

## Obesity and kidney disease

### Obesidade e doença renal

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Submitted on: 6/13/2016.

Approved on: 7/27/2016.

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DOI: 10.5935/0101-2800.20170011

#### ABSTRACT

Obesity has been pointed out as an important cause of kidney diseases. Due to its close association with diabetes and hypertension, excess weight and obesity are important risk factors for chronic kidney disease (CKD). Obesity influences CKD development, among other factors, because it predisposes to diabetic nephropathy, hypertensive nephrosclerosis and focal and segmental glomerulosclerosis. Excess weight and obesity are associated with hemodynamic, structural and histological renal changes, in addition to metabolic and biochemical alterations that lead to kidney disease. Adipose tissue is dynamic and it is involved in the production of "adipokines", such as leptin, adiponectin, tumor necrosis factor- $\alpha$ , monocyte chemoattractant protein-1, transforming growth factor- $\beta$  and angiotensin-II. A series of events is triggered by obesity, including insulin resistance, glucose intolerance, dyslipidemia, atherosclerosis and hypertension. There is evidence that obesity itself can lead to kidney disease development. Further studies are required to better understand the association between obesity and kidney disease.

**Keywords:** obesity; overweight; kidney failure, chronic.

#### RESUMO

Obesidade tem sido apontada como uma importante causa de doenças renais, incluindo a doença renal crônica (DRC). A obesidade influencia o desenvolvimento de DRC, entre outros fatores, porque predispõe à nefropatia diabética, nefrosclerose hipertensiva e glomerulosclerose segmentar e focal. O excesso de peso e a obesidade estão associados a alterações renais hemodinâmicas, estruturais e histológicas, além de alterações metabólicas e bioquímicas que levam à doença renal. O tecido adiposo é dinâmico e está envolvido na produção de "adipocinas", como a leptina, adiponectina, fator de necrose tumoral- $\alpha$ , proteína quimiotática de monócitos-1, fator de transformação do crescimento- $\beta$  e angiotensina-II. Uma série de eventos é desencadeada pela obesidade, incluindo resistência à insulina, intolerância à glicose, dislipidemia, aterosclerose e hipertensão. Há evidência de que a obesidade por si só pode levar ao desenvolvimento de doença renal. Mais estudos são necessários para melhor entender a associação entre obesidade e doença renal.

**Palavras-chave:** obesidade; sobrepeso; falência renal crônica.

#### INTRODUCTION

Chronic kidney disease (CKD) is currently a worldwide public health problem that increasingly affects individuals early in their productive years and brings negative consequences for quality of life. There is evidence that CKD is an independent risk factor for angina, acute myocardial infarction, heart failure, stroke, peripheral vascular disease and arrhythmias.<sup>1,2</sup>

The incidence and prevalence of CKD are growing and are associated to the increase in the population's life expectancy and the number of cases of systemic arterial hypertension (SAH) and *diabetes mellitus* (DM), the main causes of CKD.<sup>3,4</sup> Approximately 13% of the adult US population has CKD stages 1 to 4.<sup>5</sup> In Brazil, the incidence and prevalence of CKD are not known, but it is estimated

that currently more than 100,000 Brazilian individuals are undergoing dialysis.<sup>6</sup>

Obesity has been identified as a major cause of kidney disease, including CKD<sup>7-9</sup> with evidence of causality in several studies.<sup>3,7,10-12</sup> Due to the close association with DM and hypertension, overweight and obesity, which show epidemic proportions worldwide,<sup>13</sup> are important risk factors for CKD onset, especially in adults. Dietary aspects, including some dietary patterns have also been identified as possible risk factors for CKD.<sup>14</sup>

Obesity influences the development of CKD, among other factors, by predisposing to diabetic nephropathy, hypertensive nephrosclerosis and focal and segmental glomerulosclerosis.<sup>3,8</sup> Considering the growing trend of excess weight, which already affected half of the Brazilian population in 2013, according to the results of the latest telephone survey, VIGITEL,<sup>15</sup> an increase in the number of CKD cases is expected. In a multicentric cohort study (ELSA-Brasil), which included 15,105 Brazilian adults, the observed rate of excess weight was high, affecting 65.9% of men and 60.8% of women.<sup>16</sup>

This article discusses the pathophysiology aspects of the association between obesity and kidney disease, discussing the most important aspects and the most current evidence of this association.

