# Chapter 12
# Obesity and Metabolic Syndrome


**T. Alp Ikizler and Melis Sahinoz**

The number of patients with diabetes and chronic kidney disease (CKD) has been increasing globally, in line with the rising prevalence of diabetes, driven largely by obesity. Obesity has become a significant concern in the US and many other resource-rich countries [1, 2]. In 2017–2018, the age-adjusted obesity prevalence among U.S. adults was 42.4% [3]. By 2030, it is estimated that about 50% of all adults in the US will be classified as having obesity [4].

Obesity promotes incident CKD and progression to end stage kidney disease (ESKD), reducing in the quality of life and life expectancy. Excessive adipose tissue also negatively impacts the lipid metabolism, blood pressure and glucose control, leading to cardiovascular disease (CVD). It is important that healthcare providers understand the mechanisms of kidney disease development and progression in the setting of obesity and metabolic syndrome.

## The Role of Visceral Adiposity

Under normal conditions, adipose tissue is localized in two major areas; about 80% in the subcutaneous tissue, and approximately 20% surrounding the internal organs [i.e. visceral adipose tissue (VAT)] [5]. VAT is also more vascular, exhibit increased sympathetic innervation, have more β3-adrenergic receptors and higher metabolic activity [5]. Abnormally high accrual of visceral adipose tissue is known as visceral obesity, which is associated impaired glucose and lipid metabolism, insulin resistance and CVD [6–8].

T. A. Ikizler (✉) · M. Sahinoz
Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: alp.ikizler@vumc.org; melis.sahinoz@vumc.org



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## Renal Alterations in Obesity

Obesity, specifically visceral adiposity, is a major cause of hypertension, accounting for 65% to 75% of the risk for human primary hypertension [9]. An almost linear relationship exists between blood pressure and obesity in all population including whites, blacks, Hispanics and Asians. In addition, weight loss is shown to reduce blood pressure in both normotensive and hypertensive individuals who are obese. Increasing duration of obesity is also shown to exacerbate the obesity-induced blood pressure increase [10].

In addition to high blood pressure, obesity is associated with multiple hemodynamic alterations. Excessive adiposity increases blood and extracellular fluid volumes [10] as well as heart rate, cardiac output and venous return predisposing the heart to left ventricular hypertrophy [11].

In the kidney vasculature, excessive weight gain initially causes renal vasodilation, increased renal blood flow and glomerular filtration rate (GFR). Renal vasodilation in obesity is regulated by multiple factors, including renal compression, hyperglycemia, high protein intake, and increased blood pressure combined with impaired renal autoregulation [9]. Increased perirenal and renal sinus fat in obesity leads to compression of the thin loop of Henle and vasa recta of the medulla. This compression leads to reduced tubular flow rate and increased sodium absorption in the nephron. Subsequently, sodium delivery to macula densa decreases, resulting in feedback-mediated dilation in the afferent arterioles, and increases in the renal blood flow and GFR [10].

In addition to kidney compression, activation of the renin–angiotensin–aldosterone system (RAAS), renal mineralocorticoid receptor (MR) activation, and sympathetic nervous system activation also lead to excessive sodium reabsorption by the kidneys in the setting of obesity. [Fig. 12.1]. The resultant increased renal sodium reabsorption leads to compensatory renal vasodilation which, along with increased blood pressure, causes increased glomerular hydrostatic pressure and glomerular hyperfiltration, which may further exacerbate renal injury [10]. Sustained obesity over time with progressive renal injury aggravates hypertension and increases cardiovascular risk.

In addition, obesity-related glomerulopathy (ORG), a form of secondary focal segmental glomerulosclerosis (FSGS), is recognized as a distinct entity that occurs in the setting of obesity. ORG is characterized by glomerulomegaly, proteinuria, progressive glomerulosclerosis, and decline in kidney function [12].

