

# Impact of adipose tissue in chronic kidney disease development (Review)

DANIELA MIRICESCU<sup>1\*</sup>, DANIELA GABRIELA BALAN<sup>2\*</sup>, ADRIAN TULIN<sup>3,4</sup>, OVIDIU STIRU<sup>5,6</sup>, ILEANA ADELA VACAROIU<sup>7,8</sup>, DOINA ANDRADA MIHAI<sup>9,10</sup>, CRISTIAN CONSTANTIN POPA<sup>11,12</sup>, MIHALY ENYEDI<sup>3,13</sup>, ANDREI SORIN NEDELEA<sup>14</sup>, ADRIANA ELENA NICA<sup>15</sup> and CONSTANTIN STEFANI<sup>16\*</sup>

<sup>1</sup>Department of Biochemistry, <sup>2</sup>Discipline of Physiology, Faculty of Dental Medicine, and <sup>3</sup>Department of Anatomy, Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest;

<sup>4</sup>Department of General Surgery, 'Prof. Dr. Agrippa Ionescu' Clinical Emergency Hospital, 011356 Bucharest;

<sup>5</sup>Department of Cardiovascular Surgery, Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest; <sup>6</sup>Department of Cardiovascular Surgery, 'Prof. Dr. C.C. Iliescu' Emergency Institute for Cardiovascular Diseases, 022322 Bucharest; <sup>7</sup>Department of Nephrology and Dialysis, 'Sf. Ioan' Emergency Clinical Hospital, 042122 Bucharest; <sup>8</sup>Department of Nephrology, <sup>9</sup>Discipline of Diabetes, Nutrition and Metabolic Diseases, Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest; <sup>10</sup>Department II of Diabetes, 'Prof. N. Paulescu' National Institute of Diabetes, Nutrition and Metabolic Diseases, 020474 Bucharest;

<sup>11</sup>Department of Surgery, Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest;

<sup>12</sup>Department of Surgery, Bucharest Emergency University Hospital, 050098 Bucharest; <sup>13</sup>Department of Radiology, 'Victor Babes' Private Medical Clinic, 030303 Bucharest; <sup>14</sup>Department of Urology,

'Prof. Dr. Agrippa Ionescu' Clinical Emergency Hospital, 011356 Bucharest; <sup>15</sup>Department of Orthopedics, Anesthesia Intensive Care Unit, Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest; <sup>16</sup>Department of Family Medicine and Clinical Base,

Dr. Carol Davila Central Military Emergency University Hospital, 010825 Bucharest, Romania

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**Abstract.** Obesity is a worldwide pandemic health issue. Obesity is associated with the pathogenesis of type 2 diabetes, hypertension, dyslipidemia, cardiovascular diseases, cancer, and kidney diseases. This systemic disease can affect the kidneys by two mechanisms: Indirectly through diabetes mellitus (DM) and hypertension and directly through adipokines secreted by adipose tissue. Obesity is a risk factor for chronic kidney disease (CKD), which is associated with an increased risk of morbidity and mortality among the adult population. Increased visceral adipose tissue leads to

renal glomerular hyperfiltration and hyperperfusion, which may lead to glomerular hypertrophy, proteinuria, and CKD development. Adipokines are hormones produced by fat tissue. They are involved in energy homeostasis, sugar and fat metabolism, reproduction, immunity, and thermogenesis control. Hormones and cytokines secreted by adipose tissue contribute to the development and progression of CKD. Decreased serum or urinary adiponectin levels are specific in diabetic and non-diabetic CKD patients, while leptin presents increased levels, and both are associated with the development of glomerulopathy. Excessive adipose tissue is associated with inflammation, oxidative stress (OS), insulin resistance and activation of the renin angiotensin-aldosterone system (RAAS). Therefore, adipose tissue dysfunction plays an important role in the development of CKD.

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*Correspondence to:* Dr Daniela Gabriela Balan, Discipline of Physiology, Faculty of Dental Medicine, 'Carol Davila' University of Medicine and Pharmacy, 37 Dionisie Lupu Street, 020021 Bucharest, Romania  
E-mail: gdaniela.balan@yahoo.com

