year? How many drinks containing alcohol did you have on a typical day when you did drink? and How often did you have 6 or more drinks on one occasion? A score of greater than 3 for men and greater than 2 for women indicates a positive screening and needs to be further evaluated. Additionally, the CAGE questionnaire for excessive drinking and alcohol use disorder, which is no longer endorsed by guidelines but is still widely used in practice, asks: Have you ever felt you should cut down on your drinking? Have people annoyed you by criticizing your drinking? Have you ever felt guilty or bad about your drinking? and Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? There are also other questionnaires that can be used.

G&H How accurate are phosphatidylethanol levels?

PK Phosphatidylethanol (PEth) levels have made a remarkable contribution to our ability to diagnose and manage people who have alcohol-associated liver disease. A molecule formed exclusively in the presence of alcohol, PEth is a sensitive blood-borne biomarker that is very specific for alcohol consumption within the past 2 weeks and can reflect alcohol consumption up to 5 weeks. Reasonable cutoffs can be derived from a PEth level indicating not only whether a patient is drinking at all, but also just how much alcohol they are drinking. Very high PEth levels are reflective of increased alcohol consumption and very low levels suggest just occasional alcohol use. PEth also helps clinicians verify the clinical history patients give, as not every patient is forthcoming about their ongoing alcohol use. This is particularly important in those who may be candidates for liver transplant. However, clinicians should decide within their own practice how to incorporate PEth testing. It is probably best to let patients know they are going to be tested for alcohol use with PEth because they typically do not like surprises. When I evaluate patients for abnormal liver tests, I say that I am evaluating them for all causes of elevated liver

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tests, including alcohol. PEth testing produces very few false-positives but is not infallible. If a patient has had several blood transfusions, as an example, they might have detectable PEth levels just from other people who were drinking and donated blood. Overall, PEth is a very useful biomarker that I think should be deployed to try to reduce the morbidity and mortality that alcohol contributes to MetALD as well as to all liver diseases. In fact, alcohol contributes to morbidity and mortality in a large number of adults under the age of 50 years. This screening test warrants further examination to determine whether it can be used constructively to reduce risks and improve outcomes in our younger population.

G&H What lifestyle interventions are recommended for patients with MetALD?

PK Lifestyle interventions should include dietary changes. Mediterranean-based diets are typically recommended. Patients are instructed about foods that are highly deleterious, such as high-fructose corn syrup, and types of carbohydrates they should try to minimize. Red meats should also be minimized, and patients should eat a diverse diet every day with limited processed foods. Drinking coffee is also recommended; I tell every patient that having 2 to 3 cups of black coffee is good for the liver. Additionally, patients should ideally be exercising 5 times a week. Rigorous exercise has been strongly associated with reduced insulin resistance. Any exercise is beneficial, regardless of whether it is aerobic, weightlifting, or resistance training.

In terms of alcohol recommendations, I support the Canadian alcohol guidance, which was derived from a variety of national and international databases. The guidance states that people who have 2 drinks per week or fewer are unlikely to have any adverse health outcomes from alcohol, although 0 drinks per week is best.

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However, when people start going above 2 drinks per week, it is not liver complications necessarily or metabolic complications that increase. For instance, having 3 to 6 drinks per week is associated with higher rates of breast cancer and colon cancer. Therefore, I tell all of my patients that alcohol intake should be 2 drinks per week or fewer with or without MASLD. If a patient has evidence of fibrosis, my alcohol recommendation is 0 drinks per week—all alcohol needs to be stopped. Sometimes, that is met constructively; other times, that can be very challenging for patients to accept. What I then say is that alcohol should be kept for only special events such as a birthday or a wedding toast. Drinking should not be a regular part of food intake every week for people who have MASLD, particularly when they develop fibrosis.

G&H Is there a role for using pharmacotherapies in patients with MetALD?

PK Acamprosate and naltrexone have been approved by the US Food and Drug Administration (FDA) to treat alcohol use disorder, and societal recommendations have been made for baclofen, gabapentin, and topiramate, among others. For MetALD, clinicians usually try mainly lifestyle recommendations. However, if alcohol use turns out to be more problematic, there is no reason patients cannot try naltrexone or acamprosate. I use gabapentin as well, which seems to have some benefit. Some societies have suggested that baclofen is also an important and effective measure to trial.