## Increased Sympathetic Nervous System Activity

Obesity could also lead to elevated blood pressure and renal injury through sympathetic nervous system (SNS) activation. Multiple mechanisms has been shown to activate SNS in obesity: (1) through impairing baroreceptor reflexes; (2) activating

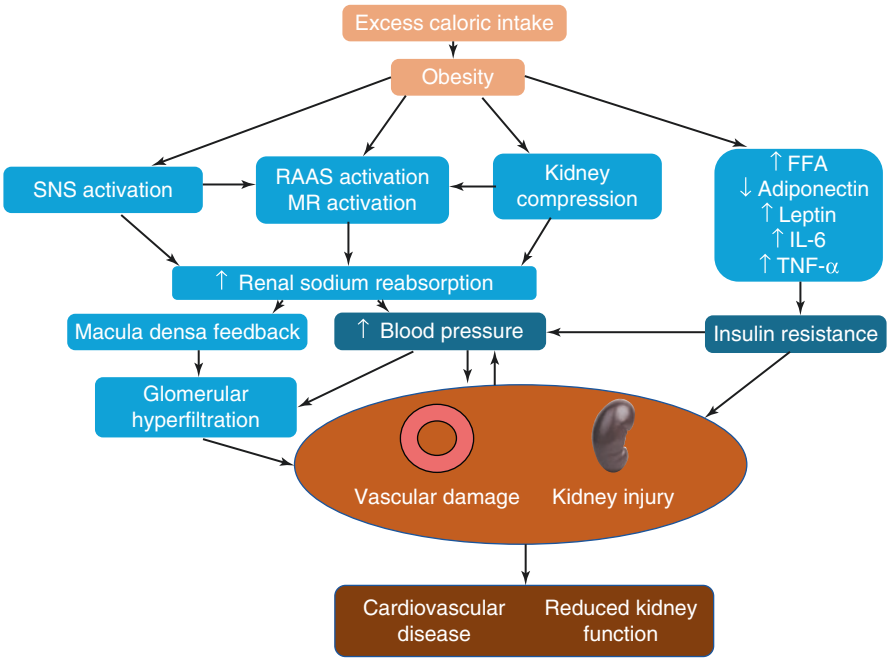


**Fig. 12.1** The interplay between obesity, hypertension, kidney injury and cardiovascular disease. *SNS* sympathetic nervous system, *RAAS* renin–angiotensin–aldosterone system, *MR* mineralocorticoid receptor, *FFA* free fatty acid, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-α

chemoreceptors in carotid bodies (especially in patients with obstructive sleep apnea and hypoxemia); (3) activating the central nervous system proopiomelanocortin (POMC) pathway through the central actions of leptin secreted by growing adipocytes [10].

## The Role of Adipose Tissue and Kidney Disease

Three types of adipocytes are found in humans; white adipose tissue (WAT), which constitutes the largest energy reservoir, brown adipose tissues (BAT), which is responsible for thermogenesis, and beige adipose tissue, that can be induced from WAT by transdifferentiation or de novo in response to hypothermia or β-adrenergic stimuli [13]. Brown adipocytes contain large number of mitochondria and uncoupling protein 1 (UCP1), which uncouples ATP generation and dissipates energy in the form of heat [14].

Adipose tissue secretes various bioactive substances and coordinates numerous metabolic and cardiovascular functions through crosstalk between the adipose and non-adipose tissues [14]. These bioactive molecules secreted by the adipocytes (i.e.

adipokines) regulate the adipose tissue microenvironment through local paracrine effects, as well as the systemic metabolism through endocrine effects.

Adipose tissue exerts its effects on the kidney through the actions of an array of adipokines and metabolites such as leptin, adiponectin, angiotensin II, tumor necrosis factor-α (TNF-α), monocyte chemotactic protein-1 (MCP-1) and transforming growth factor-beta (TGF-β) [15, 16]. The balance between these adipokines mediates the appetite, energy expenditure and glucose metabolism.

