NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

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The Relationship Between Nonalcoholic Fatty Liver Disease and Chronic Kidney Disease

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G&H Has research demonstrated that there is an association between nonalcoholic fatty liver disease, including nonalcoholic steatohepatitis, and chronic kidney disease?

CB Before answering this question, it is important to consider how nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) have been characterized and defined in the large cohort studies that have been used to investigate an association between these conditions. NAFLD represents a spectrum of fat-associated liver conditions whereby other causes of liver fat, such as alcohol intake, have been excluded. A diagnosis of NAFLD can be confirmed by a liver biopsy or an imaging investigation (eg, ultrasound), as these tests can establish the presence of liver fat. Conventionally, from data obtained in the Dallas Heart Study, a diagnosis of NAFLD can be confirmed when 5.5% of the liver is infiltrated by liver fat. However, this specific threshold is now being debated, and a lower threshold may be more appropriate to confirm a diagnosis of NAFLD. Nevertheless, the presence of liver fat is the key diagnostic criterion in NAFLD. As the liver condition progresses in a proportion of affected individuals to liver inflammation, liver fibrosis, cirrhosis, hepatocellular carcinoma, and end-stage liver disease, these conditions markedly increase the risk of liver mortality.

In contrast to establishing the presence of liver fat, a diagnosis of nonalcoholic steatohepatitis (NASH) can only be confirmed by liver biopsy and examination of liver histology. A diagnosis of NASH can occur with or without the presence of liver fibrosis. When liver fibrosis is present, it can be detected by simple imaging tests such as vibration-controlled transient elastography that measures liver stiffness as a proxy measure of liver fibrosis or, when liver fibrosis is advanced, by serum biomarker tests. This is important because the vast majority of large cohort studies that have investigated the association between NAFLD and CKD have not diagnosed NAFLD by liver biopsy. Rather, these studies have mostly used imaging modalities such as ultrasound to diagnose whether a participant has liver steatosis as the marker of NAFLD. It is important to bear in mind that liver ultrasound has relatively low sensitivity to detect low levels of liver fat (<20%) but high specificity, so it is possible for a patient to have NAFLD but have liver fat below the level of detection of liver ultrasound. Not only may NAFLD be underdiagnosed in these cohort studies, but it is usually impossible to

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determine whether patients had NASH. Consequently, in discussing the association between NAFLD and CKD, it is currently not possible to describe with any certainty the association between NASH and CKD.

As for defining and characterizing the outcome of CKD in these cohort studies, kidney biopsies have not been performed. Rather, the estimated glomerular filtration rate (eGFR) has been used to define CKD; specifically, an eGFR below 60 mL/min/1.73 m^2 is considered diagnostic of CKD stage 3 or greater. Additionally, for this diagnosis, overt albuminuria may or may not be present. Thus, it is not possible to know the specific type of CKD or the pathogenesis of kidney disease in studies that have investigated the association between NAFLD and CKD.

With these caveats, it is therefore only possible to discuss the association between NAFLD (as a diverse spectrum of fat-associated liver diseases) and CKD stage 3 or greater. That said, my collaborators and I recently published a large meta-analysis in *Gut* that included 13 cohort studies with over 1.2 million individuals, 28.1% with NAFLD and more than 33,000 with incident CKD stage 3 or above. Even after adjusting for potential confounders such as age, sex, diabetes, hypertension, and obesity, there was a robust association between NAFLD and incident CKD, with an approximately 45% increase in the risk of incident CKD with NAFLD. Specifically, over a median follow-up of 9.7 years, NAFLD was associated with a moderately increased risk of incident CKD (n=10 studies; random effects hazard ratio, 1.43; 95% CI, 1.33-1.54; I^2=60.7%). Sensitivity analyses did not alter these findings, and funnel plots did not reveal any significant publication bias.

G&H What are the main risk factors for the development of CKD in patients with NAFLD?

CB Research addressing this question is still progressing. First, it is important to bear in mind the influence of the liver itself in causing an increase in risk of CKD. Second, it should also be borne in mind that there are common risk factors shared by NAFLD and CKD that are involved in both increasing the severity of liver disease and potentially causing CKD. Those risk factors mainly involve traditional and nontraditional cardiovascular risk factors and nephrotoxins.

