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Adiponectin effects on the kidney

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Abstract

Adiponectin is a 30-kDa polypeptide secreted primarily by adipose tissue and plays a key role in kidney disease. In obesity, reduced adiponectin levels are associated with insulin resistance, cardiovascular disease and obesity related kidney disease. The latter includes microalbuminuria, glomerulomegaly, overt proteinuria and focal segmental glomerulosclerosis. Adiponectin levels in type 2 diabetics also negatively correlate with early features of nephropathy. However, in patients with established chronic kidney disease, adiponectin levels are elevated and positively predict progression of disease. The mechanism of action of adiponectin in the kidney appears to be related to AMPK activation and NADPH oxidase. Further studies are needed to elucidate this pathway and investigate the role of potential targets of adiponectin-AMPK-Nox pathway for CKD as obesity-related CKD is increasing worldwide.

Keywords

obesity; kidney disease; adiponectin; adipokines; proteinuria; albuminuria; AMP-activated protein kinase; oxidant stress

Obesity trends and impact

In 2009–2010, the prevalence of adults in the United States that were obese (Body Mass Index, BMI ≥ 30 kg/m²) was estimated to be 35.5% in men and 35.8% in women [1] and is expected to increase in the United States as well as globally. Numerous diseases are associated with obesity including cardiovascular disease, diabetes mellitus, hypertension and chronic kidney disease (CKD) [2]. With the lack of improvement in obesity trends and increase in diabetes and hypertension associated with obesity, the rate of CKD is expected to rise. Kramer et al. evaluated 5897 patients in the Hypertension Detection and Follow-Up Program over five years. At baseline the patients did not have evidence of CKD (defined as presence of 1+ or greater proteinuria on routine urinalysis and/or an estimated glomerular

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Conflicts of interest

None.

filtration rate of less than 60 ml/min/1.73 m²). After five years, the incidence of CKD was 28% in the normal BMI group, 31% in the overweight BMI group (BMI 25–29.9), and 34% in the obese group (BMI ≥ 30). These trends held true even when accounting for patients with diabetes mellitus [3]. Another study by Othman et al. found that in obese subjects with CKD the frequency of progression was higher in overweight (62.5%) and obese patients (79.5%) compared to normal weight CKD patients (44.7%) [4]. Indeed the greatest predictor of future development of ESRD in a community health population was >3+ proteinuria (HR of 7.9) followed by obesity (HR of 4.4) [5].

Obesity related kidney disease

Obesity related glomerulopathy can encompass a variety of pathologic findings including microalbuminuria, glomerulomegaly, mesangial expansion, overt proteinuria and focal segmental glomerulosclerosis. Obesity also increases risk of renal cell carcinoma, nephrolithiasis and graft loss in kidney transplant recipients [6]. Valenci et al. evaluated 207 non-diabetic obese patients (average BMI 34.7 ± 5.7 SD) compared to controls and found that the urine albumin excretion rate (UAER) was significantly higher in obese patients and, in particular, obese patients with hypertension [7]. A study cohort of patients in the Prevention of Renal and Vascular End stage Disease Intervention Trial (PREVEND IT) showed that patients with central fat distribution were at risk for diminished glomerular filtration rate and microalbuminuria even if considered to have a normal BMI [8]. Verani et al. reviewed autopsies of obese patients and found that FSGS, when present, lacked the hyperplasia of glomerular epithelial cells typically seen with idiopathic FSGS. These patients also had larger glomeruli when compared to patients without FSGS, consistent with known development of glomerulomegaly [9].

Adipokines

The link between obesity and development of chronic kidney disease (CKD) and other diseases appears to be in part related to adipokines. A major breakthrough occurred when adipose tissue was recognized to be an active endocrine organ. The cellular structure of white adipose tissue consists primarily of adipocytes and to a lesser degree pre-adipocytes, endothelial cells, fibroblasts, macrophages and leukocytes [10]. Adipocytes have been found to have an intact renin-angiotensin system and ability to secrete TNF- α , IL-6, PAI-1 and TGF- β [11]. The hormones primarily released by adipocytes are termed adipokines and include adiponectin, leptin and resistin.

