The prevalence of obesity in the United States has increased dramatically from approximately 12% in 1991 to over 20% a decade later. Individuals older than 60 years of age have experienced the most rapid increase in prevalence; 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. 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. 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.

The liver also frequently develops obesity-related complications. Nonalcoholic fatty liver disease (NAFLD) represents the most common hepatic disorder in western countries and is strongly linked with insulin resistance and obesity. Given these are common risk factors for CKD and NAFLD, it is not surprising that the two conditions are associated with one another. 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.
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 adipokines, which are derived from fat cells, fetuin-A is a 64-kDa glycoprotein produced exclusively by the liver and secreted into serum17 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 population25–27 and in patients with CKD and ESRD28,29 and associates with future risk of diabetes.30,31 Higher fetuin-A levels also associate with NAFLD, and short-term diet and exercise interventions result in declines in serum fetuin-A levels commensurate with improvement in NAFLD and decline in body weight.27,32 However, as fetuin-A is a liver-secreted protein and also induces insulin resistance, it is uncertain whether fetuin-A directly contributes to development of NAFLD, whether elevated serum levels reflect the presence or severity of NAFLD, or whether other unidentified factors simultaneously influence both.

Fetuin-A and adiponectin may work in concert to regulate insulin resistance. Genes for both proteins are located at 3q27 in the human genome; a diabetes and metabolic syndrome susceptibility locus.33,34 Serum levels of both proteins are consistently associated with key components of the metabolic syndrome, but in opposite directions. For example, higher fetuin-A levels associate with greater body mass index and hypertriglyceridemia,23 whereas lower adiponectin levels associate with the same outcomes.35,36 Treatment with pioglitazone results in a decline in fetuin-A levels37 and an increase in adiponectin levels.38,39 In a cohort of 963 individuals, we found that serum fetuin-A and adiponectin levels were inversely correlated with one another (Figure 1), thus confirming similar findings in a smaller sample by others.24 However, although these correlations are intriguing, evidence for overlapping biology remained uncertain until recently when Hennige and colleagues24 demonstrated that fetuin-A suppresses mRNA encoding adiponectin in cultured human adipocytes, and treatment of wild-type mice with fetuin-A lowered serum adiponectin levels. The effect of fetuin-A on adiponectin is specific because fetuin-A treatment did not affect levels of mRNA encoding leptin and resistin or serum levels. Collectively, these studies suggest the liver-secreted protein fetuin-A inhibits generation of adiponectin in adipose tissue. Higher fetuin-A and lower adiponectin may contribute to obesity-induced insulin resistance and development of diabetes. In turn, adiponectin is a key regulator of end-organ damage in obesity-related CKD and NAFLD (as described in the following section).

ADIPONECTIN MEDIATES CROSSTALK BETWEEN ADIPOSE, KIDNEY, AND LIVER

Adiponectin is a 30-kDa protein secreted from adipose tissue and circulates 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.35,36,42 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 conversely 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-

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**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 Spearmen correlation (r = −0.27; P < 0.001). Error bars reflect 95% confidence intervals.
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. AdipoR1 overexpression decreases hepatic enzymes involved in gluconeogenesis, 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. 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. 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 studies, however, the association between adiponectin levels and kidney disease is complex. There is a direct correlation between adiponectin levels and overt proteinuria, and studies report conflicting data between adiponectin levels and mortality in patients with CKD or coronary artery disease. Nonetheless, the inverse correlation between adiponectin and low-grade albuminuria is significant.

NAFLD strongly associates with insulin resistance and obesity 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. 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, and among individuals with NAFLD adiponectin levels are inversely correlated with the severity of hepatic fibrosis and inflammation. Adachi and colleagues 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, although the specific subtype, Nox2, is not critical to mediating onset of disease. To our knowledge, Nox4 has not been evaluated in NAFLD; however, it is stimulated by transforming growth factor-β in hepatocytes, 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.

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.49 Using conditionally differentiated podocytes, inhibition of AMPK dramatically alters podocyte morphology.49 Activation of AMPK with its analogue aminooimidazole 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.70,71 Rats fed high sucrose develop NAFLD in association with reduced AMPK.72 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.73

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,74,75 exercise,75 and insulin-sensitizing medications such as pioglitazone76,77 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,78,79 perhaps by affecting visceral adipose tissue. The sirtuin activator resveratrol also improves organ function of the heart, kidney, and liver80–82 despite high-fat feeding, which may in part be due to stimulation of AMPK.82 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 is presently incomplete. Additional studies elucidating regulatory mechanisms of fetuin-A, adiponectin, and AMPK are required. It is likely that leptin,83–86 resistin,87 free fatty acids,88,89 glucose,90 endothelial dysfunction,91,92 and other factors90 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

The authors thank Dr. Mary Whooley and the Heart and Soul Study for providing the clinical adiponectin data for this manuscript. These studies were conducted with grants from the American Diabetes Association (1-08-IG-01), American Heart Association (0575021N), and the National Institutes of Health (R01 HL096851) to Dr. Ix and grants from the National Institutes of Health (R01 DK 053867 and U01 DK 060995) to Dr. Sharma.