The etiology of CKD can be influenced by specific nephrotoxins as well as common cardiovascular disease risk factors. As mentioned previously, CKD is defined by eGFR plus or minus albuminuria, and nephrotoxins may directly influence the kidney glomeruli or renal tubules within the kidney. CKD may develop because the vasculature supplying the kidney is adversely affected. Similar to patients developing cardiovascular disease owing to atherosclerotic vascular disease, CKD (and thereby a low eGFR) may develop because atherosclerotic vascular disease occurs in renal arteries and smaller arteries within the kidney. Therefore, a compromised vascular supply to the kidney has the potential to affect the kidney and cause CKD.

Many of the cardiovascular risk factors shared by NAFLD and CKD are also associated with central obesity and the metabolic syndrome. The type of atherogenic dyslipidemia that occurs with the metabolic syndrome is referred to as the atherogenic lipoprotein phenotype (ALP), which was first described by Austin and colleagues in 1990. With the ALP, there is an increase in very-low-density lipoprotein cholesterol and atherogenic small dense low-density lipoproteins, with a decrease in high-density lipoprotein cholesterol. The metabolic syndrome is very common in NAFLD, and the ALP is likely to be a major contributor to vascular disease in the kidney and, thereby, increase the risk of CKD.

Besides the abnormal lipoprotein profile associated with the metabolic syndrome and NAFLD, there are a range of cytokines and procoagulant factors secreted from the liver that can influence the kidney. These include the coagulation-modifying factors fibrinogen and plasminogen activator inhibitor. Additionally, my collaborators and I, as well as other groups, have shown that NAFLD increases the risk of developing hypertension; therefore, there is also the potential for increased activity of the renin angiotensin system causing hypertension. Thus, these factors can potentially adversely influence the kidney directly, or indirectly by adversely affecting its vasculature.

Patients with NAFLD often do not have normal intestinal function and gut microbiota. Certain gut microbiota have been linked with increased risk of liver fibrosis in NAFLD. It is unclear whether the abnormal gut microbiota profile in NAFLD is caused by liver disease per se or whether an abnormal gut microbiota profile occurs because of dietary changes associated with NAFLD. As with obesity, the gut microbiota are often not as healthy as they should be, and an abnormal gut microbiota profile can develop with an unhealthy, refined carbohydrate-rich diet as the gut microbiota species responds to nutrient intake. Increases in dietary nutrients such as fructose (a monosaccharide occurring in corn syrup or sugar) are associated with more severe liver disease in NAFLD (ie, NASH), and increased dietary fructose can also raise serum uric acid concentrations via adenosine triphosphate depletion and effects on purine metabolism in the liver. Uric acid is a nephrotoxin, potentially further increasing the risk of renal damage with NAFLD. An unhealthy, refined carbohydrate-rich diet not only increases the risk of NASH, but also raises the risk of obesity in people who are physically inactive.

Worsening obesity further increases the risk of type 2 diabetes, hypertension, and CKD. Thus, an unhealthy diet, obesity, type 2 diabetes, hypertension, and NAFLD (and CKD) are all inextricably linked, and the complex interplay of an unhealthy diet, physical inactivity, obesity, type 2 diabetes, and hypertension all have the potential to further increase the risk of CKD in patients with NAFLD.

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Additionally, there are certain genotypes associated with more severe liver disease in NAFLD that have the potential to increase the risk of CKD. One genotype in particular to focus on is *PNPLA3-I148M*. *PNPLA3* is thought to be a lipase acting in the liver to decrease lipid droplets, but it is now known that this lipase is expressed not only in hepatocytes (where it is associated with more severe NAFLD), but also in podocytes in the kidney. Podocytes play an important role in glomerular function and form a filtration barrier with endothelial cells in the glomerulus. There is evidence that patients with *PNPLA3-I148M* may accumulate more renal lipid, which affects the functioning of the podocytes. Thus, it is plausible that a genotype that is well known to be associated with more severe liver disease in NAFLD may also be associated with increased risk of renal disease.

G&H What are the clinical implications of the association between NAFLD and CKD?

CB It is important to first diagnose both conditions. Specifically, it is important to have a high index of clinical suspicion that if a patient has one condition, the other condition may also be present (and yet undiagnosed). If a patient has CKD and abnormal liver function tests, the clinician needs to be aware that the patient may have undiagnosed NAFLD. Similarly, in a patient with known NAFLD, it is important that the eGFR has been assessed and the urine has been checked for increased albumin excretion.