Adiponectin is a 30 kDa, 244 amino acid protein hormone produced by adipocytes via the *apM1* gene. It is similar in structure to collagen VIII and X and complement factor C1q. The hormone exists as multimers in the circulation from low molecular weight, medium molecular weight and high molecular weight proteins [10]. Two types of adiponectin receptors (adipoR1 and adipoR2) were discovered in skeletal muscle, liver and endothelial cells. Their function includes anti-atherogenesis, anti-inflammation, and insulin sensitization [12]. In other studies, AdipoR1 was found to mediate increased 5' adenosine monophosphate-activated protein kinase (AMPK) and AdipoR2 can activate peroxisome

proliferator-activated receptor alpha (PPAR α) [13]. It is believed that high molecular weight adiponectin improves insulin sensitivity more than lower molecular weight multimers [14].

Adiponectin and albuminuria (early kidney disease)

In 2005, Tsioufis et al. evaluated the level of adiponectin in non-diabetic hypertensive men in relation to microalbuminuria. They found that microalbuminuria was associated with lower adiponectin levels [15]. Yano et al. examined the association between adiponectin and low-grade albuminuria in obese and lean non-diabetic patients. They found that urine albumin excretion was significantly higher in obese patients with low adiponectin levels compared to obese patients with high adiponectin levels. This held true even after adjusting for age, sex, systolic blood pressure, and fasting glucose level [16]. Ohashi et al. performed subtotal (5/6) nephrectomy on adiponectin knockout and wild type mice. They noted that urine albumin excretion, glomerular hypertrophy and tubulointerstitial fibrosis was significantly worse in the adiponectin knockout mice compared to wild type [17].

Our group demonstrated a causative relationship of adiponectin with albuminuria [18]. The adiponectin KO mice exhibited baseline increased albuminuria, as also noted by Ohashi. The adiponectin KO mice also developed podocyte foot process effacement at baseline implying that the podocyte is a key cell type involved in the initial development of albuminuria. However, glomerular basement membrane thickness, endothelial cells and mesangial cells were all similar in appearance to those of the wild type mice. These adiponectin knockout mice were then given adiponectin which was able to normalize albuminuria and restore podocyte foot process effacement. Additional studies also demonstrated expression of the AdipoR1 in podocytes and regulation of AMPK by adiponectin in podocytes.

Rutkowski and colleagues attempted to show a causative role of adiponectin in renal disease using a novel mouse model of podocyte apoptosis [19]. Using a particular injectable agent they developed a unique PODocin promoter driven cassette for Apoptosis Through Targeted Activation of Caspase 8 ("POD-ATTAC") mouse model. These mice exhibited significant kidney damage showing in changes in GFR and albuminuria based on the amount of injected agent they received. The damage included foot process effacement, mesangial expansion and glomerulosclerosis; all features that mimic aspects of human renal disease. With low doses they noted minimal nephrotic changes but with higher doses histologic changes similar to that seen with FSGS was noted.

In order to study the effect of adiponectin on the kidney, the researchers crossed these POD-ATTAC mice with mice either lacking or overexpressing adiponectin. They found that POD-ATTAC mice that overexpressed adiponectin recovered more rapidly and exhibited less interstitial fibrosis after being given the injected agent. However, POD-ATTAC mice that lacked adiponectin developed irreversible albuminuria and renal failure. This remarkable study suggests that adiponectin is renoprotective after podocyte injury and will likely give more information on kidney disease in the future using similar mouse models.

Levels of adiponectin and established kidney disease

In obese patients, plasma adiponectin concentrations have been found to be lower when compared to lean patients. It is unclear as to why this is. A recent study in mice, found that adiponectin levels are reduced within one week of a high fat diet but are then higher than levels found with standard diet after twelve weeks on the high fat diet [20]. Therefore it appears that mice have an initial decline but then they recover their adiponectin production within weeks of the high fat diet. However, persistent hypoadiponectinemia is observed in obese patients who have evidence of insulin resistance and often go on to develop diabetes. Plasma concentration has also been found to be lower in males than in females, in patients with cardiovascular disease, patients with essential hypertension with and without microalbuminuria and in renovascular hypertension [12,21–23].

