NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

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Alcohol Consumption and Nonalcoholic Steatohepatitis/ Nonalcoholic Fatty Liver Disease

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G&H Are there notable differences between alcohol-related liver disease and nonalcoholic steatohepatitis/nonalcoholic fatty liver disease other than the consumption of alcohol?

ML Histologically, alcohol-related liver disease appears to be very similar to nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH). Research is currently underway to determine if there may be histologic differences between fatty liver driven more from alcohol injury compared with metabolic disease. It is not certain whether outcomes are the same as well. However, as far as we know, patients who develop end-stage liver disease, whether from alcohol or nonalcohol-related fatty liver, have the same risk for liver cancer and decompensation of cirrhosis.

G&H Does modest alcohol consumption affect the risk of developing NASH or NAFLD in the general population?

ML Several studies have shown a benefit to moderate alcohol use in the general population in terms of decreasing the risk of fibrosis progression and decreasing poor outcomes for fatty liver. However, when looking at those studies in detail, they are often found to be missing a careful assessment of different confounding factors. People who drink moderate amounts of alcohol tend to have higher income and higher education, and they tend to exercise more and be leaner. These sociodemographic factors are also associated with better outcomes. Many studies do not measure or include this information or do not adequately account for these factors.

In the Framingham Heart Study, my group and I have looked at moderate alcohol use and how it is associated with liver fat cross-sectionally. After accounting for the aforementioned sociodemographic factors as well as several cardiometabolic factors, we found no beneficial association between alcohol consumption and liver fat. In fact, we observed that moderate alcohol use, even within what would be considered to be NAFLD, was associated with more liver fat and even measures of liver fibrosis.

Thus, the relationship between moderate alcohol consumption and the development of NASH/NAFLD is difficult to study because many issues need to be taken into consideration. One of these issues involves the comparison group. When comparing people who do not drink alcohol with those who do, the former group is heterogeneous; it includes people who never drank alcohol as well as former heavy drinkers or people who had to stop drinking because they were ill because of another reason. People who are former heavy drinkers or who have other health conditions that preclude or disincentivize them from drinking alcohol tend to have poorer outcomes compared with people who never drank alcohol. In comparison, people who drink alcohol moderately are generally healthy and likely have not had problems drinking in the past. When comparing people who currently drink with a heterogeneous group of people who do not consume alcohol, an apparent benefit of alcohol consumption may be observed. However, when light alcohol consumers are the reference group,

the apparent beneficial association of moderate alcohol consumption is often attenuated.

G&H Based on the research that has been conducted thus far, what appear to be the effects of alcohol consumption in patients who already have NASH?

ML Prospective studies evaluating the impact of alcohol use on NASH progression and incidence are lacking. Recently, studies have begun to address some of the design and confounding issues mentioned previously. My group and I have found that alcohol, even within the range that is considered to be moderate drinking, is cross-sectionally associated with increased liver fat. There have not been much data on this issue in terms of NASH, but some data from the Framingham Heart Study suggest that alcohol use is associated with increased liver stiffness, which may be related to NASH. Most well-designed studies have shown an adverse association between alcohol use and increasing liver fat. At this point, we do not have studies that define a safe level of alcohol use in people with NASH.

G&H How can moderate alcohol consumption best be defined?

ML This is a key issue that is unfortunately lacking consensus. Currently, the definition of moderate alcohol consumption varies depending on the guidelines. The US, European, and Asian-Pacific guidelines for NASH/NAFLD utilize different cutoffs for determining whether liver disease is related to alcohol use. Thus, it is confusing for providers and patients to know which cutoff should be used.

According to the NAFLD guidelines in the United States, which are set to be updated this year, consuming fewer than 21 drinks per week for men and fewer than 14 drinks per week for women is considered moderate alcohol use. Patients with fatty liver who consume alcohol under these thresholds are considered to have NAFLD if other causes of liver disease are excluded. However, we have shown in our work in the Framingham Heart Study that alcohol use below this threshold is associated with increased liver fat.

