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Obesity and chronic kidney disease. A look from the pathophysiological mechanisms, Narrative review.

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Received: August 3, 2022
Acepted: September 30, 2022
Published: September 30, 2022
Editor: Dr. Franklin Mora Bravo.

Cite:
Rico-Fontalvo J, Daza-Arnedo R, Rodríguez-Yanez T, Osorio W, Suarez-Romero B, Soto O, Montejo-Hernandez J, Cardona-Blanco M, Gutiérrez J. Obesity and chronic kidney disease. A look from the pathophysiological mechanisms, Narrative review. REV SEN 2022;10(2):97-107. DOI: http://doi.org/10.56867/32

Abstract

Introduction: Chronic kidney disease associated with obesity (CKD-WO) has increased in prevalence in recent decades. It is characterized by excess adipocytic hormonal imbalances (adipokines), deregulation of the energy balance system, and imbalances in metabolic homeostasis.

Purpose of the review: The objective of the review is to outline the different pathophysiological mechanisms' role in developing functional or anatomical kidney disease in patients with obesity. We look for updated reports that include the best survival results for patients with CKD.

Recent findings: We currently know that CKD-WO has a chronic pro-inflammatory behavior. Obesity and overweight are associated with hemodynamic, structural, and histopathological alterations in the kidney and metabolic and biochemical alterations that predispose to kidney disease, even when renal function and conventional tests are normal.

Conclusions: We classify CKD-WO in Type 1: Obesity and potentially reversible functional alterations. Type 2: Obesity and potentially non-reversible histopathological structural alterations (includes glomerulopathy associated with obesity and focal segmental glomerulosclerosis). Type 3: Obesity-related to chronic diseases (diabetes, hypertension, pulmonary hypertension, heart failure). Type 4: Obesity in the patient with renal function replacement therapy.

Keywords:

MESH: Obesity; Overweight; Renal Insufficiency, Chronic; Glomerular Filtration Rate; Albuminuria; Adiponectin.

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Obesity is a growing disease with an increased prevalence in recent decades. It is associated with a high care and economic burden for health systems derived from its relationship with cardiovascular, endocrine, psychological, and renal diseases, among others [1, 2]. The increase in obesity rates in different age groups, from children to young adults, leads us to assume that we will see more obesity-related kidney disease in the general population, with relevant implications for care systems [3]. Therefore, the knowledge and understanding of this interaction could have implications for preventing and treating kidney diseases.

Within the general population, obesity is associated with an increased risk of various pathological conditions, such as chronic arterial hypertension, chronic kidney disease (CKD), osteoarthritis, infections, obstructive sleep apnea-hypopnea syndrome (OSAHS), and diabetes mellitus, among others [3]. However, in the CKD scenario, obesity plays a dual and parallel role in the development of the disease, traditionally called the "obesity paradox," where, on the one hand, it acts as a modifiable risk factor for the development of chronic kidney disease (CKD) and on the other hand, it has been consistently associated with better survival outcomes in patients with end-stage kidney disease [1]. Therefore, in the following pages, we describe pathophysiological aspects that involve obesity in the development of chronic kidney disease.

Definition and epidemiology

Obesity is a condition characterized by abnormal or excessive adipose tissue accumulation with adverse pathological consequences and increased cardiovascular risk [4]. For its definition and diagnosis, a simple indicator, such as the relationship between weight and height, called body mass index (BMI), is calculated by dividing a person's weight in kilograms by the square of their height in meters (kg/m ^{2}). A BMI between 18.5 and 25 $^{kg/m2}$ is considered by the World Health Organization (WHO) as average weight, a BMI between 25 and 30 kg/m^2 as overweight, and a BMI > 30 kg/m^2 as obesity [5-7]. Furthermore, obesity can be classified into three levels of severity: class I (BMI 30.0 – 34.9), class II (BMI 35.0 – 39.9), and class III (BMI > 40) [8].

Over the past three decades, the prevalence of overweight and obese adults (BMI ≥ 25 kg/m^2) worldwide has increased substantially, making obesity an epidemic. Its prevalence will grow by 40% worldwide in the next decade [6]. Currently, the problem of obesity has seen a greater increase due to the increase in the affectation in children, which causes a higher prevalence of pathologies at an early age. In 2016, according to WHO estimates, some 41 million children under five were overweight or obese [7]. Obesity affects all countries, regardless of income level [7].

The prevalence of overweight and obesity in children and adolescents (5 to 19 years old) has increased dramatically, from 4% in 1975 to more than 18% in 2016. This increase was similar in both sexes: 18% of girls and 19% of boys were overweight in 2016. While in 1975, less than 1% of children and adolescents aged 5 to 19 were obese, in 2016, there were 124 million (6% of girls and 8% of children) [7]. The increasing prevalence of obesity has implications for cardiovascular diseases (CVDs) and CKD. A high body mass index (BMI) is one of the most vital risk factors for new-onset CKD [6].

Epidemiology of chronic kidney disease associated with obesity (CKD-O)

Chronic kidney disease (CKD) is a condition of interest in public health and is associated with high morbidity and mortality worldwide. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define CKD as the presence of kidney structure or function alterations for at least three months and with health implications [9, 10]. The main classificatory elements to define the presence of CKD are the estimated glomerular filtration rate (GFR) (G1 to G5) using a GFR of 60 ml/min/1.73 m^2 as the defining threshold and the urinary albumin excretion rate (A1 to A3) depending on whether the albumin/creatinine ratio in an isolated urine sample is <30, 30-300, or >300 mg/g, respectively [9, 10]. Although initially, there was some controversy about the use of GFR for the diagnosis of CKD in its early stages, recent studies have shown that both a GFR < 60 ml/min/1.73 m2 and an albumin/creatinine ratio (ACR) ≥ 1.1 mg/mmol (10 mg/g) are independent predictors of the risk of mortality and ESRD in the general population [11, 12]. Consequently, we can determine each patient's prognosis due to these categories. Global data suggest that the prevalence of CKD is between 10% and 16%, but information on population prevalence by category of GFR and ACR is scarce [13].

