# Chapter 20
# Adiposity and Kidney Disease

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**Keywords** Adipose tissue • Obesity • Kidney disease • Insulin resistance • Cardiovascular outcomes

**Key Points**

- The prevalence of chronic kidney disease (CKD) is increasing worldwide and is a global public health challenge.
- Epidemiological data suggest a potential causal relationship with adiposity.
- Clinical and laboratory studies suggest that adiposity is involved in the development and progression of kidney disease.
- Mechanisms of kidney damage in obesity include adaptation to increased body mass, activation of sympathetic nervous and renin–angiotensin systems, insulin resistance, hyperlipidemia, and release of adipokines.
- Kidney disease may also effect the association of adiposity with cardiovascular outcomes.
- In this chapter, the interactions of adiposity and kidney disease and their effects on clinical outcomes are examined.

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## Introduction

Chronic kidney disease (CKD) is increasingly common. The prevalence of CKD in the US population is 15.1 %, affecting nearly 20 million. At the end of 2009, the number of people with stage 5 CKD (glomerular filtration rate (GFR) <15 ml/min) requiring dialysis was 571,414 with a prevalence rate of about 1,700 per million population, representing over an 80 % increase in the past decade [1].

There is evidence that adiposity is involved in the development and progression of kidney disease. Although adiposity is a well known cardiovascular risk factor in the general population, epidemiological studies have raised uncertainties regarding the impact of adiposity on clinical outcomes in CKD and dialysis patients. In this chapter, we address these two issues: the effects of adiposity on kidney disease and the effects of kidney disease on the associations of adiposity on cardiovascular risk factors and cardiovascular disease.

## Effect of Adipose Tissue on Progression of Kidney Disease

### *Epidemiological Data*

In many populations, the rising trend of kidney disease has mirrored that of obesity [2, 3]. Obesity, which is mainly caused by increase in adipose tissue, has a direct relationship to the development and progression of diabetes mellitus, hypertension, and dyslipidemia. Diabetes and hypertension are well known to be the two most common causes of renal impairment. The United States Renal Data System (USRDS) lists diabetes mellitus as the etiology for end stage renal disease (ESRD) in 47 % of the prevalent dialysis population and hypertension accounts for nearly 28 %. Analyses of the Modification of Diet in Renal Disease (MDRD) [4] and Atherosclerosis Risk in Communities (ARIC) studies [5] showed that high triglycerides and low high density lipoprotein (HDL) are related to the development of CKD.

The above data raises the question whether the association of adiposity with CKD is a mere reflection of the other obesity related comorbidities such as diabetes mellitus, hypertension, and dyslipidemia or whether adiposity is an independent risk factor for kidney disease. In an analysis of the ARIC data, the odds ratio (OR) of developing CKD during a 9-years follow-up period in participants with metabolic syndrome was 1.43 and remained at 1.23 after adjusting for subsequent development of diabetes mellitus and hypertension. Compared with participants with no traits of metabolic syndrome, those with one, two, three, four, or five traits of the metabolic syndrome showed a graded increased in the OR for CKD from 1.13 to 2.45. Thus, metabolic syndrome is independently associated with an increased risk for incident CKD in non diabetic adults [6]. Johnson et al. also confirmed the earlier observation that the prevalence of metabolic syndrome increased with decreasing creatinine clearance suggesting that metabolic syndrome is an independent predictor of CKD [7].

Kidney damage is clinically manifest as loss of albumin in urine (albuminuria) or decline in GFR. Analysis of Third National Health and Nutritional Examination Survey (NHANES) data further showed that abdominal obesity was associated with both a decrease in GFR and microalbuminuria (24 h urinary excretion of albumin excretion in the range of 150–300 mg/d) [8]. This association was also seen with each of the other elements of metabolic syndrome (insulin resistance, hypertension, hypertriglyceridemia, and low HDL). Furthermore, there was a graded relationship between the components present and the corresponding prevalence of CKD and microalbuminuria. Microalbuminuria is a well known predictor of adverse cardiovascular outcomes.

