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REVIEW

Obesity in kidney disease: A heavyweight opponent

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Abstract

Obesity is an important worldwide challenge that must be faced in most developed and developing countries because of unhealthy nutritional habits. The consequences of obesity and being overweight are observed in different organs, but the kidney is one of the most affected. Excess adipose tissue causes hemodynamic alterations in the kidney that can result in renal disease. However, obesity is also commonly associated with other comorbidities such as chronic inflammation, hypertension and diabetes. This association of several aggravating factors is still a matter of concern in clinical and basic research because the pathophysiologic mechanisms surrounding chronic kidney disease development in obese patients remain unclear. This review will discuss the consequences of obesity in the context of renal injury.

Key words: Overweight; Obesity; Kidney disease; Renin-angiotensin system; Diabetes

Core tip: Obesity is unquestionably one of the biggest health challenges the modern world will face this century. It has vast effects on systemic function including cardiovascular disease, metabolic dysfunction and chronic inflammation. All of these factors have a great impact on kidney function, and current data indicate a significant correlation between obesity and kidney disease because of irregular immune activation, altered renal hemodynamics and metabolic mediator signaling. This review focuses on the most recent findings that have begun to elucidate the relationship between obesity and its effect on the kidneys.

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INTRODUCTION

Obesity is unquestionably one of the biggest health challenges the world population faces this century. Statistics indicate that more than 1.4 billion adults over 20 (35%) are overweight, with 11% falling into the obesity category according to World Health Organization statistics. Although the state of being obese and overweight has usually been associated with developed countries and high income, globalization and widespread unhealthy nutritional habits have caused these phenomena to reach epidemic proportions. As a consequence to the rise in obesity rates, comorbidities linked to this disease such as diabetes, car-

Table 1 Recent major multicenter studies regarding the impact of obesity and overweight on the incidence of kidney disease, renal function prognosis and patient survival

Cohort	Number of patients	Country	Result	Ref.
Dialysis patients	1957	Netherlands	Higher mortality with very high or low BMI (< 65 yr)	[157]
Kidney transplant	1810	Netherlands	Higher mortality and kidney graft failure	[158]
Native population	1924	Sweden	Higher Chronic Renal Failure	[13]
National Health and Nutrition Examination Survey Ⅲ	5659	United States	Higher micro-albuminuria with metabolic syndrome	[159]
Hipertension and obesity	4585	Spain	Higher risk of renal insufficiency	[160]
Native population	2585	United States	Higher risk of kidney disease	[12]
Native population	5403	Japan	Higher risk of proteinuria	[161]
Kidney transplant	51927	United States	Lower patient and graft survival. Higher chronic graft failure and delayed graft function	[162]

diovascular disease, and cancer have also increased[1].

Adipose tissue has a great impact on metabolic homeostasis and immunological function. The conjunction of the main obesity-related risk factors defines a clinical condition termed Metabolic Syndrome. This syndrome aggregates a variety of pathologies, including dyslipidemia, thrombosis, low-grade systemic inflammation, elevated blood pressure, hyperglycemia and insulin resistance. Adipose tissue possesses an important influence over the immune response profile *via* direct and indirect mechanisms through the secretion of nonesterified fatty acids, cytokines and endocrine mediators defined as adipokines. Together, these factors contribute to a systemic change in the way the body works, adapts and responds to challenges.

Although many studies have associated obesity with higher morbidity rates and obesity-related diseases[2], some groups argue the contrary. Overweight and obese patients reportedly display higher survival, while patients with low body mass are at a higher risk of general mortality and cardiovascular and many non-cardiovascular disease incidence, a phenomenon referred to as the "obesity paradox"[3,4]. These findings also highlight the complex relationship that obesity has with different pathologies and demonstrates that a closer look is needed to understand the particular effects of being obese and overweight on the organism.

OBESITY AND THE KIDNEY

Obesity affects the function of many organs. The heart is one of the main organs affected by metabolic syndrome, and obesity significantly increases the chances of cardiac dysfunction because of chronic hemodynamic burden, which causes dyspnea, edema, ongoing systemic inflammation, metabolic alterations and other related comorbidities[5]. Other organs such as the liver are also affected by this pathology, with lipid accumulation causing non-alcoholic fatty liver disease[6]. Lung function is also compromised by adipose tissue around the abdomen, rib cage and visceral cavity[7].