Given the consistent finding of hypoadiponectinemia for multiple risk factors for chronic kidney disease, one would expect to see this finding also in patients with CKD. However, with established CKD this is not generally the case and the findings are more complicated. Iwashima et al. performed a prospective study on 150 patients for 32 months. The patients were divided into stages of CKD based on an estimated creatinine clearance. They found a statistically significant association between higher plasma adiponectin level and worse degree of CKD [24]. In end stage renal disease (ESRD) patients on hemodialysis, Ignacy et al. found plasma adiponectin concentrations to be over three times higher when compared to healthy subjects (29.0 ± 2.1 vs. 8.7 ± 2.6 g/ml; $p < 0.001$) [25]. One study noted that the expression of the adiponectin gene in adipocytes is decreased with advanced CKD [26]. The reduced gene expression may be related to negative feedback in the setting of elevated total serum adiponectin.

To determine if adiponectin signaling may be defective in patients with severe kidney disease, Shen et al. evaluated the expression of adiponectin receptor mRNA on peripheral blood mononuclear cells (PBMC) in ESRD patients on hemodialysis and compared the results with matched controls. They found that AdipoR1 and AdipoR2 on PBMC were increased in patients with ESRD ($P < 0.05$ and $P < 0.007$, respectively) and there was a strong correlation between these receptor levels and subcutaneous and visceral fat [27]. These findings imply that the increased adiponectin system in CKD is not simply due to decreased renal excretion, but may be a response to other factors within the system. This finding is consistent with a study by Tsigalou et al. They found a U-shaped association of BMI with all-cause mortality in 60 hemodialysis patients followed for 4.5 years. They also noted an inverse U-shaped association for plasma adiponectin levels and all-cause mortality in these patients. They conclude that obesity or malnutrition is the driving factor for hyperadiponectinemia and that the increase in adiponectin levels is linked with mortality in ESRD patients. [28]

Idorn et al. evaluated fifty-seven non-diabetic kidney transplant recipients at baseline and three and twelve months after transplant. They found that adiponectin levels declined significantly after transplant ($P < 0.0001$), while estimated glomerular filtration rate increased ($P < 0.0005$). They also noted that eGFR, BMI and insulin sensitivity index were all associated with adiponectin levels [29]. The role of adiponectin with early onset of

kidney disease (i.e. albuminuria) appears to be fairly straight-forward, however, much more investigation is required to define the role of adiponectin in established and advanced CKD.

Adiponectin and diabetes

Kacso et al. studied patients with type 2 diabetics to determine if adiponectin levels were linked to proteinuria. This group found that low adiponectin levels predicted increased urine albumin to creatinine ratios over the one year follow-up [30]. However, the opposite appears to be true for type 1 diabetics. Saraheimo et al. evaluated adiponectin levels in type 1 diabetics from the Finnish Diabetic Nephropathy Study [31]. They divided the patients into three groups based on their degree of albuminuria: normoalbuminuria, microalbuminuria and macroalbuminuria. They found that patients with macroalbuminuria on average had a higher level of adiponectin when compared to patients with normoalbuminuria and microalbuminuria. They also found a positive correlation between serum adiponectin levels with urine albumin excretion, estimated glomerular filtration rate and waist-to-hip ratio in all groups. They also found that high adiponectin levels predicted the progression of macroalbuminuria to ESRD.

Kacso et al. also evaluated the role of adiponectin in predicting progression of renal disease in type 2 diabetics [32]. The study included eighty-six non-nephrotic patients followed for a mean of 20.5 months. Baseline eGFR was 73 ml/min/1.73 m² and urine albumin to creatinine ratio was 20.5 mg/g. At baseline they noted that adiponectin significantly correlated with urine albumin to creatinine ratio positively ($r = 0.40$, $P = 0.0001$) and BMI inversely ($r = -0.26$, $P = 0.02$). They found that adiponectin levels inversely correlated to changes in urine albumin to creatinine ratios. However there was no significant finding in prediction of change in GFR. Saraheimo and colleagues also looked at the role of adiponectin and progression of diabetic nephropathy in type 1 diabetes [33]. Again using the Finnish Diabetic Nephropathy cohort, they divided the patients into three groups based on their degree of albuminuria. Over the five year study, they found that in patients with normoalbuminuria and microalbuminuria, there was no difference in adiponectin concentrations between those who progressed and those who did not. They did note however in the macroalbuminuria group an increased adiponectin level was associated with progression to ESRD.