Thus, metabolic syndrome is independently associated with the development and progression of CKD and microalbuminuria.

**Table 20.1** Mechanisms of kidney damage

| Cardiovascular | Hypertension |
|---|---|
| Renal | Altered vascular structure and function |
| | Enhanced renin–angiotensin–aldosterone system |
| | Enhanced sympathetic nervous system |
| Metabolic | Hyperinsulinemia/insulin resistance |
| | Dyslipidemia |
| | Hypercortisolemia |
| Inflammatory | Hyperleptinemia |
| Hematological | Hypercoagulability |
| | Altered kallikrein–kinin system |

## *Renal Pathology in Adiposity*

Histologically, renal biopsies of obese patients with renal failure have shown glomerulomegaly and focal and segmental glomerulosclerosis [9, 10]. In patients with morbid obesity and a mean body mass index of 52 kg/m$^2$ glomerulomegaly, podocyte hypertrophy with expansion of mesangial matrix and mesangial proliferation were observed [11]. Metabolic syndrome is also known to be associated with greater tubular atrophy, interstitial fibrosis and vascular damage on renal histology [12].

## *Mechanisms of Kidney Damage in Adiposity*

There are several biological mechanisms through which adiposity could lead to kidney damage (Table 20.1). The pathophysiology of renal dysfunction in obesity is a combination of hemodynamic and metabolic abnormalities that include glomerular hyperfiltration, increased renal venous pressure, glomerular hypertrophy, and increased synthesis of vasoactive and fibrogenic substances (including angiotensin II, insulin, leptin, and transforming growth factor [TGF]-β). The following discussion elaborates on these mechanisms.

### Adaptation to Increased Body Mass

An increase in body mass leads to an increased excretory load of nitrogen and metabolic waste. As the nephron number is fixed, this leads to an increased work load with hyperperfusion and hyperfiltration of each nephron. Obese patients have an increase in renal plasma flow and glomerular filtration rate by 31 and 51 %, respectively, leading to an increase in filtration fraction and glomerular hypertension [13]. It has been shown that obesity related glomerular hyperfiltration ameliorates after weight loss [14].

### Adverse Effects of Obesity-Induced Sodium Retention

Obesity leads to activation of the sympathetic nervous system, in part by hyperleptinemia that stimulates the hypothalamic pro-opiomelanocortin pathway [15]. The renin–angiotensin–aldosterone system (RAAS) is also upregulated in obesity. The increased sympathetic nervous and renin–angiotensin systems lead to volume expansion and increased blood pressure. Further, the excess visceral adipose tissue may lead to physical compression of the kidneys causing increased intra renal pressures and increased tubular reabsorption of sodium [15].

The increased tubular reabsorption of sodium leads to afferent arteriolar vasodilatation and glomerular hyperfiltration [16]. The afferent arteriolar vasodilation and increased systemic arterial pressure cause an increase in hydrostatic pressure and contribute to glomerular capillary wall stress. These changes along with hyperlipidemia and hyperinsulinemia may cause glomerular injury with increased matrix accumulation and eventually glomerulosclerosis and loss of nephron function in obese subjects.

### Direct or Indirect Effects of Hyperinsulinemia/Insulin Resistance

Insulin resistance and hyperinsulinemia are important pathophysiological factors in the development of metabolic syndrome. Hyperinsulinemia contributes to renal vascular injury by stimulating smooth muscle cell proliferation [17]. Hyperinsulinemia also has direct and indirect effects on the progression of glomerular dysfunction. The direct effects include irreversible glycosylation of glomerular protein, inhibition of phosphatidylinositol-3 kinase pathway (PI-3K), and activation of mitogenic activated protein (MAP) kinase pathway leading to increased atherogenesis and endothelial dysfunction [18]. Hyperinsulinemia is also associated with decreased endothelial production of nitric oxide and increased oxidative stress leading to vascular endothelial injury. The indirect effects include activation of the renin–angiotensin–aldosterone system leading to increased angiotensin II and aldosterone levels [19]. In addition to sodium retention, elevated aldosterone promotes fibrosis and target organ dysfunction by stimulating plasminogen activator inhibitor, reactive oxygen species and TGF-β1 [19]. In vitro studies have shown that hyperinsulinemia can also induce glomerular hypertrophy both directly and indirectly via insulin like growth factor (IGF)-1 [20].