The kidney is also responsive to obesity. Several multicenter studies have identified a direct correlation between obesity and renal complications (Table 1). Obesity has a multifactorial mechanism and is considered an independent factor in chronic kidney disease (CKD) development and progression to end-stage renal disease (ESRD)[8]. Studies demonstrate that obesity-induced hypertension and diabetes are strong determinants of CKD. Analyses relating obesity and kidney transplantation revealed that in 1987, 11.6% of adults awaiting a kidney transplant were obese, and in 2001, obesity among adults rose to 25.1%[9]. Concomitantly, body mass index (BMI) among patients initiating dialysis increased from 25.7 kg/m^2 to 27.5 kg/m^2 from 1995 to 2002[10]; and when compared with normal weight persons (BMI, 18.5-24.9 kg/m^2), there is a directly proportional relationship between increased BMI and increased CKD and ESRD risk[11,12]. A study conducted by Ejerblad *et al*[13] examined the association between degrees of obesity and CKD. After making adjustments for many covariates, the investigators found a 2.8-fold increased risk of nephrosclerosis and a 7-fold increased risk of diabetic nephropathy among adults who had a BMI of 35 kg/m^2 or higher compared with a lifetime highest BMI lower than 25 kg/m^2. In adults with no diabetes or hypertension, a lifetime highest BMI of 35 kg/m^2 or higher was associated with a 2-fold increased risk of CKD. Conversely, obese patients had better recovery and benefitted from reduced body weight by diminishing proteinuria[14]. Obesity was recently demonstrated to accelerate IgA nephropathy progression[15]. In this scenario, obesity could be one of the few preventable risk factors for CKD development because it also mediates diabetes and hypertension, which are related to kidney disease progression[14,16,17].

The occurrence of obesity during early life is linked to low glomerular filtration rates (GFRs), while being overweight during adulthood doubles the chances of chronic kidney disease[18]. Many researchers have described the direct impacts obesity has on the kidneys, which include hyperfiltration, elevated glomerular tension, and podocyte stress[19]. Some researchers have also correlated obesity-related inflammation and adipokine deregulation to kidney function. The present review will focus on the impact of obesity on kidney function and discuss its influence on the progression of kidney disease.