Adipocytes and macrophages play pivotal roles in the pathophysiology of the kidney damage in the setting of obesity. Excess caloric intake leads to expansion of WAT by either hypertrophy and/or hyperplasia of adipocytes along with development of insulin resistance and dysregulation of lipid metabolism [14]. Macrophage polarization shifts from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype promoting chronic inflammation. Combined with dysmetabolism of adipokines, these factors result in oxidative stress, inflammation and fibrotic transformation in the kidneys and lead to kidney damage.

Conversely, CKD is inherently associated with insulin resistance and inflammation. Insulin resistance of CKD is multifactorial in nature and is linked to various disturbances in CKD such as physical inactivity, chronic inflammation, oxidative stress, vitamin D deficiency, metabolic acidosis, anemia, adipokine imbalance due to reduced clearance of adipokines and hyperinsulinemia due to reduced insulin clearance [17, 18]. Although the skeletal muscle is the primary site for insulin resistance in CKD [19], adipose tissue also exhibits insensitivity to the actions of insulin, which exacerbates the metabolic derangements caused by obesity and aggravates the renal injury. Furthermore, CKD promotes beiging of adipose tissue, which favors energy loss and might also worsen the kidney injury [Fig. 12.2].

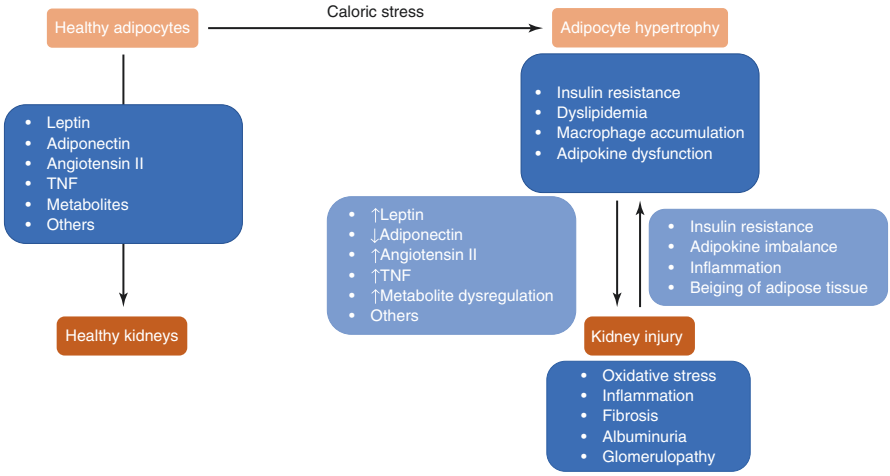


**Fig. 12.2** The crosstalk between the adipose tissue and kidneys. *TNF* tumor necrosis factor

## Metabolic Syndrome

Metabolic syndrome seems to evolve not as a linear sequence of events but as a matrix of interconnected pathways that result in multiple abnormalities in various organs. The pathogenesis of metabolic syndrome in the setting of abdominal obesity is characterized by several crucial alterations in metabolism; (1) elevated circulating free fatty acids (FFA), (2) increased intracellular lipid accumulation and insulin resistance in the adipose tissue, hepatocytes, skeletal myocytes and pancreatic β cells, (3) reduced functional activity of two insulin-sensitizing adipokines; leptin and adiponectin, and (4) enhanced macrophage infiltration in the adipose tissue with release of proinflammatory cytokines [20].

These phenomena originating in the adipose tissue and eventually affecting multiple tissues generate the clinical picture recognized as metabolic syndrome. Although there are multiple definitions for metabolic syndrome, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) is the most widely used criteria [21, 22]. The presence of any three of the following five traits is defined as metabolic syndrome: (1) abdominal obesity, defined as a waist circumference ≥ 102 cm (40 inches) in men and ≥ 88 cm (35 inches) in women; (2) serum triglycerides ≥150 mg/dL (1.7 mmol/L) or pharmacologic treatment for elevated triglycerides; (3) serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women or pharmacologic treatment for low HDL cholesterol; (4) blood pressure ≥ 130/85 mmHg or pharmacologic treatment for high blood pressure; (5) fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or pharmacologic treatment for elevated blood glucose [22].