REFERENCES

1. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS: Preva-
lence of obesity, diabetes, and obesity-re-
2. Mokdad AH, Serdula MK, Dietz WH, Bow-
3. Flegal KM, Carroll MD, Ogden CL, John-
6. Hsu CY, McCulloch CE, Iribarren C, Darbin-
7. Hsu CY, Iribarren C, McCulloch CE, Darbin-
tale S, Cassader M, Rizzetto M, Pasquali R, Marchesini G: Plasma adiponectin in nonal-
coholic fatty liver is related to hepatic insulin resistance and hepatic fat content, not to liver disease severity. J Clin Endocrinol Metab 90: 3498–3504, 2005
11. Machado M, Cortez-Pinto H: Non-alcoholic fatty liver disease and insulin resistance. Eur J Gastroenterol Hepatol 17: 823–826, 2005
17. Swallow C, Partridge E, Macmillan J, Ta-
18. Ix JH, Chertow GM, Shlipak MG, Branden-
20. Rauth G, Poschke O, Fink E, Eulitz M, Tipp-
ner S, Kellerer M, Haring HU, Na-
wratil P, Kellerer M, Haring HU, Na-
wratil P, Kellerer M, Haring HU, Na-
wratil P, Kellerer M, Haring HU, Na-
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wratil P, Kellerer M, Haring HU, Na-
wratil P, Kellerer M, Haring HU, Na-


64. Carmiel-Haggai M, Cederbaum AI, Nieto N: A high-fat diet leads to the progression of non-alcoholic fatty liver disease in obese rats. Faseb J 19: 136–138, 2005


rner R, Andreelli F, Foretz M: AMP-activated protein kinase in the regula-
72. Song Z, Deaciuc I, Zhou Z, Song M, Chen T, Hill D, McClain CJ: Involvement of AMP-
activated protein kinase in beneficial effects of betaine on high-sucrose diet-induced he-
73. Yang J, Maika S, Craddock L, King JA, Liu Niemann B, Silber RE, Rohrbach S: Age-
specific effects of short- and long-term caloric restriction on the expression of adip-
75. Yenicesu M, Yilmaz MI, Casaretto A, Han DC, Isono M, Chen S, Casaretto A, Hong SW, Wolf G, Ziyadeh FN: Leptin stimulates type I collagen production in db/db mesangial cells: Glucose uptake and TGF-
76. Davis BJ, Xie Z, Viollet B, Zou MH: Phosphorylation of LKB1 at serine 428 by protein kinase C-zeta is required for metformin-enhanced activation of the AMP-ac-
82. Han DC, Isono M, Chen S, Casaretto A, Hong SW, Wolf G, Ziyadeh FN: Leptin stimu-
lates type I collagen production in db/db mesangial cells: Glucose uptake and TGF-
84. Han DC, Isono M, Chen S, Casaretto A, Hong SW, Wolf G, Ziyadeh FN: Leptin stimu-
lates type I collagen production in db/db mesangial cells: Glucose uptake and TGF-
rlation of macrophages infiltrates hypertro-
89. Susztak K, Ciccone E, McCue P, Sharma K, Bottinger EP: Multiple metabolic hits con-
verge on CD36 as novel mediator of tubular epithelial apoptosis in diabetic nephropa-
90. Kataoka H, Sharma K: Renal handling of adi-
92. Lee IT, Lee WJ, Huang CN, H-H Sheu W: The association of low-grade inflammation, urinary albumin, and insulin resistance with metabolic syndrome in nondiabetic Taiwan-
ese. Metabolism 56: 1708–1713, 2007
93. Han DC, Isono M, Chen S, Casaretto A, Hong SW, Wolf G, Ziyadeh FN: Leptin stimu-
lates type I collagen production in db/db mesangial cells: Glucose uptake and TGF-
94. Wolf G, Ziyadeh FN: Leptin and renal fibro-
96. Angulo P, Alba LM, Petrovic LM, Adams LA, Lindor KD, Jensen MD: Leptin, insulin resis-
tance, and liver fibrosis in human nonalco-
holic fatty liver disease. J Hepatol 41: 943–949, 2004
rlation of macrophages infiltrates hypertro-
99. Susztak K, Ciccone E, McCue P, Sharma K, Bottinger EP: Multiple metabolic hits con-
verge on CD36 as novel mediator of tubular epithelial apoptosis in diabetic nephropa-
100. Kataoka H, Sharma K: Renal handling of adi-
102. Lee IT, Lee WJ, Huang CN, H-H Sheu W: The association of low-grade inflammation, urinary albumin, and insulin resistance with metabolic syndrome in nondiabetic Taiwan-
ese. Metabolism 56: 1708–1713, 2007