These findings suggest that in type 2 diabetes, low adiponectin levels are predictive of diabetic nephropathy and progression of disease. However the opposite appears to be true in type 1 diabetics in that high adiponectin levels were more predictive of severity of disease and progression. Prior et al. thought to explain this finding by focusing on the anti-inflammatory properties of adiponectin in a special group of type 1 diabetics termed the Golden Years cohort [34]. These individuals have had type 1 diabetes for fifty years or more and have been spared from the typical findings of overt nephropathy or vascular disease seen in the majority of patients with type 1 diabetes. The aim of the study was to examine adiponectin in relation to their urine albumin excretion and plasma total antioxidant status in this low risk group. The subjects were divided into groups based on gender as women have higher adiponectin levels compared to men. Each group was further divided based on their degree of albuminuria. They found that adiponectin level increased based on progressive

degrees of normoalbuminuria, microalbuminuria and macroalbuminuria. There was no statistical difference seen in women. They also noted that adiponectin level and plasma total antioxidant status showed a linear increase from normoalbuminuria, microalbuminuria to macroalbuminuria in men ($r = 0.33$, $P = 0.001$; $r = 0.48$, $P < 0.001$; $r = 0.59$, $P = 0.04$) and in women ($r = 0.25$, $P = 0.01$; $r = 0.63$, $P < 0.001$; $r = 0.79$, $P = 0.08$). They concluded from these findings that an increase in adiponectin was likely a compensatory mechanism to reduce oxidative burden in the setting of an ongoing insult.

Genetics

Menzaghi et al. aimed to study the relationship of adiponectin, its isoforms and albuminuria in the absence of potentially confounding diseases [35]. They studied a family based sample of 634 nondiabetic Italian individuals with normal kidney function (Cystatin C-GFR 60 ml/min) and on no conflicting medications. They also investigated their genetic background and addressed the specific role of the gene encoding adiponectin on that background via genotyping several adiponectin gene (ADIPOQ) single nucleotide polymorphisms (SNPs) in order to investigate if the two variables share a common background. They found that albumin:creatinine ratio was directly associated with high molecular weight adiponectin isoform ($p = 0.024$). They also found that these two variables shared some genetic correlation. ADIPOQ promoter SNP rs17300539 was associated with high molecular weight adiponectin ($p = 4.8 \times 10^{-5}$) and ACR ($p = 0.0027$). When SNP rs17300539 was added to the model, the genetic correlation was no longer significant.

Kacso et al. evaluated the relationship of the ADIPOQ gene SNP 276G > T with albuminuria in white type 2 diabetics [36]. In previous studies the correlation between plasma adiponectin and type 2 diabetic kidney disease with this polymorphism has not been clear, possibly due to ethnic differences. Including one hundred and three type 2 diabetic patients, forty-three (41.7%) had the GG genotype, 50 (48.5%) at GT and 10 (9.7%) at TT genotype. They found that plasma adiponectin was significantly higher in the TT-allele carriers than the GT and the GG carriers ($P = 0.003$). The prevalence of the T allele was higher in the normoalbuminuric patients than in albuminuric ones ($P = 0.02$). They also found that using logistic regression, predictors of albuminuria included the GG genotype ($P = 0.003$), low GFR ($P = 0.003$), and high plasma adiponectin ($P = 0.012$). Therefore it does appear that in Caucasian type 2 diabetics with albuminuria this 276G > T polymorphism of the adiponectin gene is associated with plasma adiponectin levels.

The role of oxidant stress

Susztak et al. evaluated the role of oxidative stress in podocyte apoptosis using db/db mice. [37] They found that increasing extracellular glucose rapidly stimulated generation of reactive oxygen species (ROS) through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and mitochondrial pathways. This increase in extracellular glucose and generation of ROS was followed by apoptosis of podocytes. They also found that chronic inhibition of NADPH oxidase prevented podocyte apoptosis and corrected urine albumin excretion and mesangial matrix expansion in diabetic model (db/db) mice. Our lab sought to determine whether exogenous adiponectin regulates oxidant stress in adiponectin knockout

mice. [18] It was noted that in the kidneys of the adiponectin knockout mice, Nox4 levels, as shown by real-time PCR, were significantly increased. With the administration of adiponectin, Nox4 levels were reduced back to control levels.

