Mechanisms Linking Obesity, Chronic Kidney Disease, and Fatty Liver Disease: The Roles of Fetuin-A, Adiponectin, and AMPK

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The prevalence of obesity in the United States has increased dramatically from approximately 12% in 1991 to over 20% a decade later.1,2 Individuals older than 60 years of age have experienced the most rapid increase in prevalence;3 an ominous trend because this age group experiences the greatest burden of chronic kidney disease (CKD), cardiovascular disease, and malignancy on the basis of their age alone, each of which may be exacerbated by obesity. Understanding the mechanisms linking obesity and CKD is important not only because of the societal health burden of both conditions but also because novel insights to underlying mechanisms may lead to new strategies to treat or prevent CKD and its associated comorbidities.

Obesity almost certainly indirectly contributes to CKD because obesity associates with many dominant CKD risk factors such as diabetes, hypertension, and atherosclerosis. However, obesity may also directly lead to CKD. Pathologic studies demonstrate that subjects with severe obesity develop proteinuria with pathologic findings of podocyte hypertrophy, mesangial expansion, glomerular enlargement, and focal segmental glomerular sclerosis in the absence of diabetes and hypertension.4,5 Epidemiologic studies also support a direct effect. Hsu and colleagues evaluated over 300,000 Kaiser Permanente healthcare members, among whom nearly 1500 developed ESRD over approximately 26 years.6,7 There was a graded increase in risk of ESRD for those who were overweight or obese despite adjustment for demographics, smoking, and cardiovascular disease. Even when accounting for blood pressure and diabetes at baseline, the association was only partially attenuated, and individuals with obesity remained at approximately 3-fold greater risk of ESRD. Those with extreme obesity are at even higher risk.6

The liver also frequently develops obesity-related complications. Nonalcoholic fatty liver disease (NAFLD) represents the most common hepatic disorder in western countries8 and is strongly linked with insulin resistance and obesity.9–11 Given these are common risk factors for CKD and NAFLD, it is not surprising that the two conditions are associated with one another.12,13 Intriguingly, mechanisms leading to both diseases may be interlinked through crosstalk between fat, the kidney, and liver through at least two serum proteins—fetuin-A and adiponectin. In response, both tissues exhibit similar local effects mediated through the energy sensor 5’-AMP activated protein kinase (AMPK). Here we review the current understanding of these pathways, highlighting areas that are common to obesity-related CKD and obesity-related NAFLD and that could serve as potential targets for intervention.

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FETUIN-A INDUCES INSULIN RESISTANCE AND REGULATES ADIPONECTIN

In the renal field, fetuin-A has principally been studied as an inhibitor of ectopic calcium deposition,14–16 yet fetuin-A is also an important promoter of insulin resistance. Different from adipocytes, which are derived from fat cells, fetuin-A is a 64-kDa glycoprotein produced exclusively by the liver and secreted into serum where it is found in relatively high concentrations in humans.18 Fetuin-A binds and inhibits the insulin receptor tyrosine kinase in skeletal muscle and hepatocytes, inhibiting insulin signal transduction and resulting in insulin resistance in these target tissues.19–21 Consistent with these in vitro observations, the fetuin-A null mouse is insulin sensitive, has increased skeletal muscle glycogen content, and is resistant to weight gain when challenged with a high-fat diet.22,23 Conversely, treatment of wild-type mice with fetuin-A induces insulin resistance.24 In humans, higher fetuin-A levels associate with obesity and insulin resistance in the general population.25–27 and in patients with CKD and obesity-related NAFLD (as described in the following section).

Fetuin-A and adiponectin may work in concert to regulate insulin resistance. Genes for both proteins are located at 2q24 or 2q23 per quartile. Mean estimated GFR = 71 ml/min/1.73 m² (29% with estimated GFR < 60, none with ESRD). The unadjusted Spearman correlation (r = −0.27; P < 0.001). Error bars reflect 95% confidence intervals.

Figure 1. There is an inverse correlation between serum fetuin-A levels and adiponectin in patients with stable cardiovascular disease. The association was adjusted for age, sex, race, body mass index, and estimated GFR among a population of 963 outpatients (n = 242 or 243 per quartile). Mean estimated GFR = 71 ml/min/1.73 m² (29% with estimated GFR < 60, none with ESRD). The unadjusted Spearman correlation (r = −0.27; P < 0.001). Error bars reflect 95% confidence intervals.