CKD is associated with high morbidity, mortality, and cardiovascular disease (CVD) burdens. As renal function declines, metabolic and hemodynamic disorders increase hospitalization rates, CVD, and death [4]. The known risk factors for CKD progression are relatively small, and effective therapies and strategies to slow CKD progression are limited [14]. Therefore, it is necessary to know and understand the different risk factors and their impact on kidney damage to minimize its progression, especially in active, evaluable, controllable, and follow-up interventions that can be carried out continuously, such as obesity.

To date, there is sufficient evidence to associate obesity with the development and progression of chronic kidney disease. Granular data on the prevalence of obesity in people with CKD are limited but consistent across the spectrum of kidney disease. In the 2011–2014 National Health and Nutrition Examination Survey, 44.1% of CKD patients in the United States

were also obese (21.9% obese class 1 [BMI=30 to 34.9 kg/m ^{2}] and 11.1% each with class 2 [BMI=35 to 39.9 kg/m ^{2}] and class 3 obesity [BMI≥40 kg/m ^{2}]), and the global percentage has increased by 5% in the last 12 years [15].

Focal segmental glomerulosclerosis (FSGS) is the type of glomerulonephritis most often associated with obesity [16]. The glomerular disease commonly associated with obesity is obesity-related glomerulopathy (ORG). This condition usually presents with nephrotic syndrome and progressive loss of kidney function. With the global obesity epidemic, ORG increased from 0.2% between 1986 and 1990 to 2% between 1996 and 2000, and it has become an emerging topic in nephrology [15].

Etiology and pathogenesis of CKD-AO

Obesity is characterized by excess adipocytic hormone imbalances (adipokines), dysregulation of the energy balance system, and imbalances in metabolic homeostasis [12]. There are two types of adipose tissue present in humans: white adipose tissue (WAT) and brown adipose tissue (BAT) [17-19]. Ectopic fat deposition primarily occurs in places where it is not physiologically stored, such as the liver, pancreas, heart, and skeletal muscle; secondarily, there is a change in the distribution of visceral adipose tissue with storage of adipose tissue in the intraperitoneal and retroperitoneal spaces; then comes inflammatory and adipokine dysregulation; and last, insulin resistance [20].

White adipose tissue (WAT)

White adipose tissue (WAT) is characterized by white or yellow tissue with less vascularization and innervation than brown tissue. Fat cells are between 20 and 200 µm in size and contain a single lipid vacuole (unilocular). Lipids are stored in this vacuole for use when there is energy demand. Of all the lipids comprising the white adipocyte's lipid vacuole, 90 to 99% are triacylglycerols. White adipose tissue generates a large number of adipokines. Adipokines are peptides that act as hormones or messengers that regulate metabolism. White adipose tissue is in omental, mesenteric, retroperitoneal, perirenal, gonadal, and pericardial tissue [19]. This tissue, like adipose tissue elsewhere, is composed of a variety of cells, including macrophages, neutrophils, CD4 and CD8 T cells, B cells, neutrophils, mast cells, regulatory T cells, and natural killer (NK) T cells [21, 22]. Adipose tissue is responsible for the secretion of many signaling molecules, including adipokines, hormones, cytokines, and growth factors, such as leptin, adiponectin, resistin, tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), monocytes, chemoattractant protein-1 (MCP-1), transforming growth factor-β (TGF-β), and angiotensin II [23].

Brown adipose tissue (BAT)

The brown coloration of adipose tissue is due to its being more vascularized and having a high mitochondrial content. The fat cells that comprise brown adipose tissue are multilocular or have several lipid vacuoles. These cells are polygonal in shape and measure from 15 to 50 µm. Unlike white adipose tissue, brown tissue does not store energy but dissipates it through thermogenesis. To regulate body temperature, brown adipose tissue is located at superficial and deep sites [18].

Classification of CKD-AO

It has been established that obesity is a disease with chronic pro-inflammatory behavior and multiple associated comorbidities [19]. Adipose tissue, as previously described, functions as an endocrine-active organ and is infiltrated by different cell populations that include macrophages and other cells with immune activity, such as T and B lymphocytes and dendritic cells [19]. Most of the total body fat is considered an endocrine organ system, and disturbance of this tissue results in a pathological response to positive caloric balance in susceptible individuals who directly and indirectly contribute to cardiovascular and metabolic disease. Know three main mechanisms of adipose tissue dysfunction "adiposopathy" [20]. These mechanisms include hemodynamic, metabolic, and inflammatory alterations, which are the basis of the obesity-associated CKD classification proposed in this review (Table 1).

CKD-WO type 1

Obesity produces kidney damage directly through hemodynamic and inflammatory alterations, dysregulation of growth factors and adipocytokines, and increased leptin and decreased adiponectin, even when renal function and conventional tests are expected [16]. Obesity triggers a series of events, including insulin resistance, glucose intolerance, hyperlipidemia, atherosclerosis, and hypertension, all of which are associated with increased cardiovascular risk [4, 16] (Figure 1).

Obesity leads to an increase in tubular sodium reabsorption, altering natriuresis and causing extracellular volume expansion due to activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAS) [16]. The increased tubular reabsorption of sodium and the consequent expansion of extracellular volume is a significant event in developing HTN in obesity [4, 16]. Some studies suggest that increased sodium reabsorption occurs in segments other than the proximal tubule, possibly in the loop of Henle. In addition, there is an increase in renal blood flow, glomerular filtration rate (GFR), and filtration fraction [16].