## EPIDEMIOLOGICAL ASPECTS OF OBESITY, METABOLIC SYNDROME AND KIDNEY DISEASE

Overweight and obesity have increased incidence and prevalence worldwide. In the United States, it is estimated that one third of adults are overweight and one third are obese.<sup>13</sup> Several studies have shown a significant association between obesity and kidney disease.<sup>7,3,10-12</sup> Currently, an epidemic of both overweight and obesity, as well as of chronic kidney disease can be observed and these conditions may be associated.<sup>13</sup>

In the last 15 years, a steady increase in the number of obese patients undergoing dialysis has been observed.<sup>17</sup> There is also evidence that high levels of serum creatinine are associated with an increased risk of metabolic syndrome (MS).<sup>18</sup> Moreover, there is evidence that obesity, especially when present in the early years of adulthood, is a risk factor for the development of renal carcinoma.<sup>8</sup> An association between obesity and nephrolithiasis has also been described, particularly uric acid and calcium oxalate calculi.<sup>8,9</sup>

The association between increased waist circumference, high blood pressure, high fasting glucose and dyslipidemia constitutes the condition known as metabolic syndrome, which is associated with high cardiovascular risk.<sup>19-21</sup> The role of MS as a cause of CKD has been little discussed, although it is a major cause of hypertension and *diabetes mellitus*, conditions that account for over 70% of cases of CKD.<sup>7</sup> Individuals with MS have a 2-to-3 fold higher risk of developing microalbuminuria than those without MS.<sup>22</sup>

There is evidence that all MS components show a significant association with CKD.<sup>11,12</sup> In a longitudinal study of 3,437 individuals from South Korea, CKD was associated with MS, irrespective of body weight and obesity was associated with CKD, regardless of the presence of MS.<sup>12</sup> Waist circumference and other components of MS have shown an independent association with CKD.<sup>3</sup>

There is a positive association between the number of MS components and the risk of CKD.<sup>22</sup> Central obesity seems to be more important than body mass index (BMI) as a risk factor for cardiovascular diseases and CKD.<sup>8</sup> Several renal disorders are associated with overweight, obesity and metabolic syndrome, as summarized in Table 1.

## PATHOPHYSIOLOGY OF OBESITY LEADING TO KIDNEY DISEASE

Overweight and obesity are associated with hemodynamic, structural and histopathological alterations in the kidney, as well as metabolic and biochemical alterations that predispose to kidney disease, even when renal function is normal in the conventional tests.<sup>8,23</sup> It is currently known that adipose tissue is not only a fat reservoir, but a dynamic tissue involved in the production of “adipokines”, such as leptin, adiponectin, tumor necrosis factor- $\alpha$ , monocyte chemoattractant protein-1, transforming growth factor- $\beta$  and angiotensin-II.<sup>23</sup>

A series of events is triggered by obesity, including insulin resistance, glucose intolerance, hyperlipidemia, atherosclerosis and hypertension, all of which are associated with increased cardiovascular risk. The association between CKD and dyslipidemia has also been described, but its causes are still unknown. Insulin action resistance, present in CKD, reduces the activity of lipoprotein lipase, which may be implicated in the pathophysiology of dyslipidemia in CKD.<sup>24</sup>