Also used sometimes is the emerging class for metabolic dysfunction-associated steatohepatitis (MASH) and for obesity, glucagon-like peptide-1 (GLP-1) receptor agonists. Preliminary data suggest that GLP-1 receptor agonists can also reduce alcohol consumption, particularly with the latest-generation GLP-1 receptor agonist semaglutide (Wegovy, Novo Nordisk). Larger trials are now ongoing. Hepatologists have anecdotally used semaglutide for MetALD, and there are emerging data in this area. In a patient with MASH fibrosis who also has MetALD, this is another potential option, in my opinion, and deserves further study. We have seen in our own practice that GLP-1 receptor agonists appear to reduce alcohol consumption and produce other pleiotropic benefits. Another FDA-approved medicine, resmetirom (Rezdiffra, Madrigal), has some preliminary data based on a subanalysis of one of its large registration trials, which included PEth levels. Patients in a cohort with MASH F2 and F3 fibrosis and alcohol consumption appeared to respond to resmetirom just as well as patients in the cohort without alcohol consumption with regard to MASH resolution and fibrosis regression. Other GLP-1 receptor agonists and farnesoid X receptor agonists are being studied in alcohol-associated liver disease, so hopefully the pipeline for MetALD will remain robust.

G&H How should patients with MetALD be monitored long term?

PK That depends on the clinician as well as on the clinical presentation and severity of the disease. My own approach is that if a patient has no fibrosis but is drinking more, I make some initial recommendations and then see the patient in 3 to 6 months to make sure they do not develop significant fibrosis and have curtailed alcohol use. Clinicians should continue to monitor their patients' alcohol consumption and lifestyle changes and refer to addiction medicine or other services if alcohol use remains problematic. Clinicians should also work with their dietary group and pharmacotherapy group if they have one when treating any metabolic comorbidities. The main reason to see patients back sooner is to ensure they are reducing their alcohol consumption, particularly when their levels of consumption are much higher. If patients with MetALD also have fibrotic MASH, I am much more aggressive about intervening early. When starting therapies, I typically lean most commonly toward GLP-1 receptor agonists, but if, for instance, patients do not have an elevated body mass index, these drugs probably are less desirable and also difficult to obtain. When alcohol consumption cannot be reduced, I will initiate treatment with naltrexone, acamprosate, or gabapentin in addition to referring patients to addiction medicine specialists (if I have not already done so).

G&H What further research is needed?

PK Research is needed to find the true prevalence of this disorder. A paper published several years ago from the National Health and Nutrition Examination Survey suggested that the prevalence of MASLD in the United States was 30%, the prevalence of alcohol-associated liver disease was just 1%, and the prevalence of MetALD was just 2%. Based on what we see in the clinic, MetALD may be quite a bit more prevalent than that. I think we need to get a better handle on not only how to identify people with MetALD and intervene, but also how to best screen for this condition in broad populations. Theoretically, drawing a PEth level in everyone would be one way to identify any recent alcohol use. That is not a widespread practice or possible everywhere, but it could be one way to identify problematic levels of alcohol consumption in people who have metabolic liver disease. Finally, it should be understood that when people have metabolic liver disease, other behaviors such as alcohol consumption can rise. There is ample evidence now that people who undergo bariatric surgery, particularly Roux-en-Y gastric bypass, are at increased risk of alcohol use disorder and problematic alcohol use postoperatively. More data are needed to define the cohorts at risk as well as better data on how to make sure that these individuals are appropriately monitored.

Disclosures

Dr Kwo has served on the advisory board for Aligos, Amgen, AusperBio, Gilead, Novo Nordisk, Salix, Takeda, and Target Registries; served as a consultant for Genentech, HEPQuant, Inventiva, LyGenesis, Mirum, Precision BioSciences, and Tune Therapeutics; received a research grant from Altimmune, Gilead, Novo Nordisk, Target Registries, and Ultragenyx; and received grant support from AusperBio, Madrigal, Salix, and Takeda.

Suggested Reading

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