Glomerular hyperfiltration, associated with increased blood pressure and other metabolic disturbances, such as insulin

resistance and diabetes mellitus (DM), ultimately results in kidney damage and decreased glomerular filtration [16]. On the other hand, activation of the sympathetic nervous system (SNS) also contributes to obesity-related hypertension [4]. There is evidence that renal denervation reduces sodium retention and hypertension in obesity, suggesting that obesity-induced SNS activation increases blood pressure primarily due to the stimulation of sodium retention rather than vasoconstriction [16].

The mechanisms that lead to the activation of the SNS in obesity are not yet fully understood, but several factors have been proposed as triggers of this stimulus, including hyperinsulinemia, hyperleptinemia, increased levels of fatty acids, angiotensin II, and alterations of the baroreceptor reflex.

Table 1. Classification of chronic kidney disease associated with obesity (CKD-WO)

Type	Functional alterations	Nephro-pathology	Mortality	Adiponectin
Type 1	Obesity and potentially reversible functional disorders.	No histological alterations.	There are no associated reports.	↓
Type 2	Obesity and potentially non-reversible structural alterations.	Obesity-related glomerulopathy (podocytopathy with glomerular hypertrophy). Focal and segmental glomerulosclerosis.	Directly associated with obesity.	↓↓
Type 3	Obesity-related to chronic diseases	Diabetic nephropathy Nephroangiosclerosis Glomerulopathy is associated with pulmonary hypertension or heart failure.	Doubled by chronic disease. It is the highest mortality of the group.	↓↓↓
Type 4	Obesity in the dialysis patient	-	Effect J: with increased survival at three years.	↑↑↑↑

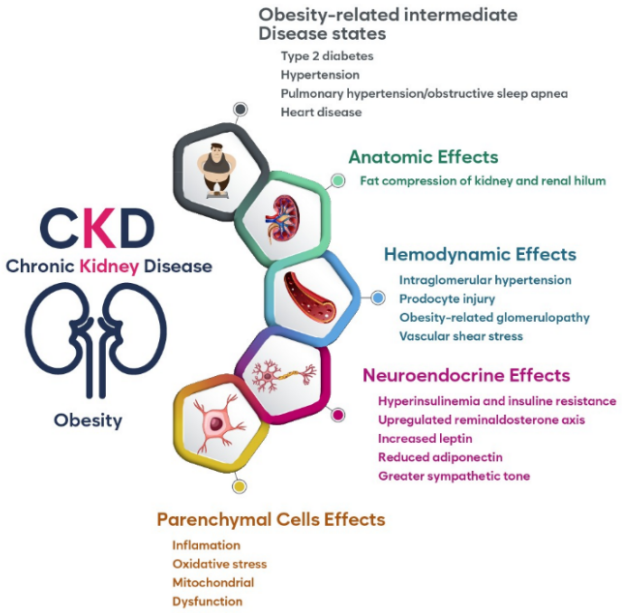

Figure 1 Functional and structural effects of obesity on the kidney

The increase in leptin levels is associated with the activation of the SNS, and its effect on increased blood pressure levels also includes inhibiting nitric oxide synthesis (a potent vasodilator) [16, 24, 25]. An increase in the production of endothelin-1 has been described in obese subjects, which further contributes to the elevation of blood pressure levels and, consequently, to renal dysfunction. Recent studies have shown that endothelin-1 is increased in patients with intradialytic hypertension, suggesting that this substance plays a key role in the genesis of hypertension in CKD patients and is possibly associated with hypertension in obese patients [16, 25]. Therefore, hemodynamic alterations in obese patients lead to CKD progression and increased cardiovascular risk from developing other diseases, such as chronic HTN. These changes are potentially reversible with obesity control.

CKD-AO Type 2

Maintaining the state of obesity beyond the functional renal effects produces irreversible structural changes at the glomerular level [25]. The study of patients with CKD and obesity has made it possible to identify glomerular disease associated with obesity, called obesity-related glomerulopathy (ORG). In this condition, glomerular hypertrophy appears to be the initial injury that stimulates podocyte effacement and triggers the local inflammatory response [25, 26]. It is relevant to mention that profibrogenic signals induce the formation of deposits in the extracellular matrix of nephrons, which leads to the thickening of the basement

membrane glomerulosclerosis and tubulointerstitial fibrosis [26]. Within the pathogenic course of the disease, the expansion of the glomerular surface leads to the podocytes being unable to cover it; this leads to their dysfunction and effacement, generating rupture of the glomerular filtration barrier with an overload of the remaining cells, which ultimately leads to hyperfiltration and proteinuria [25, 26]. However, not all patients with obesity or increased BMI develop CKD, which suggests that the increase in BMI by itself does not generate an increase in the incidence or progression of CKD, requiring additional metabolic alterations; in the following sections, some of these are described of these pathophysiological pathways common to all types of CKD.

CKD-WO Type 3

Obesity produces secondary kidney damage since it increases the risk of diabetes mellitus, hypertension, and cardiovascular damage; these pathologies cause diabetic nephropathy, nephroangiosclerosis, and glomerulopathy associated with pulmonary hypertension and heart failure. Mortality is affected by the presence of obesity and type 2 diabetes, high blood pressure, pulmonary hypertension, and heart failure. Patients with heart failure, obesity, and kidney failure suffer the worst results in survival.