\*Contributed equally

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## 1. Introduction

The kidney is responsible for multiple vital functions in the body. It regulates blood volume and pressure, reabsorbs nutrients, excretes wastes, and secretes hormones (1,2). Thyroid hormones are involved in renal development, kidney hemodynamics, glomerular filtration rate (GFR), sodium, and water homeostasis. Hypothyroidism and hyperthyroidism affect renal function (3). Acute kidney injury (AKI), chronic kidney disease (CKD), end stage renal disease (ESRD), kidney stones and kidney cancer-renal cell carcinoma, represent major kidney pathologies (3-6). AKI and CKD are associated with an increased risk of morbidity and mortality. AKI is a rapid and reversible decline in renal function and evolves rapidly to CKD (7). This acute renal injury is diagnosed based on an increase in the serum creatinine level of above  $\geq 0.3$  mg/dl ( $\geq 26.5$   $\mu$ mol/l) within 48 h; an increase in serum creatinine to  $\geq 1.5$  times baseline; or urine volume  $< 0.5$  ml/kg/h for 6 h (8). Drugs (including non-steroidal anti-inflammatory compounds), toxins, diuretics, sepsis, age, genetic factors, race, diabetes mellitus (DM), and hypertension are risk factors for AKI, which may lead to reduced GFR and further to acute tubular cell destruction (9). Worldwide, CKD is an urgent medical issue, with a rapidly increasing incidence particularly in diabetic and hypertensive patients, predisposing these patients to diabetic nephropathy, hypertensive nephrosclerosis and focal and segmental glomerulosclerosis (10-14). Anemia, dyslipidemia, malnutrition, mineral and bone disorders, are the most common complications in CKD patients (15).

The presence of albuminuria or estimated GFR (eGFR) from serum creatinine  $< 60$  ml/min/1.73 m<sup>2</sup>, is the main diagnostic criterion for CKD (16). According to the Kidney Disease Quality Outcome Initiative (K/DOQI), CKD is defined as kidney damage or GFR less than 60 ml/min/1.73 m<sup>2</sup> for 3 months or more, irrespective of the cause (17). GFR is measured from calibrated serum creatinine and estimating equations, such as the Modification of Diet in Renal Disease (MDRD) study equation or the Cockcroft-Gault formula (17).

Albuminuria is the most commonly used marker to reflect kidney damage, and elevated levels are associated with an increased risk of CKD and ESRD, independent of eGFR. Based on severity, albuminuria is classified as A1 (albuminuria  $< 30$  mg/g-optimal or normal), A2 (albuminuria 30-300 mg/g-high) and A3 (albuminuria  $> 300$  mg/g-very high) (18).

Previous studies have previously described CKD stages (18-21). CKD is an independent risk factor for many systemic disorders such as, angina, acute myocardial infarction, heart failure, stroke, peripheral vascular disease, and arrhythmias (13). According to the World Health Organization (WHO), obesity is considered a disease (22). In the Western world, obesity rates are increasing rapidly, which mirrors the increase in comorbidities such as cancer, cardiovascular diseases, diabetes, and CKD (22). Obesity is involved in the progression of CKD in two ways: Indirectly through DM and hypertension or directly through adipose tissue (13,22-26). According to the WHO, the definition of obesity is based on body mass index (BMI) as follows: Underweight ( $< 18.5$  kg/m<sup>2</sup>), normal weight (18.5-25 kg/m<sup>2</sup>), overweight (25-30 kg/m<sup>2</sup>) and

obese ( $> 30$  kg/m<sup>2</sup>), obese class I (30.0-34.9 kg/m<sup>2</sup>), obese class II (35-39.9 kg/m<sup>2</sup>) and obese class III ( $> 40$  kg/m<sup>2</sup>) (27). Between 1975 and 2016, the worldwide incidence of obesity was found to triple, with a high prevalence of overweight individuals (over 30%) and obesity (over 10%) (27). Moreover, childhood obesity is currently increasing worldwide (27, 28). In Europe, one child out of 3 is overweight or obese, and over 60% of them will be overweight before puberty or overweight in early adulthood (27,28).

Initially, adipose tissue was considered a passive reservoir for energy storage, involved in mechanical and heat insulation, involved in thermogenesis regulation. However, adipose tissue secretes various bioactive peptides, called 'adipokines', which are involved in both autocrine/paracrine and endocrine activity (29). Thus, adipose tissue may directly affect the kidney through its endocrine activity via the production of adiponectin, leptin, and other adipokines (22).

## 2. Obesity and CKD

Increased body weight is associated with lower urine pH, increased urinary oxalate and the excretion of sodium, phosphate, and uric acid (30-32). Obesity is also involved in nephrolithiasis pathogenesis (33,34).

Studies have revealed that individuals presenting with no kidney disease but with higher BMI, develop proteinuria (22,35). Patients who do not present with DM and hypertension, but who present with juvenile obesity, may present a 3-fold increased risk of CKD (36). Fox *et al* published the results of a study over a 19-year period involving 2,585 individuals. The authors observed that BMI predicted new onset kidney diseases (37). In patients with pre-existing CKD, it was also observed that increased levels of BMI led to a rapid progression of CKD (22). In obesity, the kidneys are compressed by increased visceral and retroperitoneal fat, which may increase blood pressure. Moreover, excess fat accumulation in and around the kidneys conduces to increased intra-renal pressure, impaired pressure natriuresis, and hypertension (38). In patients with visceral obesity, intra-abdominal pressure rises to 35-40 mmHg, in proportion to sagittal abdominal diameter, which leads to compression of the renal veins, lymph vessels, ureters and renal parenchyma. Increased sagittal abdominal diameter is associated with increased intra-abdominal pressure which leads to obesity-related comorbidity, such as type II diabetes, hypertension, and CKD (39).