Obesity-induced inflammation

Adipose tissue is known for its roles in lipid storage, ther-

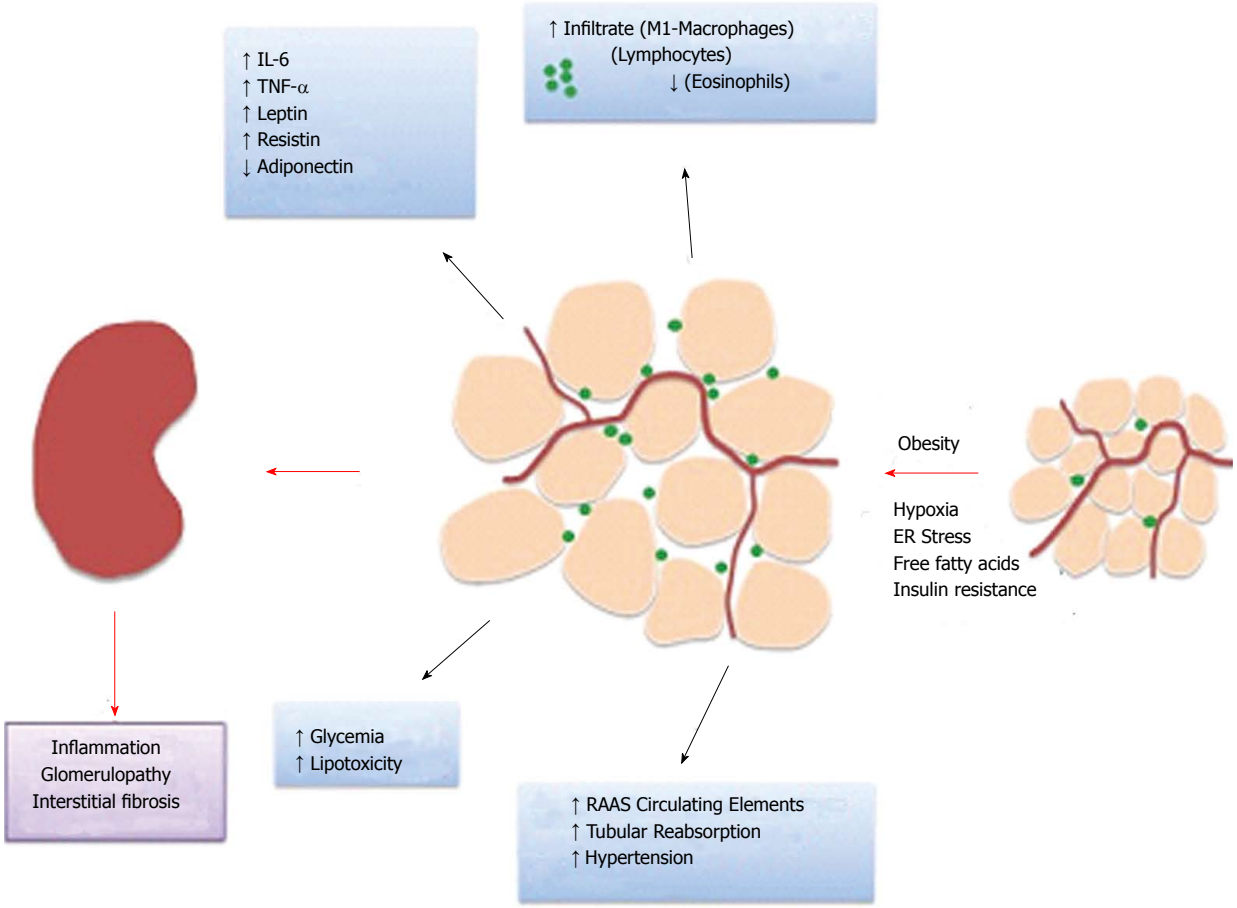

Figure 1 Main factors involved in obesity-induced inflammation, metabolic stress and hemodynamic disorder that participate in kidney function impairment. RAAS: Renin-angiotensin-aldosterone system; ER: Endoplasmic reticulum; TNF-α: Tumor necrosis factor alpha.

mogenesis and metabolic regulation. However, in recent years, focus has been given to its endocrine properties such as cytokine and adipokine secretion (Figure 1).

As previously described, obesity and diabetes are conditions that present a state of low-grade inflammation. Significant evidence supports the concept of adipose tissue as an immunomodulatory organ. Adipose tissue harbors a considerable amount of immune cells such as macrophages, lymphocytes and eosinophils. In obesity, the frequency of infiltrated cells rises, and they acquire a pro-inflammatory profile[20]. Excess free fatty acids that are present in obesity activate diverse inflammatory pathways involving endoplasmic reticulum stress[21], toll-like receptor[22,23], inflammasome and nuclear factor-κB (NF-κB) signaling activation[24,25]. In parallel, adipose tissue becomes hypoxic with adipocyte hypertrophy, which induces a change from aerobic to anaerobic glycolysis and lactate production.

With obesity, adipocyte hypertrophy and hypoxia induce cell death and resident immune cell activation, which in turn promotes inflammatory cell recruitment[26]. Macrophages constitute the principal population of resident and recruited cells in adipose tissue, which have a role in maintaining tissue homeostasis by assisting with the clearance of dead cells and debris. Because of lipid accumulation and adipocyte cell death, non-inflammatory tissue-resident M2 type macrophages and recruited monocytes undergo proliferation and macrophage M1 polarization[27-29]. These cells in turn secrete higher levels of inflammatory cytokines such as TNF-α, IL-6 and MCP-1 and lower levels of anti-inflammatory mediators such as arginase 1[28-30]. IL-4-expressing eosinophil counts also decrease with obesity, which contributes to inflammation[31]. Furthermore, $CD8^+$ and $CD4^+$ Th1 lymphocyte counts also increase while Treg numbers reduce with obesity. In accordance, B cell pro-inflammatory immunoglobulin G2c (IgG2c) production also participates in cell activation[32-35].

Proinflammatory cytokines are also produced by the renal parenchyma in response to hyperglycemia as well as vasoactive peptides such as angiotensin II and endothelin[36]. These molecules activate signaling second messengers such as protein kinase C, MAP kinase and NF-κB, which alter the gene expression of several cytokines and growth factors.

Increased TNF-α levels reduce the expression of nephrin and podocin, causing podocytopathy[37]. Similarly, IL-6 promotes adhesion molecule expression, which increases oxidative stress[38], and IL-6 receptor blockade can inhibit the progression of proteinuria, renal lipid deposition and mesangial cell proliferation[39]. An additional important growth factor for renal injury is transforming growth factor (TGF)-β, which induces podocyte apoptosis, extracellular matrix synthesis and mesangial cell pro-

liferation, thus exacerbating the development of the glomerular lesions associated with diabetes and obesity[40].

While many studies demonstrate the effect of metabolism on the immune system, studies have demonstrated that the reverse also happens; immune cell activation in adipose tissue is a determinant of obesity-linked metabolic changes such as insulin resistance[41]. For example, in response to inflammatory mediators, adipose tissue also down regulates glucose transporter GLUT4 expression, which increases insulin resistance.