CKD-WO Type 4

Higher levels of adiponectin are paradoxically associated with a threefold increased risk of death in hemodialysis patients [24]. Obesity is associated with shallow levels of adiponectin, so obesity in the hemodialysis population is a solid protective factor, with better 3-year survival results compared with patients with a standard or low body mass index.

Common pathophysiological mechanisms in CKD-AO

Lipotoxicity derived from adipose tissue.

In obese patients, excess energy leads to a chronically stressed microenvironment, which results in adipose tissue hypertrophy until adipocytes reach their growth limit [25]. At that time, the excess of toxic lipid species accumulates ectopically in different organs, inducing a harmful effect known as lipotoxicity, especially at the renal level [27]. Lipotoxicity is associated with structural and functional changes in mesangial, podocytes, and proximal tubular cells [28]. This would interfere with the insulin pathway in podocytes, which is critical for podocyte survival and structure maintenance, leading to podocyte apoptosis and inducing a compensatory hypertrophic response in the remaining podocytes [25].

Ectopic lipid deposits in the kidney contribute to local inflammation and oxidative stress [27]. In diabetic kidney disease and diabetic nephropathy models, dyslipidemia can favor the accumulation of ectopic lipids and lipid intermediates in the kidney and extrarenal tissues such as the liver, pancreas, and heart [27]. The accumulation of lipids in the renal parenchyma generates damage in various cell populations, including podocytes, proximal tubular epithelial cells, and tubulointerstitial tissue, through different mechanisms described in the following sections. It may generate long-term compromise of renal function [27].

Adipose tissue is an essential source of the production of different active protein factors, known as adipocytokines, which participate in different metabolic processes. Alterations in the secretion and signaling of adipose-derived molecules during obesity may predominantly mediate the pathogenesis of metabolic disorders [25]. The role of adipokines in the pathogenesis of CKD and obesity is described below.

Adiponectin

Adiponectin is a protein secreted mainly by WAT adipocytes; the main biological functions of adiponectin include increased fatty acid biosynthesis and inhibition of hepatic gluconeogenesis [17]. It is probably the most abundantly secreted adipokine; it forms approximately 0.05% of serum proteins and measures from 3 to 30 mg/ml in humans; for its activation, it uses two isoforms of the receptor (AdipoR1 and AdipoR2), which are seven transmembrane receptors and have a homology of 66.7% in their structure [17]. However, AdipoR1 and AdipoR2 are structurally and functionally distinct from G protein-coupled receptors because their N-terminus is intracellular, while the C-terminus is extracellular [29,30].

Adiponectin signaling is mainly based on receptor-ligand type interactions, in which adiponectin binds to its cognate receptors and initiates the activation of various intracellular signaling cascades through AMPK, mTOR, NF-κB, STAT3, and JNK [17]. Adiponectin initiates the activation of AMPK signaling mediated by the adapter protein APPL1, which binds to the intracellular domain of AdipoR. This signaling activates the biosynthesis of molecules, other regulatory proteins, and essential transcription factors. AMPK is a regulator mainly involved in cell proliferation [17].

There are two types of macrophages: M1 macrophages participate in stimulating proinflammatory factors and induce insulin resistance, and M2 macrophages block an inflammatory response and promote oxidative metabolism. In macrophages, adiponectin promotes monocyte cell differentiation to M2 macrophages and suppresses their differentiation to M1 macrophages, showing proinflammatory and anti-inflammatory effects. Fur-

thermore, it activates the anti-inflammatory factor IL-10 but reduces proinflammatory cytokines such as IFN-γ, IL-6, and TNF-α in human macrophages [17].

CKD patients show elevated levels of C-reactive protein (CRP), IL-6, and TNF-α and have aberrant activation of toll-like receptor (TLR)-4 [25]. In a study conducted in 2005 in 29 nondiabetic stage 5 CKD patients and 14 healthy controls, it was identified that CKD patients had elevated expression of the TLR4 gene and protein, and stimulation of TLR-4 in vitro induced the activation of TNF-α and NF-κB in C2C12 cells. This activation indirectly suggests that TLR-4 might promote muscle inflammation in CKD patients [31].

Adiponectin levels are considered predictive of CKD since they are increased in predialysis patients with ESRD [17, 2, 9, 32]. Additionally, a 2008 prospective study in nondiabetic primary CKD patients identified elevated adiponectin levels as a novel predictor of CKD progression in men [33]. Animal studies (mice) show that adiponectin deficiency is related to several histological alterations, including segmental fusion podocyte processes, albuminuria, and increased kidney oxidative stress [34].

On the other hand, in obese patients, the production of adiponectin is decreased, which is believed to generate a protective function in the kidney [29]. However, paradoxically, some studies show that patients with CKD and chronic kidney disease on dialysis (CKD) have high levels of adipokines. The explanations for this situation are controversial. It has been suggested that they could correspond to a compensatory mechanism. Other considerations suggest a decreased sensitivity to adiponectin or reduced adiponectin clearance [35].

Leptin

Regardless of the presence of obesity, patients with CKD have high levels of serum leptin. Leptin is a protein of 167 amino acids, with a molecular mass of approximately 16 kDa, encoded by the LEP gene [23], secreted mainly by adipocytes; it is a pleiotropic adipokine. Circulating leptin reaches the target organs, where it binds to specific receptors (known as ObR, LR, or LEPR); five isoforms of the leptin receptor are known in humans (ObRa, ObRb, ObRc, ObRd, and Obie), of which only the ObRb isoform (long isoform) is considered a fully active receptor, as it is capable of fully transducing an activation signal in the cell. This isoform is highly expressed in the central nervous system (CNS), especially in the hypothalamus, where it regulates the secretory activity of this organ. Five major signaling pathways mediate the effects of leptin. These pathways include the JAK-STAT, PI3K, MAPK, AMPK, and mTOR signaling pathways [23].