There may be some degree of feedback between NADPH oxidase and adiponectin as well. Furukawa et al. studied obese KKAY mice and found that increased oxidative stress resulted in a decrease in plasma adiponectin level. They found that treatment with a NADPH oxidase inhibitor, apocynin, lead to an increase in adiponectin gene expression and plasma adiponectin levels [38]. This finding may help explain why type 1 diabetics or patients with chronic kidney disease have higher adiponectin levels rather than suppression.

AMPK pathway

AMPK is highly expressed in the kidney with involvement in podocyte function and diabetic renal hypertrophy [39]. Our lab looked at the role of adiponectin and AMPK [33]. In cultured podocytes, adiponectin administration resulted in increased activity of AMPK. Podocyte permeability to albumin and podocyte dysfunction was also reduced by adiponectin and AMPK alike. As mentioned previously, adiponectin appeared to reduce protein levels of NADPH oxidase Nox4 in podocytes. Interestingly, AMPK activation resulted in similar findings. The kidneys of high fat diet fed mice, a model for diabetes, resulted in a marked increase in fibrosis with suppression of AMPK activity [20]. Administration of an AMPK activator (AICAR) reduced renal hypertrophy, urine hydrogen peroxide and urine and renal monocyte chemotactic protein-1 (MCP-1). Cammisotto et al. demonstrated the presence of a functional AdipoR1 receptor in all the cells of the renal glomeruli by incubating them in vitro with adiponectin. Using immunogold labeling, electron microscopy revealed AdipoR1 and catalytic AMPK sub-units $\alpha 1$ and $\alpha 2$ in normal rat glomeruli. Incubation in adiponectin or AICAR led to the activation of phosphorylation of catalytic AMPK [40].

At times of high glucose or excess energy stores, AMPK activity is inhibited and mRNA translation of non-essential pathways are up-regulated and the cells are able to grow in size. Chronically suppressed AMPK leads to features consistent with obesity related CKD including cellular hypertrophy, accumulation of matrix molecules and mesangial expansion [41].

Clinical treatments

Nakamura and colleagues evaluated the effects of renal angiotensin system blockade using ACEi (perindopril) or ARB (telmisartan) medications on adiponectin levels in patients with essential hypertension. They noted that telmisartan appears to be more effective than perindopril in raising adiponectin levels [42]. The explanation behind this lies in the fact that ARB medications can function as ligands for peroxisome proliferator-activated receptor (PPAR) γ and stimulation of this receptor has been demonstrated to raise adiponectin levels. Notably however, in these non-diabetic patients, urine albumin and glycosylated hemoglobin A1c did not change significantly at the end of the 48 week study.

Watanabe and colleagues compared three months of treatment with the angiotensin receptor blocker, losartan, and the calcium channel blocker, amlodipine. [43] These hypertensive patients were treated with the medication for three months and again ARB treatment was also associated with increased adiponectin levels.

Balducci et al. evaluated the anti-inflammatory effects of exercise in patients with type 2 diabetes and metabolic syndrome [44]. Eighty-two patients were randomized into four groups: sedentary control; receiving counseling to perform low-intensity physical activity; performing prescribed and supervised high-intensity aerobic or aerobic plus resistance exercise (with the same caloric expenditure) for twelve months. At baseline and every three months, inflammatory biomarkers including adiponectin levels were measured. Notably, they found that in the supervised high-intensity aerobic group and the aerobic plus resistance group, adiponectin levels increased significantly and albuminuria decreased. BMI, fat and fat-free mass did not change significantly during the study period in all groups, however waist circumference improved significantly in the aerobic and aerobic plus resistance exercise group.

Navaneethan and colleagues looked at severely obese type 2 diabetic patients undergoing different types of bariatric surgery and evaluated the changes in albuminuria and adiponectin with resulting weight loss [45]. In this small study evaluating fifteen consecutive type 2 diabetic patients with severe obesity ($\text{BMI } 49 \pm 9 \text{ kg/m}^2$), nine patients underwent Roux-en-Y gastric bypass (RYGB) and the remainder underwent other types of bariatric surgeries. They found that despite both groups developing a lower BMI following surgery, only in the RYGB group was there a statistically different increase in high molecular weight adiponectin and a decrease in urine albumin to creatinine ratio.