**TABLE 1** RENAL ABNORMALITIES ASSOCIATED WITH OVERWEIGHT, OBESITY AND METABOLIC SYNDROME

Hemodynamic/Physiologic changes	Effective plasmatic flow increase
	GFR increase
	Filtration fraction increase
	Magnitude increase of albuminuria/proteinuria
Anatomic changes	Kidneys' weight increase
	Glomerular surface increase
	Glomerulomegaly
	Glomerular basement membrane increase
	Mesangial matrix expansion
	Mesangial cell proliferation
	Mesangial cell proliferation
Pathology	Decrease in the number of podocytes per glomeruli
	Increase in the length of podocyte processes
	Increase in the proportional number of glomeruli with segmental and global sclerosis
Chronic kidney disease/ Glomerulopathies	Obesity-associated glomerulopathy/FSGS
	Diabetic nephropathy
	Hypertensive nephrosclerosis
	FSGS
Other renal/urologic complications	IgA nephropathy
	Higher incidence of renal carcinoma
	Higher incidence of nephrolithiasis (uric acid and calcium oxalate)
End-stage renal disease (ESRD)	Higher incidence of surgical complications and graft loss in the context of kidney transplantation
	Higher incidence of ESRD

\* GFR: Glomerular Filtration Rate; FSGS = Focal and segmental glomerulosclerosis. Adapted from Kopple & Feroze, 2011.

Obesity leads to increased renal tubular sodium reabsorption, impairing pressure natriuresis and causing volume expansion due to the activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). Compression also occurs in the kidneys, especially when visceral obesity is present.<sup>3,7,8</sup>

The increase in sodium reabsorption and consequent extracellular volume expansion is a central event in the development of SAH in obesity. Some evidence suggests that an increase in sodium reabsorption occurs in some segments in addition to the proximal tubule, possibly in the loop of Henle.<sup>7</sup> Also, there is an increase in renal blood flow, glomerular filtration rate (GFR) and filtration fraction.

Glomerular hyperfiltration, associated with increased blood pressure and other metabolic alterations such as insulin resistance and DM, finally result in kidney damage and reduced GFR<sup>3,7,8</sup>. The sympathetic nervous system (SNS) activation also

contributes to obesity-related hypertension. There is evidence that renal denervation reduces sodium retention and hypertension in obesity, suggesting that SNS activation induced by obesity increases blood pressure mainly due to the sodium retention stimulus, rather than vasoconstriction.

The mechanisms that lead to SNS activation in obesity are not yet fully understood, but several factors have been proposed as triggers for this stimulus, including hyperinsulinemia, hyperleptinemia, increased levels of fatty acids, angiotensin II levels and baroreceptor reflex alterations.<sup>3,7,8</sup> The increase in leptin levels is associated with SNS activation and its effect on blood pressure level increase also includes nitric oxide synthesis inhibition (potent vasodilator).

An increased production of endothelin-1 has also been described in obese subjects, which further contributes to the elevation of blood pressure levels and consequently to renal dysfunction.<sup>3</sup> Recent studies have shown that endothelin-1 is increased in patients with intradialytic hypertension,<sup>25</sup> suggesting

that this substance plays a key role in the genesis of hypertension in patients with CKD and is possibly associated with hypertension in obese patients.

Adipose tissue accumulation, especially in visceral adiposity, causes kidney compression, and a consequent increase in intrarenal pressure. The excess of retroperitoneal adipose tissue involves the kidneys and penetrates the renal hilum up to the medulla, causing compression of the renal medulla and increased hydrostatic pressure of the renal interstitial fluid. Excess visceral fat also increases the intra-abdominal pressure, causing further renal compression.<sup>3,8</sup> The physical compression of the kidney causes increased extracellular matrix formation in the renal medulla. As the kidneys are surrounded by a capsule, which has low compliance, extracellular matrix accumulation can further exacerbate intrarenal compression and increase the hydrostatic pressure of the interstitial fluid.