Obesity and the adipokine imbalance

In addition to cytokines, adipose tissue is also responsible for the production of many endocrine mediators termed adipokines, which regulate inflammation, food consumption and link immune and metabolic functions. Amongst these are leptin, adiponectin, visfatin, resistin, intelectin and others. These factors are mostly secreted by adipocytes and have imbalanced expression in obesity. Many studies have documented the importance of these cytokines in the regulation of metabolism and inflammation and suggest a role for these cytokines in obesity-related metabolic and inflammatory distortion. Although there is still much to elucidate regarding the role of adipokines in kidney disease, recent studies now have begun to clarify the influence of these mediators in kidney pathology.

Leptin and kidney disease

Leptin was the first adipokine to be characterized and is the best described in the literature. It is secreted by different adipose compartments and induces signaling through Ob-a to Ob-f subtype receptor activation, and the Ob-Rb receptor is the most important. Its main actions are on the nervous system and kidneys. Leptin acts on the nervous system by stimulating neuropeptides that promote satiety and energy consumption. It has been suggested that one develops leptin resistance in obesity because of the absence of many of its effects despite elevated adipokine levels. Hyperleptinemia has also been associated with many cardiovascular and immunologic dysfunctions[42].

Many reports have linked obesity and leptin to hypertension. Studies indicate that this adipokine activates the sympathetic nervous system and may suppress parasympathetic nerve activity, which alters baroreflex control[43,44]. Leptin also increases renal sympathetic nerve activity, as demonstrated by studies on ObR deletion in the central nervous system[45]. Because the sympathetic nervous system contributes to CKD, leptin hypertensive actions may promote kidney disease.

Leptin also holds important pro-inflammatory activity. Its structure resembles other cytokines such as IL-2 and can stimulate many immune cells. Studies demonstrate that leptin induces the production of inflammatory cytokines as IL-6 and TNF-α by monocytes and additionally induces chemokine ligands, reactive oxygen species production and macrophage and monocyte proliferation[42]. Leptin also polarizes $CD4^+$ lymphocytes toward a Th2 profile, which increases the production of inflammatory cytokines such as IL-2 and IFN-γ[42]. Therefore, excess leptin, which is characteristic during obesity, is an important mediator of obesity-related immune and metabolic dysfunction.

Recent studies have also suggested that leptin imposes an important action in the kidneys, as this mediator localizes mainly to the organ after injection[46]. CKD patients demonstrate high leptin levels, as do ESRD patients, and hemodialysis fails to lower these values[47,48]. The kidneys also express the Ob-Ra and Ob-Rb leptin receptor isoforms[49]. In vitro, leptin induces glomerular endothelial cell proliferation, which is augmented in the presence of angiotensin Ⅱ and increases TGF-β1 production. Furthermore, leptin infusion into rats *in vivo* also induced proteinuria, glomerular endothelial cell proliferation and TGF-β1 production and increased collagen type Ⅳ expression[50]. This adipokine also induced type I collagen in mesangial cells, confirming data that link obesity, glomerulosclerosis and glomerulomegaly, which is defined as obesity-related glomerulopathy[51,52].

Adiponectin and kidney disease

Adiponectin is another adipokine with immunomodulatory and metabolic actions. It is present in plasma at a considerable concentration[53], and its receptors R1, R2 and T cadherin are expressed by a wide range of tissues. Adiponectin is negatively correlated with hypertension[54]. It exerts its metabolic actions by increasing glucose uptake and fatty acid oxidation and inhibiting gluconeogenesis. In addition to improving insulin sensitivity, it also possesses potent anti-inflammatory properties[42].

Unlike leptin, low serum adiponectin levels are found in obese patients, and its production is reduced by hypoxia, inflammatory mediators such as IL-6 and oxidative stress[55-57]. Hypoadiponectinemia has been linked to diverse complications in obesity. Mice lacking adiponectin display increased susceptibility to high-fat diet-induced insulin resistance[58]. Moreover, adiponectin overexpression in high-fat diet-fed animals caused less fat accumulation and reduced adipose tissue macrophage infiltration, and it prevented premature death[59].

Recent studies have begun to elucidate the role of adiponectin in kidney injury. Current data demonstrate that adiponectin is secreted not only by adipocytes but also renal tubular cells[60]. Research indicates that plasma adiponectin is inversely correlated with albuminuria in obese patients[61]. Adiponectin-null mice also develop albuminuria and podocyte damage as well as glomerular oxidative stress[62]. These mice also display more expressive albuminuria, fibrosis and macrophage infiltration after 5/6 nephrectomy[63]. Moreover, mice overexpressing adiponectin recover more rapidly and exhibit less interstitial fibrosis after podocyte-specific damage[64]. Metabolic syndrome has also been associated with low adiponectin levels and worse prognosis after kidney transplantation[65]. These data are controversial, however, as some studies describe a direct link between adiponectin levels

and mortality in advanced CKI and kidney transplant patients[66,67]. While recent work suggests that adiponectin causes less intense ischemia-reperfusion kidney injury[68], the contrary was observed when exogenous adiponectin was administered[69]. Furthermore, kidney function also influences adiponectin levels because the kidneys are responsible for its elimination, and kidney transplantation significantly reduces the adiponectin concentration[70].