### Renal Lipotoxicity

Increased cellular lipid content leads to intracellular shunting of excess fatty acids towards synthesis of products that induce cell damage [21–23]. This impairs function of the individual cells and causes inflammation, apoptosis and cell necrosis. Lipotoxicity is associated with progression of metabolic syndrome and can involve multiple organs including kidney, liver, skeletal, pancreas and cardiac cells [22, 23]. In the kidneys, dyslipidemia increases the amount of lipoprotein being filtered in the Bowman's capsule, damaging glomerular and tubular cells, promoting fibrosis and enhancing endothelial dysfunction and atherosclerosis [24, 25].

### Adipose Tissue as an Endocrine Organ

Adipose tissue secretes a wide range of protein and non proteinfactors, termed adipokines. A number of adipokines including leptin, adiponectin, adipsin, resistin, visfatin, tumor necrosis factor (TNF)-α, transforming growth factor β (TGF-β), interleukin(IL)-1β, IL-6, monocyte chemoattractant protein-1, macrophage migration inhibitory factor, nerve growth factor, vascular endothelial growth factor, plasminogen activator inhibitor 1, insulin like growth factor-1, retinol binding protein are secreted by adipose tissue. An imbalance of these adipokines is observed in patients with kidney disease leading to chronic inflammation which implicated in the development and progression of hypertension and endothelial dysfunction.

Leptin is a proinflammatory adipokine that is anorexigenic and is primarily cleared by the kidney [26, 27]. Leptin levels are elevated in patients with obesity who are predisposed to glomerulosclerosis. In glomerular endothelial cells, leptin stimulates cellular proliferation, TGF-β1 synthesis, and type IV collagen production [28]. In the mesangial cells, leptin upregulates synthesis of TGF- β2 receptor and

type 1 collagen production [29, 30]. These result in focal glomerulosclerosis and mesangial proliferation. Leptin also activates the sympathetic nervous system and enhances sodium reabsorption leading to hypertension, proteinuria and progression of kidney disease [31]. There is also evidence to suggest that leptin and TGF-β1 promote mesangial sclerosis by different mechanisms and act synergistically to potentiate mesangial matrix production.

Adiponectin is a peptide secreted exclusively by adipocytes that has antiatherogenic, anti-inflammatory, and insulin sensitizing effects. Plasma adiponectin level is negatively associated with fat mass [32]. Three adiponectin receptors AdipoR1, AdipoR2 and T-cadherin have been identified. AdipoR1 is most abundantly expressed in muscle, AdipoR2 in the liver and T cadherin on vascular endothelial and smooth muscle cells [33, 34]. These receptors are linked to activation of AMP-activated kinase (AMPK) pathways. Activation of AMPK by adiponectin results in stimulation of fatty acid oxidation in the skeletal muscles, inhibition of hepatic gluconeogenesis and stimulation of nitric oxide production in the endothelial cells [35, 36]. Adiponectin displays anti-inflammatory properties by inhibiting NF-κβ activation and TNF-β synthesis and by inducing anti inflammatory cytokines such as IL-10, IL-1 receptor antagonist [37, 38]. The insulin sensitizing effect of adiponectin is explained by stimulation of glucose uptake and oxidation of fatty acids in skeletal muscles and liver cells, induction of insulin signaling in skeletal muscle cells and suppression of liver gluconeogenesis.

Metabolic syndrome correlated positively with leptin and inversely with adiponectin levels. Serum adiponectin is inversely associated with increased cardiovascular risk [39, 40]. The adiponectin/receptor system is upregulated in ESRD likely as a counter regulatory response to the uremic milieu. In animal studies, administration of adiponectin was shown to decrease albuminuria and mesangial sclerosis.