ADIPONECTIN MEDIATES CROSSTALK BETWEEN ADIPOSE, KIDNEY, AND LIVER

Adiponectin is a 30-kDa protein secreted from adipose tissue and circulated in multimers ranging from trimers to 12- to 18-mers.40 Adiponectin improves insulin sensitivity and decreases the adverse effects of inflammatory mediators in vascular cells, and the high-molecular-weight multimers may be more potent.40,41 Despite its source from adipose tissue, individuals with obesity consistently have lower serum adiponectin levels.35,36 The mechanisms for this paradox are uncertain but may reflect inhibition of gene expression and secretion.43 Adiponectin null mice have increased susceptibility to insulin resistance with high-fat feeding,44 and treatment with adiponectin reversely improves insulin sensitivity.

The best-characterized receptors for adiponectin are the AdipoR1 and AdipoR2 receptors; the former is ubiquitously expressed, whereas the latter is found primarily in hepatocytes.45 Both contain seven transmembrane domains but are structurally and functionally distinct from G-protein-coupled receptors. Unlike G-protein-coupled receptors, the amino (N)-termini of both receptors are intracellular and the C-terminal end is extracellular and binds adiponectin.46 Although the intracellular signaling cascade is not known,47 the func-
tion of these receptors was recently elucidated through genetic manipulations in mice. Overexpression of both receptors in liver of db/db mice improves insulin sensitivity,46 AdipoR1 overexpression decreases hepatic enzymes involved in gluconeogenesis,46 whereas AdipoR2 overexpression increases glucose uptake by stimulating glucokinase and peroxisome proliferator-activated receptor-α (PPARα). Genes downstream of PPARα such as acyl-CoA oxidase 1 and uncoupling protein 2 are also stimulated by AdipoR2 overexpression.46 Studies of specific deletions in AdipoR1 or AdipoR2 demonstrate that AdipoR1 predominantly mediates stimulation of AMPK, whereas AdipoR2 mediates stimulation of PPARα.

The potential link between adiponectin and albuminuria was initially raised in a clinical study of men with essential hypertension in which serum adiponectin and albuminuria levels were inversely correlated.48 Because adiponectin levels are secreted from adipocytes and related inversely to the amount of adiposity, these data identify adiponectin as a candidate mediator of adipose and kidney crosstalk. Others observed similar inverse correlations in cross-sectional studies49,50; however, the association between adiponectin levels and kidney disease is complex. There is a direct correlation between adiponectin levels and overt proteinuria,51–53 and studies report conflicting data between adiponectin levels and mortality in patients with CKD or coronary artery disease.36,54–56 Nonetheless, the inverse correlation between adiponectin and low-grade albuminuria prompted us to investigate whether a relative adiponectin deficiency has a causative role in abnormal glomerular function.49

The C57BL/6 adiponectin null mouse exhibits albuminuria, and pathologic evaluation demonstrates foot process effacement of podocytes under baseline conditions.49 Podocytes express the AdipoR1 receptor, and treatment with adiponectin normalizes albuminuria and restores foot process architecture. We hypothesize the renal pathology in these animals may result from oxidative stress because they also have higher urine hydrogen peroxide levels than control mice. When the null mice are treated with exogenous adiponectin, albuminuria decreases to levels similar to wild-type controls. This effect is mediated through adiponectin stimulation of the AMPK pathway, a key regulator of intracellular energy status with potent anti-proliferative effects. AMPK suppression of an isoform of NADPH oxidase (Nox4) may account for the improvement in podocyte cytostructure in adiponectin-treated animals. Additional support for the renal protective effects of adiponectin are provided by a recent study using the 5/6 nephrectomy model,57 in which adiponectin also inhibited albuminuria and fibrosis. Collectively, these data suggest adiponectin protects against albuminuria through an AdipoR1 receptor pathway by stimulating AMPK and inhibiting reactive oxygen species. Whether additional renal effects are mediated through AdipoR2 is currently unknown.

NAFLD strongly associates with insulin resistance and obesity9–11 and represents a spectrum of liver pathology ranging from hepatic steatosis to inflammation and fibrosis characteristic of nonalcoholic steatohepatitis and cirrhosis. Although hepatic steatosis may be benign, factors triggering fibrosis and steatohepatitis may also be the consequence of reactive oxygen species by driving peroxidation of hepatic lipids and inducing mitochondrial damage.58–60 Similar to its effect on podocytes, recent studies suggest that adiponectin inhibits this critical transition.