For this reason, the main physiological function of leptin is to transmit information to the hypothalamus about the amount of energy stored, such as the mass of adipose tissue, and to influence energy expenditure by reducing appetite. It regulates energy metabolism, affects food intake, coagulation processes, angiogenesis, insulin-related functions, and vascular remodeling, and is also a molecular proinflammatory [36].

Leptin affects appetite, and hyperleptinemia has been shown to contribute to obesity-associated hypertension by overactivation of the sympathetic nervous system [37]. Regarding the course of CKD, leptin can modulate different signaling pathways in the kidney because glomerular and mesangial endothelial cells express abundant leptin receptors [25]. Leptin increases the expression of profibrotic genes, such as TGF-β1 and proinflammatory cytokines [25]. The increase in the expression of TGF-β also contributes to the development of renal fibrosis by binding to specific receptors at the renal level; it stimulates the expression of profibrotic factors in a positive feedback loop. In addition, TGF-β1 is a potent initiator of renal mesangial cell proliferation [25].

Due to its relatively small size, leptin freely crosses the kidneys' glomerular filter and is reabsorbed in the proximal convoluted tubules [23]. Thus, elevated leptin status may indicate poor kidney function [36]. It promotes inflammation and lipid disorder, which contribute to CKD risk [36]; it is considered a "uremic toxin," being implicated both in the progression of kidney disease through prehypertensive and profibrotic effects, as well as in the development of complications related to CKD (chronic inflammation, protein loss) [38].

As previously mentioned, leptin stimulates the proliferation of renal glomerular endothelial cells. It increases the expression of TGF-β1, a key mediator of hydrogenation in these cells; the increase in leptin levels also contributes to the increase in the expression of type IV collagen in the kidney and induces glomerular mesangial cell proliferation by activating the PI3K pathway. Mesangial cell hypertrophy increases the amount of filtered protein and albumin reaching proximal tubule cells and, as a result, activates inflammatory pathways and fibrosis [23].

There may be an increase in the synthesis of the TGF β-1 receptor secreted by endothelial cells, which acts in a paracrine manner on the mesangium by binding to its receptor and activating the synthesis of extracellular matrix (ECM) proteins, including collagen, fibronectin, tenazine, and proteoglycans; an increase in the level of TGF β-1 leads to the accumulation of ECM and, consequently, to glomerular fibrosis and glomerulosclerosis. In podocytes, leptin contributes to downregulating proteins responsible for proper glomerular filtration, including podocin, nephrin, podoplanin, and podocalyxin. In proximal convoluted tubule (PTC) cells, leptin reduces the cells' metabolic activity by activating the mTOR signaling pathway [23].

On the other hand, leptin inhibits appetite and increases energy expenditure, leading to anorexia and malnutrition in

CKD patients, particularly in cases of maintenance hemodialysis [36]. Therefore, an elevation of leptin would indicate not only kidney damage but also a more significant progression of secondary complications [39].

Obesity increases the load on the kidneys, is a risk factor for kidney injury, and contributes to associated metabolic disorders. Therefore, taking into account the inhibitory effects of leptin on obesity, it can be considered that it can protect against kidney injury [39, 40]. An experimental study published in 2017 showed that leptin decreased caloric intake and glucose levels in diabetic rats [41], and a retrospective study was published that same year showing that meterleptin, a recombinant human methionyl leptin, reduces the body weight and daily insulin dose in type 1 diabetes mellitus [42]. Meterleptin exerts therapeutic effects in lipodystrophy [43], indicating that leptin is likely to apply in metabolic disorders [36].

Other adipokines

The main adipokines correspond to adiponectin and leptin, as previously described. In addition, visfatin and resistin activity are distinguished, showing proinflammatory properties and atherogenic effects [25]. Visfatin stimulates the expression of TGF-β1, plasmin activator inhibitor or gene-1 (PAI-1), and type I collagen, which has been shown to play an important role as a profibrotic agent. However, resistin stimulates the production of adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1). It promotes the activation of the renal sympathetic system. The levels of these adipokines are markedly elevated in obesity and CKD, correlating with proinflammatory parameters and a decreased glomerular filtration rate (GFR) [25, 37].

During obesity, the renin-angiotensin-aldosterone system (RAS) is overactivated, and adipose tissue produces or stimulates some of its components. Therefore, overstimulation of the RAS in obese patients, associated with glomerulomegaly and dysregulation of sodium/glucose reabsorption, generally leads to glomerular hypertension and hyperfiltration [25].

Another adipokine to consider is the activity of the proinflammatory adipokine lipocalin 2 (LCN2), also called neutrophil gelatinase-associated lipocalin (NGAL), which has been studied as a functional biomarker for both acute kidney disease and CKD(25). LCN2 is known for its role in the innate immune response by binding to siderophores derived from bacterial infection. However, LCN2 is secreted not only by neutrophils but also by other tissues, such as the liver, lungs, and, of interest for this article, the kidney [25]. Elevated serum and urine LCN2 levels have been reported in kidney injury due to increased expression of LCN2 in the distal renal tubule and impaired reabsorption in the proximal tubule [44]. Adipose tissue can also produce angiogenic factors such as vascular endothelial growth factor (VEGF). This element could induce the de novo formation of largely defective glomerular capillaries within the kidney, contributing to the glomerular hypertrophy characteristic of ORG (25) (Figure 2).