Epidemiological data suggest that metabolic syndrome is an independent risk factor for incident CKD [23–25]. A stepwise increase in the hazard ratio of CKD was also observed with a greater number of metabolic syndrome components [23]. In a recent study, changes in the metabolic syndrome status altered the 10-year risk of CKD development, suggesting that lifestyle modifications may decrease the prevalence of CKD [24]. While it is not clearly established which component(s) lead to increased risk for incident CKD, it is likely that multiple mechanisms are in play predisposing individuals with MS to subsequent kidney disease. Although not studied in detail, MS could also potentially increase the risk for progression of prevalent CKD. Overall, prevention and treatment of MS is likely to be beneficial in patients with or at risk for kidney disease.

## Quantification of Adipose Tissue in Chronic Kidney Disease

Monitoring body composition and fat content accurately is very important and could be challenging in patients with kidney disease due to inherent abnormalities in their metabolism. Hence, it is important to know the anthropometric measures and body composition assessment tools that are used to measure adiposity in

CKD. BMI is a simple, cheap and widely recognized standard measure to assess adiposity. The standard adult weight status categories defined by the World Health Organization (WHO) (<18.5 kg/m$^2$: underweight, 18.5–24.9 kg/m$^2$: normal weight, 25.0–29.9 kg/m$^2$: overweight, and ≥ 30 kg/m$^2$: obese), are also valid in the CKD population [26]. However, BMI is not an ideal marker of obesity for several reasons as it cannot differentiate between increased adiposity and muscularity. Also, BMI is limited in identifying visceral adiposity, the compartment associated with insulin resistance and atherogenic abnormalities [27]. Waist-to-hip ratio, waist-to-height ratio, waist circumference, and the conicity index are also used to estimate abdominal fat depots. Waist-to-hip ratio is associated with cardiovascular events and mortality and is less influenced by muscle and bone mass than BMI. Waist circumference is also a simple but reliable market of visceral fat and is correlated with cardiovascular disease risk factors. However, the efficacy of the latter two parameters is limited in peritoneal dialysis patients [5]. Maximum abdominal circumference (MAC), triceps (TSF) and subscapular skinfolds (SSF), and arm circumference are alternative methods to assess subcutaneous adipose tissue (SAT), but these measurements require enough experience and are influenced by fluid status, sex and age. Dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis, computed tomography and magnetic resonance imaging are more precise and reliable methods to estimate body composition in dialysis patients. DEXA is a direct method that is considered the gold standard for assessing body composition in patients with CKD; however, it is not readily available and can be influenced by a number of CKD related factors such as hydration status. In patients on maintenance hemodialysis (MHD), multi-frequency bioelectrical impedance (MF-BIA) is recommended as the preferred method to assess body composition [26]. Abdominal magnetic resonance imaging (MRI) and computerized tomography (CT) may also provide accurate assessment of the SAT and VAT however, they are not feasible in clinical practice due to cost and long exploration time.

## Treatment

Treatment of metabolic syndrome is focused on weight management and the treatment of cardiovascular risk factors if they persist after lifestyle modifications [28–30]. Treating obesity with lifestyle modifications or medication slows the progression of kidney disease and reduces albuminuria [31].

### *Lifestyle Modifications*

Diet with or without exercise is shown to be effective in reducing weight, proteinuria and blood pressure [32–36]. However, no specific dietary pattern or popular diet has been observed to be superior to other diets in promoting weight loss in the

general population or in patients with CKD [37, 38]. Individualized diets based on patients' comorbidities and preferences is required to achieve weight loss with the help of a registered dietitian nutritionist.

Exercise reduces BMI, systolic and diastolic blood pressure, and improves quality of life in patients with kidney disease [31]. A meta-analysis showed that exercise was associated with a slight increase in eGFR in non-dialysis CKD patients but this was limited to studies with a duration of less than 3 months [39]. Diet and exercise can also improve metabolic profile in overweight or obese stage 3–4 CKD patients [40].