Resistin and visfatin

Resistin is a recently discovered adipokine with inflammatory properties. Some works suggest that this mediator increases insulin resistance, while others fail to find this correlation[71,72]. Although in mice, it is expressed mainly by adipocytes, in humans it is produced principally by macrophages and monocytes. Although there are still few data on its impact on renal function, some research indicates that serum resistin levels are strongly associated with decreased GFRs and inflammatory biomarkers in CKD[71].

Adipose tissue and the kidneys also synthesize visfatin, and this is upregulated in type-2 diabetic rats, inducing fibrosis and inflammatory pathway activation[73]. In CKD patients, higher visfatin levels also are correlated with decreased GFR and endothelial dysfunction[74,75]. Furthermore, another study with human plasma determined that this mediator was also linked to creatinine levels, inflammation and endothelial damage in kidney recipients, which is negatively related to plasma albumin levels[19].

OBESITY AND RAAS IN KIDNEY DISEASE

The pathophysiologic mechanism surrounding CKD development in obese patients remains unclear, but many events must be linked to ESRD such as altered renal hemodynamics, insulin resistance, hyperlipidemia, inflammation and oxidative stress (Figure 1). Hemodynamic alterations such as higher renal plasma flow, GFR and filtration fraction were linked to obesity when compared with the levels in non-obese patients[76,77]. The effect of BMI on renal hemodynamics was also proven by another work in which GFR and effective renal plasma flow (ERPF) were evaluated with a high-sodium diet. According to this study, ERPF and the GFR were statistically increased when individuals were exposed to a high-sodium diet and compared to another group that was exposed to a low-sodium diet without a change in filtration fraction (FF). However, increased sodium intake-induced changes in the GFR and FF were significantly greater in people with a BMI $\geqslant$ 25 kg/m^2[78]. The hemodynamic effects of overweight on kidney function and albuminuria are enhanced with hypertension, which itself is a clinical complication of obesity. Chagnac *et al*[79] demonstrated that glomerular hyperfiltration could have a relevant role in development of hypertension in obese patients by increasing postglomerular oncotic pressure and proximal tubular sodium reabsorption.

As an individual gains weight, renal mass as well as the glomerular diameter increases[80]. Podocytes are highly specialized cells that support the glomerular basement membrane (GBM) and play an important role in the glomerular filtration barrier *via* their foot processes. With glomerular hypertrophy, podocytes must cover a larger area by expanding these processes. If this podocyte enlargement is not proportional to glomerular hypertrophy, this adaptation could cause podocyte detachment and consequently a loss selectivity of serum protein selectivity[81,82]. Considering that podocytes are cells with limited capacity for cell division and replacement, proteinuria may be detected as is commonly observed in obese patients. Supporting this hypothesis, individuals who reduced their body mass also had significant reductions in proteinuria[14,83].

Extensive studies demonstrate that a lack of podocytes covering the GBM results in the formation of denuded areas, which trigger matrix deposition resulting in glomerulosclerosis in experimental models as well as in human biopsies[84-87]. As kidney injury persists, kidney fibrosis becomes an inevitable outcome in which epithelial-mesenchymal and endothelial-mesenchymal transition events generate matrix-producing fibroblasts in the interstitial space that contribute to renal fibrosis. Accumulation of matrix elements caused by the fibrotic process progressively alters normal kidney architecture by contraction and increased stiffness, resulting in disrupted blood flow supply and nephron function[88,89].

Once a number of podocytes are injured, a vicious cycle starts in which other podocytes also become damaged, accelerating podocyte deterioration and glomerulosclerosis[90]. The extensive loss of glomeruli imposes excessive stress on the remaining glomeruli because of hemodynamic alterations and glomerular hypertrophy, which can subsequently cause further sclerosis of the remaining glomeruli[91]. This could explain the progressive spreading of glomerular damage in later disease stages in which patients develop chronic renal failure[90]. The approach of using new agents to avoid podocyte lesions in different models of acute and chronic kidney disease resulted in less matrix deposition and consequent glomerulosclerosis[92,93].

