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# Adiponectin effects on the kidney

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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.



## Obesity trends and impact

In 2009–2010, the prevalence of adults in the United States that were obese (Body Mass Index, BMI $\geq$ 30 kg/m$^2$) 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

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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 filtration rate of less than 60 ml/min/1.73 $m^2$). 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 $\geq$ 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 $\pm$ 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-$\alpha$, IL-6, PAI-1 and TGF-$\beta$ [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, AdiopoR1 was found to mediate increased 5′ adenosine monophosphate-activated protein kinase (AMPK) and AdiopR2 can activate peroxisome proliferator-activated receptor alpha (PPAR$\alpha$) [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