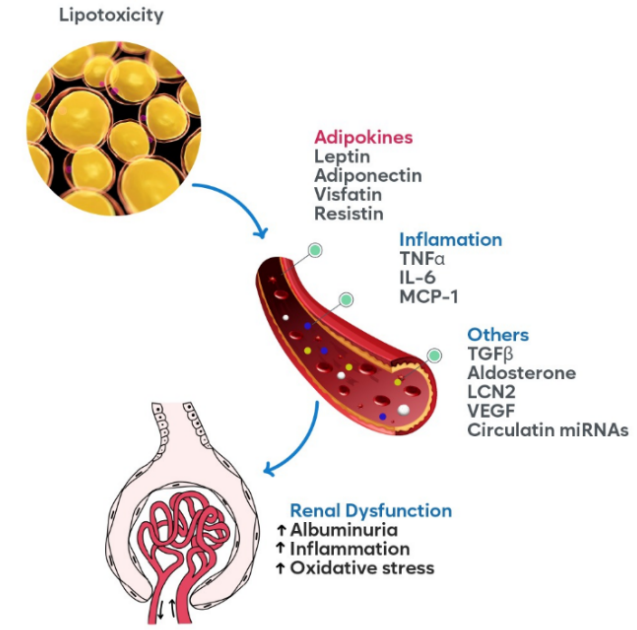

Figure 2. Lipotoxicity and its effect on the kidney

Conclusions

Obesity and overweight are associated with hemodynamic, structural, and histopathological alterations in the kidney and metabolic and biochemical alterations that predispose to kidney disease, even when renal function and conventional tests are normal. Therefore, the renal effects of obesity are structural and functional. Several mechanisms involving obesity as a generator of renal alterations have been described. Considering the pathophysiological bases, we propose a classification of CKD-AO based on four types.

Abbreviations

CKD: chronic kidney disease.
CKD-AO: disease-associated chronic kidney disease.
VEGF: vascular endothelial growth factor.
OR: odds ratio.

Supplementary information

Supplementary materials have not been declared.

Acknowledgments

Does not apply.

Author contributions

Jorge Rico-Fontalvo: Conceptualization, Data Curation, Formal Analysis, Fundraising, Research, Methodology, Project Management, Resources, Software, Writing – original draft.
Rodrigo Daza-Arnedo: Conceptualization, Supervision, Validation, Visualization, Writing: review and editing.
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Juan Camilo Gutiérrez: Conceptualization, Supervision, Validation, Visualization, Writing: review and editing.
All authors read and approved the final version of the manuscript.

Financing
The authors provided research expenses.

Availability of data or materials
The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable academic request.

Statements
Ethics committee approval and consent to participate
Does not apply to narrative reviews.

Consent to publication
It does not apply when images or photographs of the physical examination, X-rays/tomographies/MRIs of patients are not published.

Conflicts of interest
The authors report having no conflicts of interest.

References

1. Azhar A, Hassan N, Tapolyai M, Molnar MZ. Obesity, Chronic Kidney Disease, and Kidney Transplantation: An Evolving Relationship. Week Nephrol. 2021 Mar;41(2):189-200. **DOI**: 10.1016/j.semnephrol.2021.03.013. **PMID**: 34140097.

2. Barbieri D, Goicoechea M, Sánchez-Niño MD, Ortiz A, Verde E, Verdalles U, Pérez de José A, Delgado A, Hurtado E, Sánchez-Cámara L, Lopez- Lazareno N, García -Prieto A, Luño J. Obesity and chronic kidney disease progression-the role of a new adipocytokine: C1q/tumor necrosis factor-related protein-1. Clin Kidney J. 2018 October 11;12 (3):420-426. **DOI**: 10.1093/ckj/sfy095. **PMID**: 31198543; **PMCID**: PMC6543966.

3. Kopp JB, Rosenberg AZ, Levi M. Introduction: Obesity and the kidney. Week Nephrol. 2021Jul;41 (4):295. **DOI**: 10.1016/j.semnephrol.2021.06.001. **PMID**: 34715959.

4. Hall JE, Mouton AJ, da Silva AA, Omoto ACM, Wang Z, Li X, do Carmo JM. Obesity, kidney dysfunction, and inflammation: interactions in hypertension. Cardiovasc Res. 2021 Jul 7;117 (8):1859-1876. **DOI**: 10.1093/cvr/cvaa336. **PMID**: 33258945; **PMCID**: PMC8262632.

5. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022 Apr;12 (1):7-11. **DOI**: 10.1016/j.kisu.2021.11.003. Epub 2022 March 18. **PMID**: 35529086; **PMCID**: PMC9073222.

6. Kovesdy CP, Furth S, Zoccali C; World Kidney Day Steering Committee. Obesity and kidney disease: Hidden consequences of the epidemic. Saudi J Kidney Dis Transpl. 2017 Mar-Apr;28 (2):241-252. **DOI**: 10.4103/1319-2442.202776. **PMID**: 28352003.

7. World Health Organization -WHO. Obesity and overweight [Internet]. **Available at**: https://www.who.int/es/news-room/fact-sheets/detail/obesity-and-overweight

8. Lin X, Li H. Obesity: Epidemiology, Pathophysiology, and Therapeutics. Front Endocrinol (Lausanne). 2021 September 6;12:706978. **DOI**: 10.3389/fendo.2021.706978. **PMID**: 34552557; **PMCID**: PMC8450866.

9. Gorostidi M, Santamaría R, Alcázar R, Fernández-Fresnedo G, Galcerán JM, Goicoechea M, et al. Spanish Society of Nephrology document on KDIGO guidelines for the assessment and treatment of chronic kidney disease. Nephrology. 2014 May 21;34 (3):302-16. English Spanish. **DOI**: 10.3265/Nephrology.pre2014.Feb.12464. Epub 2014 March 6. **PMID**: 24798565.

10. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020 Oct;98 (4S):S1-S115. **DOI**: 10.1016/j.kint.2020.06.019. **PMID**: 32998798.