In obesity, the renin-angiotensin-aldosterone system (RAAS) is commonly activated and is one of the strongest links to renal injury. All of the major components necessary to generate angiotensin Ⅱ (Ang Ⅱ) are found in the kidney[94]. The RAAS is a well-known mechanism to regulate blood pressure, fluids and electrolyte balance[95], and its activation impairs normal pressure natriuresis, increases renal tubular sodium reabsorption, and causes volume expansion. Physical compression of kidneys by visceral adipose tissue in obesity exacerbates these responses and increases blood pressure, leading to hypertension in obese subjects.

RAAS effects are obtained when angiotensinogen (AGT), the precursor of bioactive angiotensin peptides, is cleaved by both renin and angiotensin converting enzyme (ACE) to generate Ang Ⅱ. Ang Ⅱ, which is the active peptide and is the main effector of RAAS, pos-

sesses a dual role in physiology. Ang Ⅱ helps maintain long-term blood pressure and blood volume in the body; conversely, it has also been considered a multifunctional cytokine that plays a role in cell proliferation, hypertrophy, superoxide production, inflammation and extracellular matrix deposition[96]. Ang Ⅱ plays an endocrine role, and its participation in the development of obesity was evidenced by several works in which AGT, ang Ⅱ and ang Ⅱ receptor-deficient mice were protected against high-fat diet-induced obesity[97-99].

There are several pathophysiological conditions, including hypertensive models, in which Ang Ⅱ, in response to increased arterial blood pressure, increases efferent glomerular arteriole resistance and induces TGF-β production[100]. It also impairs the auto-regulation of afferent arterioles by avoiding vasoconstriction[101]. Taken together, Ang Ⅱ directly and indirectly enhances capillary filtration pressure and promotes proteinuria, which is one of the most important factors involved in renal disease progression. Moreover, Ang Ⅱ is also involved in nephrin dephosphorylation during podocyte apoptosis[102], which is a protein that is part of the slit diaphragm and binds to the adjacent nephrins of other podocytes. Ang II decreases the synthesis of negatively charged proteoglycans that are present on the glomerular basement membrane, which impairs the filtration of high molecular weight proteins by electrostatic repulsion[103].

Human adipose tissue expresses all of the RAAS components, including angiotensin, ACE, renin and the AT1 and AT2 receptors. Consequently, the AGT produced by adipose tissue contributes significantly to circulating AGT levels. In humans and mice, a strong relationship has been observed between increased AGT gene expression and obesity[104], supporting a role for adipose AGT in hypertensive obese patients. Weight reduction reduced blood pressure through systemic RAAS suppression and decreased AGT, renin and aldosterone levels in adipose tissue and plasma[105]. Mice with adipose tissue-restricted AGT expression were normotensive, whereas when adipose AGT was overexpressed, the mice became hypertensive[106]. Ang Ⅱ is also involved in adipocyte metabolism by influencing leptin and adiponectin release. Once leptin levels are increased, Ang Ⅱ promotes a number of cellular processes that attenuate leptin signaling and contribute to leptin resistance, which is common in obesity[107]. Conversely, adiponectin was upregulated when RAS was blocked by an ACE inhibitor or Ang II receptor blocker, suggesting Ang Ⅱ participation in the inhibition of adiponectin release[108].

Not only AGT but also aldosterone levels are increased in obese patients. Aldosterone is a mineralocorticoid hormone that is produced in the adrenal glands in response to Ang Ⅱ and a high extracellular potassium concentration, which increases blood pressure *via* sodium retention in the collecting duct. Aldosterone is correlated with increased blood pressure[109] and can also be produced by adipocytes through pathways that are dependent on the Ang Ⅱ-ATI receptor axis and calcineurin signaling[110] as well as pathways that are independent of Ang Ⅱ, in which adipocytes secrete factors that may stimulate the adrenal gland and increase circulating aldosterone levels, resulting in mineralocorticoid receptor activation and increasing blood pressure and hypertension[111]. Aldosterone binds to cytosolic mineralocorticoid receptors and promotes cell signaling pathways, endothelial dysfunction, inflammation and fibrosis independently and in concert with Ang Ⅱ[112]. Moreover, Ang Ⅱ activates the mineralocorticoid receptor in the absence of aldosterone and promotes kidney injury[113,114]. Blocking the mineralocorticoid receptors with antagonists attenuates obesity-induced hypertension and glomerular hyperfiltration[115].

