ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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NASH in Special Populations

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G&H What most accounts for the increase in cases of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in the United States?

AS I think the increase is, in large part, related to modernized lifestyles, more calorically dense foods, easily accessible processed or fast foods, less dietary fiber intake, and reduced physical activities. Like in other industrialized countries in the world, the increased prevalence of nonalcoholic fatty liver disease (NAFLD) in the United States is largely attributed to the steep rise in obesity, which is, in turn, the consequence of these changes in people's lifestyles.

G&H Which population groups might be regarded as "special populations" in terms of NAFLD risk?

AS NAFLD occurs in both sexes, regardless of race/ethnicity, and spans a wide range of age groups, from children to octogenarians, but gender difference exists in the frequency of NAFLD. Several large epidemiologic studies reported that the prevalence of NAFLD is higher in men than women. This gender difference disappears after menopause. Notably, postmenopausal women who are on hormone replacement therapy (HRT) are at a decreased risk for NAFLD compared with postmenopausal women who are not on HRT. So, when we look at overall NAFLD, including from simple steatosis to nonalcoholic steatohepatitis (NASH), women of reproductive age have some protection from NAFLD, probably via a protective effect of estrogen. However, it appears to me that sex and menopause modulate the risk of steatosis, NASH, and NASH fibrosis differently. I think this requires further investigation.

In terms of race/ethnicity, Hispanics and Asians are at a higher risk for NAFLD, while African Americans are at the lowest risk among different race/ethnic groups, with non-Hispanic whites in the middle. Recent research shows that the majority of the race/ethnicity difference can be explained by *PNPLA3* gene polymorphisms.

The age effect on NAFLD differs in men vs women. In general, the prevalence of NAFLD increases as age progresses among women, especially after menopause, but not among men. In contrast, for men, the prevalence peaks between age 30 and 50 years, then it declines.

G&H Which population groups at risk for NAFLD or NASH may be the most challenged or need the most attention?

AS Asian and Hispanic groups are more at risk, as metabolic derangements and NAFLD are more likely to develop in them, even in those with a lower body mass index (BMI). Across the race/ethnicity groups, postmenopausal women probably require special attention. Also, older persons who have a long history of obesity and insulin resistance require special attention because these persons likely have more advanced NASH.

G&H What do we know about sex differences and NASH, and how does—or how should—this knowledge translate into screening and management strategies?

AS As I mentioned, the impacts of sex and reproductive status on NAFLD are not so simple. I believe the impacts

differ, depending on the disease stages involved in the NAFLD spectrum. Based on my previous analyses, estrogens appear to be protective against steatosis and NASH fibrosis, but there are some inconsistent findings related to sex difference in NASH features. Estrogen actions are known to be diverse, and circulating estrogens do not necessarily reflect estrogen effects in tissues and cells. I am not yet comfortable at this point to make any recommendation on pharmaceutical intervention in peri- and postmenopausal women. However, it would be safe to say that we need to more closely manage these special subgroups of patients at and after menopause. Certainly, I would be more aggressive about lifestyle modification, diets, and regular exercise, and I would advise patients to minimize weight gain during the drastic physiologic transition.

G&H What do we know about age differences? How can the risks of NAFLD and NASH be intercepted in young at-risk persons?

AS Clinical pictures of NAFLD observed among the older population are not so homogeneous. Older age is an established clinical predictor of advanced fibrosis among patients with NAFLD. On the other hand, steatosis not related to obesity or metabolic syndrome may develop in a certain percentage of persons in their older age. This might be attributed to age-related decline in mitochondrial function, as opposed to increased influx of free fatty acids to the liver caused by insulin resistance. This condition appears to be benign and should be distinguished from the situation seen in older patients who have a long history of obesity and insulin resistance. Based on my experience, NAFLD mostly develops in younger adults, especially men. Metabolic features begin to develop in persons during their late 20s to 40s. Education and lifestyle intervention should be applied in younger adults, and it would be even better if lifestyle interventions could start in childhood and adolescence.

G&H What did you learn about the impact of emotional illness on liver disease in your study on NAFLD in persons with mood disorders?

AS Considerable evidence suggests that emotional illnesses could lead to various metabolic derangements and proinflammatory conditions, such as diabetes mellitus and atherosclerosis. In liver disease, the impact of mood disorders on disease severity and progression has not been fully investigated. When we analyzed a large patient cohort of NAFLD, we found a dose-dependent association between the severity of depression and severity of hepatocyte ballooning. The association was observed in 2 different patient populations, 1 at a liver clinic and the other at a bariatric center, and was not altered after adjusting for treatment status or alcohol consumption. Because hepatocyte ballooning is 1 of the strongest histologic predictors of advanced fibrosis, patients who have depressive symptoms may require special attention. However, further studies are required before we make any clinical recommendations on this issue.