Often, patients with NAFLD, CKD, or both need lifestyle advice focused on eating a healthier diet and increasing physical activity levels. Losing weight and increasing physical activity levels in sedentary individuals help lower blood pressure, which in turn benefits kidney function and decreases the risk of CKD. Losing weight and increasing physical activity also help decrease liver fat and liver inflammation in NAFLD. Finally, losing weight and increasing physical activity have proven benefits in the vasculature and are to be recommended for patients with NAFLD. Because patients with NAFLD and CKD are at markedly increased risk for cardiovascular disease, they may also need specific treatment to decrease their blood pressure or improve their lipid profile (with agents such as statins as proven drugs that attenuate the risk of cardiovascular disease).

For a patient with NAFLD who has obesity or type 2 diabetes, agents such as glucagon-like peptide-1 (GLP-1) receptor agonists that lower glucose also confer cardiovascular benefits and renal protection. Thus, a patient with NAFLD may benefit from treatment with a GLP-1 receptor agonist because of the aforementioned effects. Emerging research is showing that GLP-1 receptor agonists may also be beneficial for treating the early stages of liver disease in NAFLD. These agents may not benefit the liver directly, but indirectly by decreasing appetite and calorie intake, ameliorating body fat, and benefiting diabetes by lowering glucose concentrations. Because GLP-1 receptor agonists also have direct benefits on the kidney and its vasculature via effects on endothelial dysfunction and inflammation, they are potentially useful for treating patients who have increased susceptibility to NAFLD and CKD.

Finally, it is now known that sodium-glucose cotransporter-2 (SGLT2) inhibitors, which have been used for the treatment of hyperglycemia in type 2 diabetes for the past decade, also have beneficial effects on the kidney and the heart. SGLT2 inhibitors slow the progression of kidney disease, reduce the risk of heart failure, and lower the risk of renal failure and death in people with kidney disease and type 2 diabetes. SGLT2 inhibitors also protect the kidney in patients with CKD who do not have diabetes. Thus, this class of drugs may be useful in patients with NAFLD at increased risk for cardiovascular disease and CKD.

G&H Could you expand on the extrahepatic effects of NAFLD?

CB Research by my collaborators and I, as well as other groups, has shown over the past decade that NAFLD is a

multisystem disease. NAFLD not only increases the risk of severe liver disease and CKD (as previously discussed), but also increases the risk of type 2 diabetes, cardiovascular disease, and certain cardiac diseases. In addition, we now know that NAFLD increases the risk of certain extrahepatic cancers such as breast cancer and colon cancer. NAFLD not only increases the risk of cirrhosis, end-stage liver disease, and primary liver cancer, but has important implications beyond the liver that also affect the kidney. Thus, NAFLD, CKD, and other diseases such as cardiovascular disease, type 2 diabetes, and cardiac disease are all linked, and it is now becoming apparent that these individual conditions have the potential to adversely influence each other. For example, NAFLD and type 2 diabetes form a vicious spiral of adverse outcomes affecting both conditions: NAFLD increases the risk of developing type 2 diabetes, and type 2 diabetes increases the risk of developing more severe liver disease (eg, liver fibrosis and hepatocellular carcinoma) in patients who have established NAFLD. Thus, NAFLD represents a key multimorbid liver condition and is a multisystem disease. It is therefore important that clinicians caring for patients with NAFLD are aware of the close links between NAFLD and these other common diseases. With the weight of the research conducted thus far, it is now time to consider a holistic approach to the treatment of NAFLD to improve the overall well-being of this patient group.

In addition, the implications for children with obesity are very important and should not be forgotten. We have known for years that pediatric obesity is a major risk factor for type 2 diabetes. We now know that obesity in children is also a cause of pediatric NAFLD, and NAFLD in children is not a harmless condition. Recent research has shown that children and young adults with NAFLD are also at increased risk of future vascular disease in early adulthood. Although it is not currently known whether these children and young people with NAFLD are also at increased risk for CKD, based on the evidence previously discussed in adults, I would expect them to be.

G&H What are the priorities of research regarding NAFLD and CKD?

CB The main priority is to better understand the pathogenesis of renal disease in NAFLD and also what is mediating the association between NAFLD and CKD. In addition, NAFLD researchers need to think more about what renal endpoints (relevant to CKD) should be measured and potentially added as secondary outcomes when testing liver-specific treatments in phase 3 clinical trials for NAFLD and NASH. At the very least, in defining secondary outcomes, I consider that it would be helpful to measure the eGFR, the 24-hour urine albumin excretion rate, and possibly also the urine albumin/creatinine ratio at baseline and the end of study.

Disclosures

Dr Byrne has no relevant conflicts of interest to disclose.

Suggested Reading

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