Resistin is secreted by both adipocyte and immunocompetent cells [41]. Plasma resistin level increases with progressive renal insufficiency [42] and early studies suggest an association with obesity and insulin resistance [43] though the exact pathophysiological role is unknown.

Visfatin is a proinflammatory adipocytokine [44]. In uremic patients, visfatin level was independently associated with sVCAM-1, a marker of endothelial damage [45]. The relationship between visfatin and insulin resistance is unknown.

## Management

There is substantial evidence that adipose tissue and obesity are related to the progression of renal disease. If managed effectively in the early stages, most of the physiological and structural changes may be reversible.

Weight loss and physical activity are recommended as first line therapy. The reduced calorie DASH (dietary approaches to stop hypertension) diet and a Mediterranean diet have both been demonstrated to reduce risk of metabolic syndrome [46, 47]. Fiber and other phytonutrients in fruits and vegetables have been shown to reduce cholesterol and markers of inflammation. Increased dietary intake of fiber was associated with decreased C reactive protein and mortality in patients with CKD [48]. An inverse association between the intake of dairy and metabolic syndrome has also been reported. As patients with metabolic syndrome are salt sensitive, dietary restriction of sodium may be beneficial by lowering blood pressure [49]. In patients with CKD, nonsurgical weight loss interventions reduce proteinuria and blood pressure and prevent decline in renal function [50]. In morbidly obese individuals with glomerular hyperfiltration, surgical interventions normalize GFR and reduce blood pressure and microalbuminuria [50].

As obesity is associated with increased activation of the renin–angiotensin system, treatment with angiotensin receptor blocking agents should be considered especially in patients with hypertension and proteinuria.

Adiponectin is an anti-inflammatory and antiatherogenic adipokine and interventions to improve adiponectin levels may be considered to improve long term outcomes. Improvement in adiponectin levels and insulin resistance was observed with RAAS blockade with either angiotensin converting enzyme blocker or angiotensin receptor [51]. Peroxisome proliferator activated receptor (PPAR) gamma ligands such as thiazolidinediones have also been shown to increase adiponectin levels and improve insulin resistance [52]. Further prospective studies are required to address the potential therapeutic role of adipokines is progression of renal disease.

Dietary management and physical activity remain cornerstones of therapy and early interventions targeted towards hypertension, adiposity and insulin resistance might minimize renal damage associated with obesity.

## Effects of Kidney Disease on Associations of Adiposity with Cardiovascular Disease

In contrast to the data in the general population, dialysis patients with higher body mass index have lower mortality compared to those dialysis patients with normal body mass index [53]. Strikingly, these data have been consistent in several studies patients [54–63]. Thus, it has been suggested that obesity is protective in dialysis patients [56]. In other words, as the associations of body size with mortality appear to vary depending upon the presence or absence of advanced kidney failure, it can be said that kidney disease is an effect modifier of this association.

However, there are three problems with the suggestion that adiposity is protective in dialysis patients. First, the real paradox of the "BMI paradox" in dialysis patients is the possible association of high BMI with inflammation yet decreased mortality. Adipocytes are rich sources of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which in turn stimulate the production of C-reactive protein (CRP) in the liver [64]. It was shown in a cross-sectional study that abdominal adiposity is strongly associated with elevated CRP levels in dialysis patients [65]. Further, the cross-sectional associations of high BMI, abdominal adiposity and other components of metabolic syndrome [66–68] with inflammation in stage III CKD have been demonstrated. Therefore, the current evidence suggests that in stages III and V of CKD, obesity is associated with inflammation as in the general population.