This increase in intrarenal pressure, in turn, compresses the loop of Henle and peritubular capillaries (vasa recta), which reduces the flow of fluids through the renal tubules leading to sodium reabsorption by them.<sup>3,7,8</sup>

Another important factor in the pathophysiology of obesity renal complications is the so-called “lipotoxicity”, which refers to the disorders caused by the exacerbated metabolism of fatty acids in non-adipose tissue, such as skeletal muscle, pancreatic islets, myocardium and possibly the kidneys.

In “overnutrition” states, the supply of fatty acids to the tissues exceeds the metabolic needs, leading to a compensatory increase in their oxidation. The increase in fatty acid metabolism leads to the production and release of several substances harmful to the cells, such as the products of lipid peroxidation and triglycerides, which can induce apoptosis and fibrosis in non-adipose tissues.<sup>3,7,8</sup>

Obesity is also associated with inflammation, as an increase in the production of inflammatory cytokines such as tumor necrosis factor- $\alpha$ , interleukin-6 and C-reactive protein can be observed, being called “adipokines” by some authors because of their production by adipocytes. Inflammation itself is a risk factor for renal function loss.<sup>26,27</sup> Renal fibrosis (interstitial and glomerular), in addition to the irreversible accumulation of extracellular matrix in kidney tissue, is associated with inflammation, processes that may be associated with the “adipokines”.<sup>3,8</sup>

There is also evidence that obesity itself increases albumin excretion, which progressively increases with

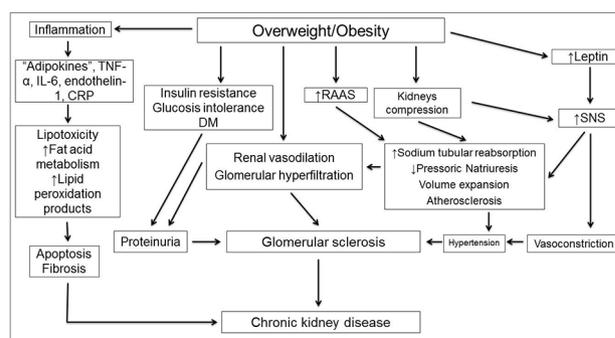
obesity severity and, in rare cases, can lead to nephrotic syndrome.<sup>7</sup> Obesity has also shown to be an important risk factor for renal disease progression in patients with glomerulopathies, such as in IgA nephropathy.<sup>28</sup>

Focal and segmental glomerulosclerosis (FSGS) is the type of glomerulonephritis most often associated with obesity.<sup>29</sup> FSGS associated with obesity typically presents with nephrotic syndrome and progressive renal function loss. The morphological findings include glomerulomegaly, predominance of perihilar variant and mild podocyte fusion.<sup>29</sup> Weight loss, either by dieting or through bariatric surgery, leads to proteinuria reduction.<sup>8</sup>

The association between obesity, MS and nephrolithiasis has been observed in some studies, mainly due to increased serum uric acid levels in obese individuals.<sup>30</sup>

Although obesity represents a major risk factor for the development of cardiovascular disease, some studies have shown that obesity is a protective factor in individuals with end-stage CKD (undergoing dialysis),<sup>8,31</sup> perhaps because malnutrition is associated with higher mortality when compared to obesity. However, even in patients undergoing dialysis, visceral obesity is associated with increased risk of coronary calcification and adverse cardiovascular events.<sup>17</sup> The pathophysiology of obesity-related kidney disease is shown in Figure 1.

**Figure 1.** Pathophysiology of the association between obesity and kidney disease. Adapted from Silva Junior & Matos, 2016.



## CONCLUSION

The incidence of obesity has been increasing worldwide and is an important risk factor for kidney disease. There is evidence that obesity alone can lead to the development of kidney diseases, including chronic kidney disease, glomerulopathy and nephrolithiasis. The pathophysiology of obesity-related kidney disease includes anatomic and hemodynamic alterations in the renal system. More studies are required to better understand the association between obesity and kidney disease.

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