## *Drug Therapy*

Several medications are approved for weight loss along with diet and exercise. Table 12.1 summarizes the weight loss medications that can be considered for patients with kidney disease. Several other medications are either contraindicated in kidney disease (phentermine-topiramate) or discontinued from the market due to significant complications (lorcaserin, sibutramine).

**Table 12.1** Weight loss medications for patients with kidney disease

| | Dosing | Mechanism of action | Side effects | Notes |
|---|---|---|---|---|
| Orlistat | 120 mg TID with meals | Inhibits gastric and pancreatic lipase; fat malabsorption | Flatulence, fecal incontinence, oily rectal leakage | Does not require renal dose adjustment |
| Bupropion-naltrexone ER | 8 mg/90 mg daily increase to 32 mg/360 mg daily | Anorexiant; bupropion (dopamine/norepinephrine reuptake), naltrexone (opioid antagonist) | GI symptoms, headache, dizziness, hepatotoxicity, dry mouth, elevated BP and HR, palpitations | Increased creatinine |
| GLP-1 receptor agonist | 0.6 mg SC daily and weekly increase to 3 mg SC daily | Stimulates insulin secretion, inhibit glucagon, regulate appetite and calorie intake | GI symptoms, decreased appetite, dizziness, abdominal pain, increased HR, hypoglycemia, increased lipase | Use caution when initiation or escalating dose in patients with kidney disease: Postmarketing data points to renal impairment |

Data source: US Food and Drug Administration [41]
*TID* three times daily, *ER* extended release, *GI* gastrointestinal, *BP* blood pressure, *HR* heart rate, *GABA* gamma aminobutyric acid, *GLP-1* Glucagon-like peptide-1, *SC* Subcutaneous

### *Bariatric Surgery*

Treatment with lifestyle modifications and medications does not always yield satisfactory results and certain patients may benefit from bariatric surgery. Medicare requirements for bariatric surgery are BMI $\geq$ 35 kg/m$^2$, the presence of at least one obesity-related comorbidity and failed medical treatment of obesity [42]. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy are the two procedures that are used most frequently [43]. The main mechanisms in promoting weight loss is reduced hunger. Studies comparing the outcomes in patients who undergo bariatric surgery with non-surgically treated patients show that bariatric surgery is associated with a slower eGFR decline and a lower risk of kidney failure [43–45].

### *Management Obesity in Patients with ESKD*

The benefit of weight loss remains controversial in patients with kidney failure. Data from observational studies indicate higher BMI is protective in patients on maintenance hemodialysis [46, 47]. However, abdominal adiposity, which is a better measure to assess obesity in this population, is associated with higher risk of death in ESKD [48, 49]. Kidney transplantation, which is associated with improved survival in ESKD, is usually not offered to patients with severe obesity due to risk of graft loss and delayed graft function. However, most patients with kidney failure have trouble in losing weight with lifestyle modifications or medical treatment. Weight loss in patients on peritoneal dialysis is particularly more challenging due to increased appetite, glucose load from the dialysate and fluid overload [50]. Bariatric surgery should be considered in patients with ESKD, who are candidates for kidney transplantation, given the large benefits of kidney transplantation [51]. However, it is important to note the risks associated with bariatric surgery, some of which are; micronutrient deficiencies, hyperoxaluria and increased risk of nephrolithiasis. Thus, careful evaluation is warranted in selecting patients for bariatric surgery.

## Conclusion

The pathogenetic pathways of obesity, hypertension and other elements of the metabolic syndrome are intertwined, all contributing to the renal injury implicated in metabolic syndrome. Prevention, accurate assessment and effective treatment of obesity, metabolic syndrome, and diabetes are crucial to prevent the development and progression of kidney damage and importantly, to reduce cardiovascular mortality in this population. More effective strategies targeting the distinct pathways involved in the interplay between metabolic syndrome and kidney disease are required to reduce the cardiorenal, metabolic and other obesity-associated diseases.

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