Second, high BMI might result from high muscle mass, fat mass or both. It is possible that high BMI due to high muscle mass might be more protective than high BMI due to high fat mass. In 70,028 patients initiated on hemodialysis in the USA from 1/96 to 12/98 with reported measured creatinine clearances at initiation of dialysis, BMI in conjunction with 24-h urinary creatinine excretion (an indicator of muscle mass) was used to estimate body composition and the effects of estimated body composition on all-cause and cardiovascular mortality were examined [54]. High body size was associated with better survival. However, compared to normal BMI, normal or high muscle patients, those with high BMI and low muscle mass had increased mortality, whereas those with high BMI and normal or high muscle mass had decreased mortality. These data suggest that high BMI is not uniformly associated with better survival and the body composition is important in high BMI dialysis patients. In another study of incident peritoneal dialysis patients, similar results were shown [68].

Third, previous studies have shown that in dialysis patients, adiposity and high BMI is associated with diabetes [69], inflammation [70], coronary calcification [71, 72] and carotid atherosclerosis [73]. These data raise the question that if adiposity is associated with diabetes, inflammation, coronary calcification and atherosclerosis in dialysis patients, how is adiposity associated with better survival in dialysis patients?

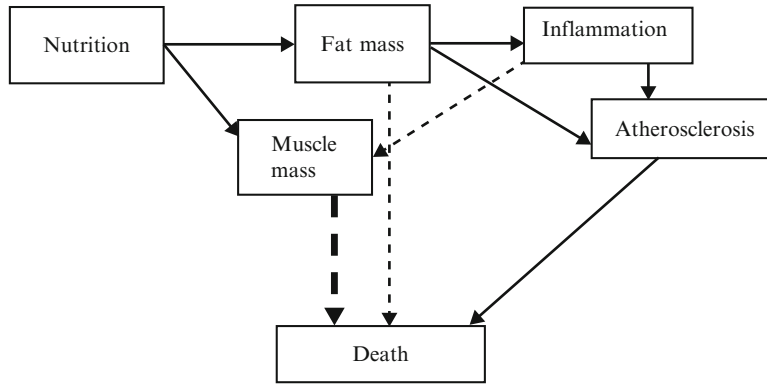


**Fig. 20.1** Directed acyclic graph of the hypothesized associations of nutritional status with inflammation, atherosclerosis, and death. Dotted lines represent a negative effect, whereas the *unbroken lines* represent a positive effect

We propose the following framework (Fig. 20.1) to integrate these seemingly contradicting data. In Fig. 20.1, dotted lines represent a negative effect, whereas the unbroken lines represent a positive effect.

When the association of high BMI with survival is examined in dialysis patients, there might actually be two issues that are examined- what is the effect of nutrition on survival and what is the effect of adiposity on atherosclerotic events and cardiovascular events? We hypothesize that the effects of nutrition on survival are much stronger than the effects of atherosclerotic events on survival in dialysis patients. Further, we also propose that the effects of nutrition on survival might differ based on body composition (muscle versus fat). Better nutrition as evidenced by higher muscle mass decreases the hazard of death from concomitant cardiovascular and non-cardiovascular events resulting in the lowest cardiovascular and non-cardiovascular deaths. On the other hand, fat mass has dual effects; a negative effect on death as a result of nutrition and a positive effect on death mediated through its association with inflammation and atherosclerosis. Thus, compared to undernutrition, adiposity decreases the hazard of death from concomitant disease processes but is associated with inflammation, oxidative stress and atherosclerotic events in dialysis patients as in the general population. In other words, adiposity confers a survival advantage over undernutrition but not compared to higher muscle mass in dialysis patients.

Further, as shown in Fig. 20.1, the above paradigm could also incorporate the current theories on the association of inflammation with malnutrition, in particular, the observed associations of inflammation with decreased muscle mass in dialysis patients [74, 75]. In other words, the association of inflammation with loss of muscle mass does not contradict adipose tissue as a source of inflammation in CKD.

## Conclusion

In summary, obesity is a risk factor for renal dysfunction, as evidenced by albuminuria and loss of GFR. Potential mechanisms include hemodynamic changes, lipotoxicity, and inflammation. The association of adiposity with cardiovascular outcomes in ESRD remains controversial and further studies will shed light on this complex issue.

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