G&H How best can a clinician relate the importance of diet and help facilitate diet modification in a patient at risk?

AS It appears that capacities to store excess energy in a form of fats significantly differ among persons. Patients who can store a larger amount of fats in subcutaneous adipose tissues tend to be at a lower risk for development of metabolic derangements and NAFLD. Some morbidly obese patients could have a relatively healthy liver, which can be explained by this theory. On the other hand, when patients have a limited capacity for development of subcutaneous adipose tissues, excess energy could be distributed among normally lean, ectopic places, such as muscles, visceral organs, and vessels, leading to various metabolic derangements, including NAFLD. An extreme clinical example is lipodystrophy. We theorized that even among a nonlipodystrophic population, interindividual variance in the capacity of subcutaneous fat storage may explain a part of disease severity of NAFLD. Our previous analysis showed that men who preferentially stored fat in peripheral adipose depots (larger circumferences of extremities relative to BMI with smaller abdominal girths) were less likely to have severe hepatic fibrosis than men who stored less fat in peripheral adipose depots. In contrast, premenopausal women who had enlarged extremities relative to their BMI were at an increased risk for having more severe hepatic fibrosis. After menopause, however, the relationship between adipose depot size and hepatic fibrosis became more male-like. We do not know why premenopausal women showed contrasting results compared with other groups, and this requires further investigation.

As to clinical recommendations, I think it would be reasonable to recommend paying more attention to men and postmenopausal women who have leaner extremities relative to their body size and instruct a tighter control of food intake vs physical activities.

G&H What is your view about the role of statins/lipid-lowering drugs in reversing NASH and liver fibrosis?

AS The 2 main drug classes of importance are fibrates and statins. Fibrates are peroxisome proliferator-activated receptor α agonists that facilitate mitochondrial fatty acid oxidation. So, under an increased free fatty acid influx

to the liver, use of fibrates is theoretically beneficial in patients with NAFLD. Recently conducted small studies showed some biochemical benefits of fibrates in NAFLD, although, to my knowledge, histologic improvement has not been proven.

Statins are very interesting agents, and I believe they have various potential health benefits in patients with NAFLD. They are potent cholesterol-lowering agents and can significantly reduce cardiovascular risks in those who are at a high risk. They are also known to be anti-inflammatory, antioxidative, and antithrombotic. Because oxidative stress is one of the main disease-driving mechanisms in NASH, statins may be beneficial from that perspective. Further, statins are known to protect endothelial cells, enhance nitric oxide production, and reduce hepatic sinusoidal pressure. Because sinusoidal endothelial dysfunction appears to precede inflammation and fibrosis in NAFLD, usage of a statin might be beneficial against disease progression.

Overall, I believe statins are beneficial in patients with NAFLD, not only for cardiovascular risk reduction, but also the above-mentioned potential "hepatic" benefits. We now have enough safety evidence to prove that statins are safe even in patients with chronic liver diseases, and, in patients with NAFLD, the risk-benefit ratio of using statins is favorable. Many patients with NAFLD who visit our clinic have been advised to suspend statin use due to their chronic liver enzyme elevation. We usually recommend resuming statins unless patients have decompensated cirrhosis.

G&H What advice do you have for the practicing clinician about NAFLD and NASH identification and intervention?

AS Because the majority of patients with NAFLD have simple steatosis, which is a benign condition, it is very important to focus our care on those who are at a high risk for NASH, especially those with advanced NASH. At our clinic, we look for signs of insulin resistance, obstructive sleep apnea, hypothyroidism, vitamin D deficiency, and central body fat distribution in addition to actual BMI and also evaluate chronicity and the degree of liver enzyme elevation over time. When a patient shows multiple risk factors, we calculate the NAFLD fibrosis score to further stratify patients based on the likelihood of having advanced fibrosis. If patients show a declining trend of platelet counts over years, then disease progression is suspected, and we assess liver morphology and spleen size by ultrasound.

In terms of therapeutic intervention, we do not have a single treatment that would be effective for most patients. NAFLD is in fact a multifactorial disease, and we do need to personalize our approach based on our assessments. Given the limited pharmacologic options, I believe risk-factor elimination, including lifestyle modification, is the fundamental approach needed.

We instruct patients in lifestyle modification and how to correct vitamin D deficiency and insufficiency, and if liver enzyme elevation persists, we consider vitamin E supplementation at a dosage of 800 IU/day, although we need to keep in mind that response to vitamin E is observed in a limited population. Considering overall health benefits to patients, we should emphasize lifestyle modifications and develop multidisciplinary approaches, which also help to reduce cardiovascular risks among patients with NAFLD.

Dr Suzuki has no relevant conflicts of interest to disclose.

Suggested Reading

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