It should be noted that having a drinks-per-week calculation is a simplification of alcohol use because people do not always drink in a balanced way. People may binge drink, which is defined as having more than 4 drinks in approximately 2 hours for women and having 5 or more drinks in that time period for men. Thus, people may have different patterns of alcohol use, some of which are more associated with liver fat than others. This issue is often not captured well in studies or in clinical practice. It appears, at least in some of the work that my group and I have done, that the way people consume alcohol also matters.

G&H Why might consumption of alcohol have negative effects on NASH or liver fat?

ML It is well known that alcohol consumption causes an acute increase in fat in the liver. The effect on NASH likely involves the same mechanism. There may be disruptions to repair mechanisms in the liver as a result of alcohol use. Additionally, alcohol adds to the caloric load, given the calories associated with the drink itself and also the increased food consumption that often occurs while drinking alcohol. Increased calories can also contribute to liver fat.

G&H Should all patients with NASH avoid alcohol consumption?

ML It depends on the individual patient and his or her stage of liver disease as well as his or her relationship to alcohol (ie, how alcohol is used). If a patient has advanced fibrosis (eg, 1 stage before cirrhosis), I am fairly aggressive about advising him or her not to consume alcohol. If a patient with early-stage fibrosis does not want to give up alcohol, I recommend that he or she follows the US dietary guidelines. These state that women should not have more than 1 drink of alcohol in a drinking occasion and no more than 7 drinks within a week, and that men should not have more than 2 drinks of alcohol in a drinking occasion and no more than 14 drinks within a week. These guidelines are stricter than some of the other recommendations. If patients have early-stage fibrosis, alcohol is likely contributing to their liver fat, so if they still want to consume alcohol, I think they should at least follow the US dietary guidelines for healthy people and also have a discussion about the risks with their provider.

G&H Is any special monitoring required in these patients?

ML I do not think there should be special monitoring per se. These patients should just be monitored for progression of their liver disease. In addition, it is important for patients to have a relationship with their provider so they feel comfortable talking about drinking alcohol. Only 1 out of 6 American adults, even those who drink heavily or binge drink regularly, have talked about alcohol with their doctor. Having a doctor address alcohol, not just at the first encounter but also at subsequent encounters, as well as making sure that alcohol use has not changed, is very important, especially in the COVID-19 era. There

has been a drastic increase in alcohol use, particularly among young women, during the COVID-19 pandemic. Doctors often talk about alcohol use during their initial encounter with a patient, but may not address it again. However, alcohol use may change over time. Alcohol needs to be a part of routine conversation because it is a contributor to liver fat, and alcohol use may be a behavior worth modifying. Recommendations should be tailored as the patient's liver disease or alcohol use changes. If patients have alcohol-related liver damage and stop drinking, they can recover and likely even experience reversal of early stages of fibrosis as well.

G&H What are the priorities of research in this area?

ML More information is needed to understand the amount of alcohol associated with progression of disease. It can be difficult to measure progression of disease in NASH. Most studies have been cross-sectional, and specific recommendations for patients are based on very limited data. Therefore, additional longitudinal studies are needed.

G&H Are there any upcoming studies or developments that you would like to mention?

ML There is talk about changing the name of NAFLD to metabolic-associated fatty liver disease or another, more descriptive name. A multistakeholder group will meet this summer for an international consensus discussion led by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. One of the consequences of this potential name change is that alcohol would not specifically be part of the definition anymore. The fatty liver community does not want this change to be interpreted as not caring about alcohol or not thinking that alcohol influences liver fat anymore. Alcohol use is still very important, but we are starting to understand that alcohol is one of likely many risk factors that can contribute to liver fat and that it can be difficult to determine which is the driving factor to liver disease. It is likely more of a continuum than initially thought.

Disclosures

Dr Long has no relevant conflicts of interest to disclose.

Suggested Reading

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