Previous studies performed on obese dogs, rabbits and even humans have demonstrated that retroperitoneal fat encapsulates the kidneys, adheres tightly to the renal capsule, and invades the renal sinuses, causing additional compression and increasing intra-renal pressure (40,41). Animals fed a hypercaloric diet, such as rabbits, accumulate fat in the renal sinuses, followed by the distortion and prolapse of the renal medullary ducts of Bellini, and urinary outflow restriction (42,43). In obese adults, a higher amount of retroperitoneal and renal sinus fat is associated with hypertension. Moreover, higher BMI seems to be correlated with a decrease in GFR, which will conduce over time to a rapid loss of GFR, and an increased incidence of ESRD (44). In obese adults, central obesity is associated with a 70% increased risk of microalbuminuria when compared with lean adults (45).

Obesity can alter renal hemodynamics through two pathogenic mechanisms: Glomerular hyperperfusion and hyperfiltration (46,47). To describe glomerular hyperperfusion and hyperfiltration, Henegar *et al* conducted a study on non-obese dogs fed a high-fat diet for 7-9 or 24 weeks. The study reported increased blood pressure, pulse rate, GFR and renal plasma flow in the obese vs. the lean dogs. Increased plasma levels of insulin and renin were detected in dogs treated with the fat diet, compared with the control group. The histological analysis revealed enlarged Bowman's space, increased glomerular cell proliferation, increased mesangial expression, thickening of the basement membranes and even higher expression for renal transforming growth factor (TGF)- $\beta$ . Interestingly, the study did not find any association between the glomerulosclerosis score of the obese dogs and the lean dogs. Acute obesity did not conduce to renal scarring, instead chronic obesity was involved in renal scarring (46). Chronic obesity contributes to CKD progression by glomerular hyperfiltration, microalbuminuria/proteinuria development, hypofiltration and decreased GFR (48-50).

Ectopic lipid accumulation, together with renal sinus fat accumulation, may lead to glomerular hypertension development and increased glomerular permeability, caused by the hyperfiltration associated with glomerular filtration barrier damage, leading to glomerulomegaly and focal or segmental glomerulosclerosis (51-54).

Glomerular hyperfiltration, glomerular hypertrophy and increased filtration fraction promote proteinuria and glomerulosclerosis, processes that further stimulate the renin angiotensin-aldosterone system (RAAS), release of TGF- $\beta$ , a cascade of events that cause kidney damage (55).

Adipose tissue expresses all RAAS components; angiotensin receptors 1 and 2 are present in human and animal adipocytes (56,57). Sodium retention and aldosterone secretion are normal RAAS functions, but in adipose tissue it may be involved in obesity-related hypertension. Moreover, adipocytes from inflamed visceral and perivascular tissues are involved in RAAS activation (58). In obese individuals, increased levels of angiotensin II, directly contribute to the increase in oxidant stress (OS) at the vascular level (59). Boustany *et al* conducted a study on rats fed a high-fat diet for 11 weeks to induce obesity. The results of the study revealed higher systemic blood pressure, increased levels of the plasmatic angiotensin and angiotensin gene expression in the retroperitoneal adipose tissue (60).

In patients with metabolic syndrome, which is characterized by the presence of hypertension, dyslipidemia and insulin resistance, angiotensin II presents higher levels (61). Adipocytes may contribute up to 30% to the production of circulating angiotensinogen II (58). Increased angiotensin II levels affect renal hemodynamic, contributing to hyperfiltration, glomerulomegaly, and further focal glomerulosclerosis via afferent arteriolar dilation. Moreover, afferent renal arteriolar vasoconstriction, angiotensin II with endocrine and paracrine properties, links the intrarenal and the systemic RAAS. Adipose tissue dysfunction, together with insulin resistance and hypertension contributes to CKD development and eventually to ESRD (61). In vascular tissue, aldosterone may induce mineralocorticoid receptor activation, promoting vascular stiffness caused by oxidative stress (OS) (62), inflammation (63), maladaptive immune modulation, and fibrosis (58).