Individuals with NAFLD have lower serum adiponectin levels than healthy subjects,10,61,62 and among individuals with NAFLD adiponectin levels are inversely correlated with the severity of hepatic fibrosis and inflammation.61,63,64 Adachi and colleagues65 evaluated the influence of adiponectin on hepatic stellate cells, a key cell-type promoting liver fibrosis. Adiponectin treatment suppressed the proliferation of hepatic stellate cells in a dose-dependent fashion in vitro. As with podocytes, this effect is mediated through activation of AMPK. Inhibiting AMPK restores proliferation and results in downregulation of the antioxidant enzymes superoxide dismutase 2 and catalase. In independent studies, NAFLD also associates with an increase in NADPH oxidase activity,66 although the specific subtype, Nox2, is not critical to mediating onset of disease.59 To our knowledge, Nox4 has not been evaluated in NAFLD; however, it is stimulated by transforming growth factor-β in hepatocytes,67 thus Nox4 may contribute to the transition from steatohepatitis to fibrosis and inflammation. Therefore, current evidence suggests the fat-derived hormone adiponectin inhibits the transition from hepatic steatosis to fibrosis through an AMPK-dependent pathway, accompanied by suppression of reactive oxygen species, similar to the effect of adiponectin on podocytes.

INHIBITION OF AMPK TRIGGERS THE ONSET OF OBESITY-RELATED END-ORGAN DISEASE

From a teleological perspective, why excess fat would lead to albuminuria and NAFLD is unclear. One explanation may be provided through AMPK. This protein is a serine/threonine kinase that plays a critical role in sensing energy availability at the cellular level. Upon exposure to low glucose or decreased energy stores, AMPK inhibits mRNA translation and protein synthesis of pathways that are nonessential in the short term. In turn, during times when food is plentiful, AMPK activity is inhibited, mRNA translation is up-regulated, and the cells and organism can grow in size. Because most animals do not have continuous access to calories, this function may be critical to evolutionary success. However, what would be the response in the modern situation wherein there is a constant and abundant access to calories? This scenario might result in chronic deactivation of AMPK and promote cellular protein synthesis. The pathways involved in mRNA translation and protein synthesis leading to kidney disease have recently been elegantly reviewed.68,69 Insights into the role of AMPK on kidney function are in their infancy. However, recent studies suggest AMPK
suppression leads to cellular hypertrophy, accumulation of matrix molecules, and mesangial expansion that are hallmarks of obesity-related CKD. Activated AMPK is predominant in podocytes under basal conditions in wild-type mice. With adiponectin depletion, AMPK is inactivated in podocytes and associated with foot process effacement. Using conditionally differentiated podocytes, inhibition of AMPK dramatically alters podocyte morphology. Activation of AMPK with its analogue aminomidazole carboxamide ribonucleotide restores podocyte morphology in vitro and normalizes albuminuria in vivo in the adiponectin null mouse.

In contrast to its emerging role in kidney disease, the role of AMPK in NAFLD is better studied. AMPK activation plays a major role in mediating the effects of adiponectin in blocking accumulation of liver fat. Rats fed high sucrose develop NAFLD in association with reduced AMPK. Activation of AMPK in the liver leads to fatty acid oxidation, inhibition of glucose production, and inhibition of lipogenesis and protein synthesis. Mice with genetically engineered chronic liver disease and AMPK activation are resistant to weight gain and accumulation of liver fat when fed high-fat diets.

Intriguingly, therapeutic maneuvers with potential beneficial effects on obesity, the kidney, and liver are related to decreasing fetuin-A levels, increasing adiponectin, and AMPK stimulation. Caloric restriction, exercise, and insulin-sensitizing medications such as pioglitazone are each associated with declines in levels of serum fetuin-A, increases in adiponectin levels, and stimulation of AMPK. Angiotensin II infusion lowers adiponectin levels, and angiotensin converting enzyme inhibitors and angiotensin receptor blockers raise adiponectin levels, perhaps by affecting visceral adipose tissue. The sirtuin activator resveratrol also improves organ function of the heart, kidney, and liver despite high-fat feeding, which may in part be due to stimulation of AMPK. Future studies should evaluate whether direct administration of adiponectin or novel agents such as the sirtuin activators have therapeutic potential in patients with obesity and evidence of kidney and liver disease.

In conclusion, excessive caloric intake contributes to adiposity and initiates a cascade that ultimately leads to end-organ dysfunction including obesity-related CKD and NAFLD. Recent studies demonstrate that fetuin-A and adiponectin are key proteins orchestrating organ crosstalk between liver and fat cells and between fat cells and the kidney and liver, respectively. Adiponectin influences changes in end-organ targets, at least in part through AMPK in early stages of disease. These discoveries demonstrate that obesity-related CKD and NAFLD share several similar biologic mechanisms (Figure 2); however, the understanding of these overlapping pathways are presently incomplete. Additional studies elucidating regulatory mechanisms of fetuin-A, adiponectin, and AMPK are required. It is likely that leptin, resistin, free fatty acids, glucose, endothelial dysfunction, and other factors also play important roles in the development of both diseases. Although it may prove challenging to understand this complex biology, analyses from multiorgan integrative studies will provide the insights needed to counter the increasingly prevalent and devastating effects of obesity.

**DISCLOSURES**

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