11. Salvador González B, Rodríguez Pascual M, Ruipérez Guijarro L, Ferré González A, Cunillera Puertolas O, Rodriguez Latre LM. Chronic kidney disease in Primary Care: prevalence and associated risk factors [Chronic kidney disease in Primary Health Care: prevalence and associated risk factors]. Primary Care. 2015 Apr;47 (4):236-45. Spanish. **DOI**: 10.1016/j.aprim.2014.06.003. Epub 2014 September 9. **PMID**: 25212720; **PMCID**: PMC6985625.

12. Lakkis JI, Weir MR. Obesity and Kidney Disease. Program Cardiovasc Dis. 2018 Jul-Aug;61 (2):157-167. **DOI**:

10.1016/j.pcad.2018.07.005. Epub 2018 July 5. **PMID**: 29981350.

13. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013 June 4;158 (11):825-30. **DOI**: 10.7326/0003-4819-158-11-201306040-00007. **PMID**: 23732715.

14. Anderson AH, Xie D, Wang X, Baudier RL, Orlandi P, Appel LJ, et al; CRIC Study Investigators. Novel Risk Factors for Progression of Diabetic and Nondiabetic CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2021Jan;77 (1):56-73.e1. **DOI**: 10.1053/j.ajkd.2020.07.011. Epub 2020 Aug 28. **PMID**: 32866540; **PMCID**: PMC7752839.

15. Friedman AN, Kaplan LM, le Roux CW, Schauer PR. Management of Obesity in Adults with CKD. J Am Soc Nephrol. 2021 February 18;32 (4):777–90. **DOI**: 10.1681/ASN.2020101472. Epub ahead of print. **PMID**: 33602674; **PMCID**: PMC8017542.

16. Silva Junior GB, Bentes AC, Daher EF, Matos SM. Obesity and kidney disease. J Bras Nefrol. 2017 Mar;39 (1):65-69. Portuguese, English. **DOI**: 10.5935/0101-2800.20170011. **PMID**: 28355395.

17. Choi HM, Doss HM, Kim KS. Multifaceted Physiological Roles of Adiponectin in Inflammation and Diseases. Int J Mol Sci. 2020 Feb 12;21 (4):1219. **DOI**: 10.3390/ijms21041219. **PMID**: 32059381; **PMCID**: PMC7072842.

18. Frigolet ME, Gutiérrez-Aguilar R. The colors of adipose tissue. Gac MedMex. 2020;156 (2):142-149. English. **DOI**: 10.24875/GMM.M20000356. **PMID**: 32285854.

19. Chen Y, Dabbas W, Gangemi A, Benedetti E, Lash J, Finn PW, Perkins DL. Obesity Management and Chronic Kidney Disease. Week Nephrol. 2021Jul;41 (4):392-402. **DOI**: 10.1016/j.semnephrol.2021.06.010. **PMID**: 34715968.

20. Neeland IJ, Poirier P, Després JP. Cardiovascular and Metabolic Heterogeneity of Obesity: Clinical Challenges and Implications for Management. Circulation. 2018 March 27;137 (13):1391-1406. **DOI**: 10.1161/CIRCULATIONAHA.117.029617. **PMID**: 29581366; **PMCID**: PMC5875734.

21. Bjørndal B, Burri L, Staalesen V, Skorve J, Berge RK. Different adipose depots: their role in the development of metabolic syndrome and mitochondrial response to hypolipidemic agents. J Obes. 2011;2011:490650. **DOI**: 10.1155/2011/490650. Epub 2011 February 15. **PMID**: 21403826; **PMCID**: PMC3042633.

22. Johnson AR, Milner JJ, Makowski L. The inflammation highway: metabolism accelerates inflammatory traffic in obesity. Immunol Rev. 2012 Sep;249 (1):218-38. **DOI**: 10.1111/j.1600-065X.2012.01151.x. **PMID**: 22889225; **PMCID**: PMC3422768.

23. Korczynska J, Czumaj A, Chmielewski M, Swierczynski J, Sledzinski T. The Causes and Potential Injurious Effects of Elevated Serum Leptin Levels in Chronic Kidney Disease Patients. Int J Mol Sci. 2021 Apr 28;22 (9):4685. **DOI**: 10.3390/ijms22094685. **PMID**: 33925217; **PMCID**: PMC8125133.

24. Goicoechea M. Obesity and Progression of Kidney Disease. Nephrology up to date 2022(February): nephrology_al_dia

25. Martin - Taboada M, Vila - Bedmar R, Medina-Gómez G. From Obesity to Chronic Kidney Disease: How Can Adipose Tissue Affect Renal Function? Nephron. 2021;145 (6):609-613. **DOI**: 10.1159/000515418. Epub 2021 April 21. **PMID**: 33882488.

26. D'Agati VD, Chagnac A, de Vries AP, Levi M, Porrini E, Herman-Edelstein M, Praga M. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. Nat Rev Nephrol. 2016 Aug;12 (8):453-71. **DOI**: 10.1038/nrneph.2016.75. Epub 2016 June 6. **PMID**: 27263398.

27. Opazo - Ríos L, Mas S, Marín-Royo G, Mezzano S, Gómez-Guerrero C, Moreno JA, Egido J. Lipotoxicity and Diabetic Nephropathy: Novel Mechanistic Insights and Therapeutic Opportunities. Int J Mol Sci. 2020 Apr 10;21 (7):2632. **DOI**: 10.3390/ijms21072632. **PMID**: 32290082; **PMCID**: PMC7177360.