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References

1. Flegal KM, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA: The Journal of the American Medical Association*. 2012; 307(5):491–497.
2. Patterson RE, Frank LL, Kristal AR, et al. A comprehensive examination of health conditions associated with obesity in older adults. *American Journal of Preventive Medicine*. 2004; 27(5):385–390. [PubMed: 15556738]
3. Kramer H, Luke A, Bidani A, et al. Obesity and prevalent and incident CKD: the hypertension detection and follow-up program. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation*. 2005; 46(4):587–594. [PubMed: 16183412]
4. Othman M, Kavar B, El Nahas AM. Influence of obesity on progression of non-diabetic chronic kidney disease: a retrospective cohort study. *Nephron Clinical Practice*. 2009; 113(1):c16–c23. [PubMed: 19590231]
5. Hsu CY, Iribarren C, McCulloch CE, et al. Risk factors for end-stage renal disease: 25-year follow-up. *Archives of Internal Medicine*. 2009; 169(4):342–350. [PubMed: 19237717]
6. Eknoyan G. Obesity and chronic kidney disease. *Nefrologia: Publicacion Oficial de la Sociedad Espanola Nefrologia*. 2011; 31(4):397–403. [PubMed: 21623393]

7. Valensi P, Assayag M, Busby M, et al. Microalbuminuria in obese patients with or without hypertension. *International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity*. 1996; 20(6):574–579.
8. Pinto-Sietsma SJ, Navis G, Janssen WM, et al. A central body fat distribution is related to renal function impairment, even in lean subjects. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation*. 2003; 41(4):733–741. [PubMed: 12666059]
9. Verani RR. Obesity-associated focal segmental glomerulosclerosis: pathological features of the lesion and relationship with cardiomegaly and hyperlipidemia. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation*. 1992; 20(6):629–634. [PubMed: 1462993]
10. Adamczak M, Wiecek A. The adipose tissue as an endocrine organ. *Seminars in Nephrology*. 2013; 33(1):2–13. [PubMed: 23374889]
11. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *The Journal of Clinical Endocrinology and Metabolism*. 2004; 89(6):2548–2556. [PubMed: 15181022]
12. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocrine Reviews*. 2005; 26(3):439–451. [PubMed: 15897298]
13. Yamauchi T, Kadowaki T. Physiological and pathophysiological roles of adiponectin and adiponectin receptors in the integrated regulation of metabolic and cardiovascular diseases. *International Journal of Obesity*. 2008; 32(Suppl. 7):S13–S18. [PubMed: 19136982]
14. Fisher FM, Trujillo ME, Hanif W, et al. Serum high molecular weight complex of adiponectin correlates better with glucose tolerance than total serum adiponectin in Indo-Asian males. *Diabetologia*. 2005; 48(6):1084–1087. [PubMed: 15902402]
15. Tsioufis C, Dimitriadis K, Chatzis D, et al. Relation of microalbuminuria to adiponectin and augmented C-reactive protein levels in men with essential hypertension. *The American Journal of Cardiology*. 2005; 96(7):946–951. [PubMed: 16188522]
16. Yano Y, Hoshida S, Ishikawa J, et al. Differential impacts of adiponectin on low-grade albuminuria between obese and nonobese persons without diabetes. *Journal of Clinical Hypertension*. 2007; 9(10):775–782. [PubMed: 17917505]
17. Ohashi K, Iwatani H, Kihara S, et al. Exacerbation of albuminuria and renal fibrosis in subtotal renal ablation model of adiponectin-knockout mice. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2007; 27(9):1910–1917.
18. Sharma K, Ramachandrarao S, Qiu G, et al. Adiponectin regulates albuminuria and podocyte function in mice. *The Journal of Clinical Investigation*. 2008; 118(5):1645–1656. [PubMed: 18431508]
19. Rutkowski JM, Wang ZV, Park AS, et al. Adiponectin promotes functional recovery after podocyte ablation. *Journal of the American Society of Nephrology: JASN*. 2013; 24(2):268–282. [PubMed: 23334396]
20. Decleves AE, Mathew AV, Cunard R, et al. AMPK mediates the initiation of kidney disease induced by a high-fat diet. *Journal of the American Society of Nephrology: JASN*. 2011; 22(10):1846–1855. [PubMed: 21921143]
21. Shibata R, Ouchi N, Murohara T. Adiponectin and cardiovascular disease. *Circulation Journal: Official Journal of the Japanese Circulation Society*. 2009; 73(4):608–614. [PubMed: 19261992]
22. Mallamaci F, Zoccali C, Cuzzola F, et al. Adiponectin in essential hypertension. *Journal of Nephrology*. 2002; 15(5):507–511. [PubMed: 12455716]
23. Adamczak M, Czerwińska B, Chudek J, et al. Renal extraction of circulating adiponectin in patients with renovascular hypertension. *Acta Physiologica Hungarica*. 2007; 94(1–2):143–148. [PubMed: 17444282]
24. Iwashima Y, Horio T, Kumada M, et al. Adiponectin and renal function, and implication as a risk of cardiovascular disease. *The American Journal of Cardiology*. 2006; 98(12):1603–1608. [PubMed: 17145218]
25. Ignacy W, Chudek J, Adamczak M, et al. Reciprocal association of plasma adiponectin and serum C-reactive protein concentration in haemodialysis patients with end-stage kidney disease—a follow-up study. *Nephron Clinical Practice*. 2005; 101(1):c18–c24. [PubMed: 15886491]