Many clinical trials have been performed to mitigate the effects caused by RAAS. Multiple pharmacological strategies are used to treat CKD patients to diminish proteinuria and blood pressure. These strategies comprehend the use of RAAS-blocking agents alone or combined with ACE inhibitors, angiotensin-receptor blockers, direct renin inhibitors and mineralocorticoid-receptor antagonists[116]. The combination of a pharmacological therapy with reduced sodium intake was a better choice to diminish blood pressure and proteinuria than combined therapies[117]. Attempts to antagonize aldosterone receptors demonstrated promising results to diminish glomerulosclerosis[118].

In summary, the obesity-RAAS-hypertension axis is closely related to renal disease, as the increased release of adipose tissue derived-RAAS elements into the circulation can alter hemodynamic homeostasis. Increased Ang Ⅱ, AGT and aldosterone levels promote increased tubular reabsorption, leading to arterial hypertension and renal vasodilation. These events contribute to glomerular hypertension, which is an important factor in glomerulosclerosis and CKD progression.

OBESITY AND DIABETES IN RENAL DISEASE

Obesity is an important risk factor for hypertension and type 2 diabetes development, which are the leading causes of end-stage renal disease. The relationship between obesity, diabetes and kidney disease is very close because obesity and diabetes alter renal function, leading to renal disease. These renal alterations in both cases include anatomical, physiological and pathological changes (Figure 1).

Physiological and hemodynamic alterations are largely responsible for the subsequent anatomical and histopathological modifications. Among the major hemodynamic changes in obese and/or diabetic patients are increased GFR and intraglomerular capillary pressure[119,120]. Such alterations lead to diabetic nephropathy, increases in kidney weight and size, increased glomerular size, podocyte hypertrophy and mesangial matrix expansion[121].

Diabetes-related renal injuries can be grouped into

Table 2 Summary of the most important changes in the kidney during diabetes

Stages	Features
1 and 2	Hyperfiltration and renal hypertrophy
3	Microalbuminuria and hypertension as clinical features. As histological features: arteriolar hyalinosis, glomerular basement membrane thickening and mesangial matrix expansion
4 (Diabetic Nephropathy)	Proteinuria, nephrotic syndrome and decreased GFR
5	End-stage renal disease

Adapted from Amann *et al*[150]. GFR: Glomerular filtration rate.

five stages that comprise the remodeling that occurs throughout diabetic nephropathy. These stages are summarized in Table 2.

Although obesity and diabetes *per se* are responsible for renal injury, some other factors usually present in these conditions significantly aggravate renal damage such as blood pressure, hyperlipidemia, hyperglycemia, genetic factors[122] and inflammation. Some of these conditions are described in the following sections.

Hypertension in diabetes-related kidney disease

Hypertension and diabetes are two important risk factors in the development of kidney diseases, and when they are present simultaneously, they aggravate renal injury.

Hypertension-induced kidney damage in obesity and diabetes follows a very similar sequence of events including increased renal tubular sodium reabsorption as well as RAAS and sympathetic nervous system activation[123-125]. Such an increase in blood pressure along with increased glomerular capillary pressure and GFR are main contributors to the initial renal damage in obesity and diabetic nephropathy[126].

Given the importance of hypertension in worsening renal injury, especially in diabetic nephropathy, many studies have been performed to demonstrate the importance of controlling blood pressure when treating diabetic nephropathy, and the recommended blood pressure is less than 130/80 mmHg[127]. Several clinical trials have also been developed and have demonstrated renal protection when low blood pressure is achieved[128].

Renin-angiotensin system blockade is an important treatment for controlling blood pressure and decreasing proteinuric kidney disease progression[129-131]. Angiotensin Ⅱ-receptor blocker (ARB) therapy helps prevent the progression from normoalbuminuric (Albumin-Creatinine Ratio < 30 mg/g creatinine) to albuminuric stages (ACR 30-100 mg/g creatinine)[132]. Another important strategy is combined therapy with ARB and ACE inhibitors, which demonstrates a greater decrease in proteinuria than monotherapy[133].

Hyperlipidemia in obesity and diabetes

Dyslipidemia is an important component of metabolic syndrome and is often directly related to obesity and diabetes. Patients with diabetic nephropathy usually have several changes in their lipid profile[134], and the presence of increased blood lipid levels is a risk factor for albuminuria[135]. Several studies have demonstrated a correlation between triglyceride and cholesterol levels with renal function markers. Ravid and colleagues[136] observed a significant and positive correlation between total cholesterol and albuminuria in type 2 diabetic patients in a five-year cohort. Similarly, Klein *et al*[137] noted that type 1 diabetic patients with elevated total cholesterol and low HDL levels also had higher incidence of renal failure.