28. Zhu Q, Scherer PE. Immunologic and endocrine functions of adipose tissue: implications for kidney disease. Nat Rev Nephrol. 2018 Feb;14 (2):105-120. **DOI**: 10.1038/nrneph.2017.157. Epub 2017 December 4. **PMID**: 29199276.

29. Akingbemi BT. Adiponectin receptors in energy homeostasis and obesity pathogenesis. Program mole Biol Transl Sci. 2013;114: 317-42. **DOI**: 10.1016/B978-0-12-386933-3.00009-1. **PMID**: 23317789.

30. Zha D, Wu X, Gao P. Adiponectin and Its Receptors in Diabetic Kidney Disease: Molecular Mechanisms and Clinical Potential. Endocrinology. 2017 July 1;158 (7):2022-34. **DOI**: 10.1210/en.2016-1765. **PMID**: 28402446.

31. Verzola D, Bonanni A, Sofia A, Montecucco F, D'Amato E, Cademartori V, Parodi EL, Viazzi F, Venturelli C, Brunori G,

Garibotto G. Toll-like receptor 4 signaling mediates inflammation in skeletal muscle of patients with chronic kidney disease. J Cachexia Sarcopenia Muscle. 2017 Feb;8 (1):131-144. **DOI**: 10.1002/jcsm.12129. Epub 2016 October 18. **PMID**: 27897392; **PMCID**: PMC5326826.

32. Guebre-Egziabher F, Drai J, Fouque D. Adiponectin and chronic kidney disease. J Ren Nutr. 2007Jan;17 (1):9-12. **DOI**: 10.1053/j.jrn.2006.10.003. **PMID**: 17198925.

33. Kollerits B, Fliser D, Heid IM, Ritz E, Kronenberg F; MMKD Study Group. Gender-specific association of adiponectin as a predictor of progression of chronic kidney disease: the Mild to Moderate Kidney Disease Study. Kidney Int. 2007 Jun;71 (12):1279-86. **DOI**: 10.1038/sj.ki.5002191. Epub 2007 April 25. **PMID**: 17457380.

34. Sharma K, Ramachandrarao S, Qiu G, Usui HK, Zhu Y, Dunn SR, Ouedraogo R, Hough K, McCue P, Chan L, Falkner B, Goldstein BJ. Adiponectin regulates albuminuria and podocyte function in mice. J Clin Invest. 2008 May;118 (5):1645-56. **DOI**: 10.1172/JCI32691. **PMID**: 18431508; **PMCID**: PMC2323186.

35. Navarro-Díaz M, Serra A, López D, Granada M, Bayés B, Romero R. Obesity, inflammation, and kidney disease. Kidney Int Suppl. 2008 Dec; (111):S15-8. **DOI**: 10.1038/ki.2008.518. **PMID**: 19034319.

36. Mao S, Fang L, Liu F, Jiang S, Wu L, Zhang J. Leptin and chronic kidney diseases. J Recept Signal Transduct Res. 2018 Apr;38 (2):89-94. **DOI**: 10.1080/10799893.2018.1431278. Epub 2018 February 1. **PMID**: 29388492.

37. Briffa JF, McAinch AJ, Poronnik P, Hryciw DH. Adipokines as a link between obesity and chronic kidney disease. Am J Physiol Renal Physiol. 2013 Dec 15;305 (12):F1629-36. **DOI**: 10.1152/ajprenal.00263.2013. Epub 2013 October 9. **PMID**: 24107418.

38. Katsiki N, Mikhailidis DP, Banach M. Leptin, cardiovascular diseases, and type 2 diabetes mellitus. Minutes Pharmacol Sin. 2018Jul;39 (7):1176-1188. **DOI**: 10.1038/aps.2018.40. Epub 2018 June 7. **PMID**: 29877321; **PMCID**: PMC6289384.

39. de Luis DA, Perez Castrillón JL, Dueñas A. Leptin and obesity. Minerva Med. 2009 Jun;100 (3):229-36. Epub 2008 Apr 4. **PMID**: 19182739 .

40. Mao S, Fang L, Liu F, Jiang S, Wu L, Zhang J. Leptin and chronic kidney diseases. J Receive Signal Transduct Res 2018 Apr; 38(2):89-94. **DOI**: 10.1080/10799893.2018.1431278. **PMID**: 29388492

41. da Silva AA, Hall JE, do Carmo JM. Leptin reverses hyperglycemia and hyperphagia in insulin-deficient diabetic rats by pituitary-independent central nervous system actions. PLoS One. 2017 Nov 30;12 (11):e0184805. **DOI**: 10.1371/journal.pone.0184805. **PMID**: 29190687; **PMCID**: PMC5708697.

42. Vasandani C, Clark GO, Adams.HUet B, Quiiner C, Garg A. Efficacy and Safety of Meterleptin Therapy in Patients With Type 1 Diabetes: A Pilot Study. Diabetes care 2017 May;40 (5):694-697. **PMID**: 28223297

43. Brown RJ, Meehan CA, Cochran E, Rother KI, Kleiner DE, Walter M, Gorden P. Effects of Meterleptin in Pediatric Patients With Lipodystrophy. J Clin Endocrinol Metab. 2017 May 1;102 (5):1511-1519. **DOI**: 10.1210/jc.2016-3628. **PMID**: 28324110; **PMCID**: PMC5443330.

44. Abella V, Scotece M, Conde J, Gómez R, Lois A, Pino J, Gómez-Reino JJ, Lago F, Mobasheri A, Gualillo O. The potential of lipocalin-2/NGAL as biomarker for inflammatory and metabolic diseases. Biomarkers. 2015;20 (8):565-71. **DOI**: 10.3109/1354750X.2015.1123354. Epub 2015 December 15. **PMID**: 26671823; **PMCID**: PMC4819811.

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