26. Marchlewska A, Stenvinkel P, Lindholm B, et al. Reduced gene expression of adiponectin in fat tissue from patients with end-stage renal disease. *Kidney International*. 2004; 66(1):46–50. [PubMed: 15200411]
27. Shen YY, Charlesworth JA, Kelly JJ, et al. Up-regulation of adiponectin, its isoforms and receptors in end-stage kidney disease. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association*. 2007; 22(1):171–178.
28. Tsigalou C, Chalikias G, Kantartzi K, et al. Differential effect of baseline adiponectin on all-cause mortality in hemodialysis patients depending on initial body mass index. Long-term follow-up data of 4.5 years. *Journal of Renal Nutrition: The Official Journal of the Council on Renal Nutrition of the National Kidney Foundation*. 2013; 23(1):45–56.
29. Idorn T, Hornum M, Bjerre M, et al. Plasma adiponectin before and after kidney transplantation. *Transplant International: Official Journal of the European Society for Organ Transplantation*. 2012; 25(11):1194–1203. [PubMed: 22994569]
30. Kacso I, Lenghel A, Bondor CI, et al. Low plasma adiponectin levels predict increased urinary albumin/creatinine ratio in type 2 diabetes patients. *International Urology and Nephrology*. 2012; 44(4):1151–1157. [PubMed: 21993769]
31. Saraheimo M, Forsblom C, Fagerudd J, et al. Serum adiponectin is increased in type 1 diabetic patients with nephropathy. *Diabetes Care*. 2005; 28(6):1410–1414. [PubMed: 15920060]
32. Kacso IM, Bondor CI, Kacso G. Plasma adiponectin is related to the progression of kidney disease in type 2 diabetes patients. *Scandinavian Journal of Clinical and Laboratory Investigation*. 2012; 72(4):333–339. [PubMed: 22486808]
33. Saraheimo M, Forsblom C, Thorn L, et al. Serum adiponectin and progression of diabetic nephropathy in patients with type 1 diabetes. *Diabetes Care*. 2008; 31(6):1165–1169. [PubMed: 18346990]
34. Prior SL, Tang TS, Gill GV, et al. Adiponectin, total antioxidant status, and urine albumin excretion in the low-risk “Golden Years” type 1 diabetes mellitus cohort. *Metabolism: Clinical and Experimental*. 2011; 60(2):173–179. [PubMed: 20188385]
35. Menzaghi C, De Cosmo S, Copetti M, et al. Relationship between ADIPOQ gene, circulating high molecular weight adiponectin and albuminuria in individuals with normal kidney function: evidence from a family-based study. *Diabetologia*. 2011; 54(4):812–818. [PubMed: 21229348]
36. Kacso IM, Trifa AP, Popp RA, et al. Association of 276G > T adiponectin gene polymorphism to plasma adiponectin and albuminuria in type 2 diabetic patients. *International Urology and Nephrology*. 2012; 44(6):1771–1777. [PubMed: 22222620]
37. Susztak K, Raff AC, Schiffer M, et al. Glucose-induced reactive oxygen species cause apoptosis of podocytes and podocyte depletion at the onset of diabetic nephropathy. *Diabetes*. 2006; 55(1):225–233. [PubMed: 16380497]
38. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *The Journal of Clinical Investigation*. 2004; 114(12):1752–1761. [PubMed: 15599400]
39. Hallows KR, Mount PF, Pastor-Soler NM, et al. Role of the energy sensor AMP-activated protein kinase in renal physiology and disease. *American Journal of Physiology Renal Physiology*. 2010; 298(5):F1067–F1077. [PubMed: 20181668]
40. Cammisotto PG, Bendayan M. Adiponectin stimulates phosphorylation of AMP-activated protein kinase alpha in renal glomeruli. *Journal of Molecular Histology*. 2008; 39(6):579–584. [PubMed: 18941912]
41. Ix JH, Sharma K. Mechanisms linking obesity, chronic kidney disease, and fatty liver disease: the roles of fetuin-A, adiponectin, and AMPK. *Journal of the American Society of Nephrology: JASN*. 2010; 21(3):406–412. [PubMed: 20150538]
42. Nakamura T, Kawachi K, Saito Y, et al. Effects of ARB or ACE-inhibitor administration on plasma levels of aldosterone and adiponectin in hypertension. *International Heart Journal*. 2009; 50(4):501–512. [PubMed: 19609054]