Although these studies demonstrate significant correlations between dyslipidemia and impaired renal function in diabetic subjects, little is known about the mechanisms by which the increased lipid profile causes kidney damage. Studies have demonstrated lipid deposits in the glomeruli and in the mesangium of obese individuals, suggesting that these lipids may cause kidney damage and lipotoxicity[138]. This glomerular lipotoxicity would be because of renal sterol-regulatory element-binding protein (SREBP-1 and 2) expression, whereas lipotoxicity causes tubulointerstitial fibrosis and inflammation in the proximal tubule epithelial cells[139]. Furthermore, alterations in the coagulation-fibrinolytic system, increased atherosclerosis and endothelial cell damage can also cause or aggravate diabetic nephropathy[140].

Hence, the importance of lipid control in the maintenance of kidney function in diabetic patients has been postulated[141].

Hyperglycemia in diabetes-related renal injury

Vascular alterations in diabetes are largely due to increased blood glucose levels. Hyperglycemia promotes microvascular injury by several mechanisms. The most important mechanisms are as follows: increased intracellular advanced glycated end product (AGE) formation; interaction between AGEs and their receptors, with consequent disruption of cell signaling and function; constant protein kinase C activation[142]; and increased hexosamine pathway activity[143]. Renal endothelial and mesangial cells are susceptible to such hyperglycemia-induced changes[144]. Thus, the hyperglycemia-induced alterations that occur in the kidney are similar to those described above but generate characteristic damage to renal cells. Because of AGE-driven structural changes in extracellular matrix proteins, metalloproteinases lose their ability to degrade the matrix efficiently, which causes basement membrane thickening[145]. In the mesangium, AGE-induced changes include increased pericyte apoptosis and increased vascular endothelial growth factor expression, and these changes in turn cause glomerular hyperfiltration[146].

Because hyperglycemia causes severe damage to the kidneys and other organs, several studies were developed to demonstrate the importance of glycemic control to prevent diabetic nephropathy. One of these clinical trials, the Diabetes Control and Complications Trial, compared conventional and intensive insulin therapy in type 1 diabetic patients. Over approximately 6.5 years, decreased risks for microalbuminuria and overt nephropathy were

observed with intensive glycemic control[147,148]. The Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation clinical trial, which was based on type 2 diabetic patients, also observed a reduction in albuminuria and nephropathy progression with insulin therapy intensification in late disease[149].

TREATMENTS AND PHARMACOLOGICAL INTERVENTION

Most treatments and approaches to reduce kidney injury in obese patients focus on managing associated risk factors such as hypertension, diabetes and hyperlipidemia using strategies as nutritional counseling, pharmacological interference and in some cases, surgery.

Dietary treatment consists on the change in nutritional habits and lifestyle. Eating smaller portions, increasing water consumption, minimizing salt ingestion and practicing physical activities are essential for weight reduction. Such practices can prevent and treat obesity which in turn reduces the risk of CKD. However this is a measure that brings long-term results. Treatment of patients with severe obesity focuses on reduction of proteinuria levels. Currently, several studies point out to the combined therapy of RAS inhibitors (ACE inhibitors and Ang Ⅱ receptor antagonists); low calories and low salt diets as presumably the best therapeutic options for obese patients with high levels of proteinuria[117].

Weight loss is also an important factor in this treatment regimen. Surgical intervention to treat obesity is a strategic option that can diminish levels of proteinuria in obese patients by mainly reducing hyperfiltration, attenuating obesity-mediated dyslipidemia and insulin resistance, reducing blood pressure and altering adipokine levels such as leptin and adiponectin which have direct a effect on podocytes, therefore improving kidney function[14,151,152]. Even modest weight loss has been associated with a substantial reduction in blood pressure and risk of diabetes[153]. The benefits of bariatric surgery are attributed to sympathetic nervous system suppression, decreasing therefore overall renal sympathetic activity and reduction on sodium reabsorption[154].

Once patients begin to lose weight, longer-term maintenance is difficult and even with continued treatment, patients may regain their normal condition. To prevent this, there is a need for adjunctive therapies for patients who are not able to lose weight or sustain weight loss solely with lifestyle changes[155]. In this scenario, the introduction of pharmacological treatment by the use of, for instance, noradrenergic agents, gastrointestinal lipase inhibitors and serotonin receptor agonists become an alternative and efficient strategy towards weight loss[156].

CONCLUSION

Obesity has great influence on end-stage renal disease, and it can be either the cause of renal alterations and kidney injury or an aggravating factor when other conditions such as hypertension and diabetes are established. All of these factors represent severe insults to the kidney, resulting in high costs to health systems to manage dialysis patients as well as those with post- cardiovascular events. Therefore, studies that relate these factors are important for developing new strategies to treat obese patients with renal disease to reduce patient mortality and improve quality of life.

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