43. Watanabe S, Okura T, Kurata M, et al. The effect of losartan and amlodipine on serum adiponectin in Japanese adults with essential hypertension. *Clinical Therapeutics*. 2006; 28(10):1677–1685. [PubMed: 17157123]
44. Balducci S, Zanuso S, Nicolucci A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD*. 2010; 20(8):608–617.
45. Navaneethan SD, Kelly KR, Sabbagh F, et al. Urinary albumin excretion, HMW adiponectin, and insulin sensitivity in type 2 diabetic patients undergoing bariatric surgery. *Obesity Surgery*. 2010; 20(3):308–315. [PubMed: 20217955]

Practice points

- Adipose tissue is an active endocrine organ, secreting adipokines including adiponectin, leptin and resistin.
- Adiponectin has multiple functions including insulin sensitization, anti-inflammation and anti-atherogenesis.
- Kidney disease associated with obesity includes microalbuminuria, enlarged kidneys, overt proteinuria and focal segmental glomerulosclerosis.
- Low serum adiponectin levels are associated with obesity, insulin resistance, type 2 diabetes, cardiovascular disease, male gender and hypertension and correlate with degree of albuminuria.
- Chronic kidney disease and type 1 diabetes are associated with elevated adiponectin levels. The former cannot simply be explained by decreased renal excretion.
- Adiponectin confers protective effects on podocytes via the AMPK pathway
- Angiotensin receptor blockers appear to increase serum adiponectin levels in hypertensive patients.
- In type 2 diabetics with metabolic syndrome, exercise was shown to result in an increase in serum adiponectin levels.

Research agenda

- Further studies are needed to understand why adiponectin levels decrease in the setting of obesity and type 2 diabetes but increase in type 1 diabetes and chronic kidney disease.
- Further understanding of the effect of adiponectin on podocytes, focusing on AMPK and NADPH oxidase.
- Clinical studies evaluating the potential beneficial effects of angiotensin receptor blockers or other interventions on serum adiponectin level in diabetic and obese patients should be investigated.

Summary

As obesity persists, it is expected that the rates of diseases associated with this epidemic, including chronic kidney disease, will rise as well. Microalbuminuria, enlarged kidneys, overt proteinuria and focal segmental glomerulosclerosis are all seen with obesity related glomerulopathy.

Adipose tissue is an active endocrine organ, secreting adipocytes including adiponectin, leptin and resistin. Adiponectin has multiple functions including insulin sensitization, anti-inflammation and anti-atherogenesis. Obesity results in low serum adiponectin levels of unclear mechanism. Hypoadiponectinemia in humans is associated with insulin resistance, cardiovascular disease, and albuminuria. In mouse models, adiponectin knockout mice exhibit features consistent with obesity related glomerulopathy. Administration of adiponectin in mouse models has been shown to reverse some of this glomerulopathy.

Adiponectin appears to function via AMPK with resulting effect on NADPH oxidase. Inhibition of NADPH oxidase prevented podocyte injury in diabetic mouse models. Furthermore administration of adiponectin and AMPK both have been shown to improve podocyte dysfunction in mouse models of kidney disease.

Angiotensin receptor blockers and exercise appear to increase adiponectin levels in a select group of patients. Yet further investigation is needed to understand if this translates into clinical significance.