### 3. Adipose tissues as an endocrine organ

White adipose tissue exhibits endocrine, paracrine, and autocrine activities. The adipocytes secreted are involved in body weight regulation (leptin and adiponectin), in local inflammation (TNF- $\alpha$ , IL-6 and IL-1 $\beta$ ), in vascular function and even in breeding (64). Cytokines, hormones, leptin, and adiponectin are secreted also by brown adipose tissue, which acts as an endocrine organ (64). The last form of adipose tissue, perivascular adipose tissue, is located around the coronary artery, the aorta (periaortic adipose tissue), and the microcirculatory bed of the kidney and adipose tissue, which releases adiponectin, leptin, interleukin (IL)-6, and tumor necrosis factor (TNF)- $\alpha$ . In men, the most common form of obesity is central or abdominal obesity, and consists of an accumulation of visceral adipose tissue (64). According to various studies, this type of obesity has been associated, with a higher risk of diseases such as insulin resistance, type 2 diabetes, and cardiovascular risk (65-67). Adipose tissue presents a variety of cell populations such as macrophages, endothelial cells, fibroblasts, and leukocytes (64). Hypercaloric diet consumption induces lipid accumulation in adipocytes, triggering cellular stress and activation of c-Jun N-terminal kinase (JNK) and nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells (NF- $\kappa$ B) signaling pathways (64). These inflammatory signaling pathways are involved in the phosphorylation of different proteins and transcriptional factors, causing an increased secretion of proinflammatory molecules (TNF- $\alpha$ , IL-6), leptin, chemokines [monocyte chemoattractant protein 1 (MCP-1)], and proatherogenic mediators [plasminogen activator inhibitor-1 (PAI-1)] (64). Obesity can be defined as a proinflammatory state of low grade, where the adipokine secretion increases with visceral fat mass. IL-6 and TNF- $\alpha$  activate the production of other inflammatory cytokines, such as C-reactive protein (CRP) (59,64). Inflammation is associated with leukocyte infiltration, via NADPH oxidase and reactive oxygen species (ROS) generation. Hydroxyl radical (HO $\cdot$ ), anion superoxide radical (O $_2^{\cdot-}$ ) and hydrogen peroxide (H $_2$ O $_2$ ) are ROS generated by inflammatory pathways, adipokine increased levels (leptin) and leukocyte infiltration in white adipose tissue (59). In isolated adipocytes, it was reported that TNF- $\alpha$  suppresses insulin signal transduction and expression of the insulin receptor, leading to hyperglycemia, and even to pancreatic  $\beta$ -cell destruction. Hyperglycemia induces OS (59).

Obesity stimulates the production of leptin, which further increases OS, activity of the sympathetic nervous system (SNS) similar to sleep deprivation (68) leading to glomerulosclerosis, renal fibrosis and finally proteinuria (69). In obese patients, renal compression conduces to increased sodium reabsorption, promoting renal vasodilatation, glomerular hyperfiltration, and increased renin secretion (38). Fat accumulation in and around the kidney, leads to OS, mitochondrial dysfunction, and endoplasmic reticulum stress (70).

### 4. Adiponectin and CKD

Adipocytes secrete adiponectin, a 26.4-kDa protein, which presents in healthy individuals and has anti-inflammatory, anti-atherogenic and insulin-sensitizing properties, being involved in lipid and glucose metabolism, partially through

activation of AMPK (69,71). Decreased levels of adiponectin are associated with several systemic disorders such as insulin resistance, obesity, type II diabetes (early stages) and dyslipidemia (72). Adiponectin levels are significantly decreased in obesity, being negatively correlated with the percent of fat mass (72). Based on distributions and molecular affinities of adiponectin complexes, adiponectin presents two receptors. Adiponectin receptor 1 (AdipoR1) is mainly expressed in skeletal muscle and is moderately expressed in other tissues, such as heart and brain (73). At the renal level, AdipoR1 is found in the glomerulus and proximal tubule. AdipoR2 is predominantly expressed in the liver. Adiponectin binds to AdipoR1 and AdipoR2 and further activates the AMPK signaling pathway which is involved in energy homeostasis (73). Moreover, adiponectin activates *in vitro* the MAPK signaling pathway, increasing glucose uptake (73).

Kuo and co-researchers conducted a study which included 196 non-diabetic CKD patients with eGFR ranging between 10 and 60 ml/min/1.73 m<sup>2</sup>, divided into two groups based on the presence of metabolic syndrome. The study reported, over a period of 5 years, 48 (24.5%) incident cases of end-stage renal disease (ESRD) and 33 (16.8%) deaths. Adiponectin levels were inversely related to BMI ( $r=-0.29$ ;  $P<0.001$ ) and waist circumference ( $r=-0.35$ ;  $P<0.001$ ). A decreased adiponectin level was associated with a higher risk of ESRD independent of conventional risk factors, BMI, and even metabolic syndrome (74).

Coimbra *et al* studied 194 ESRD patients on dialysis and 22 controls and evaluated the lipid profile [lipoprotein subpopulations and oxidized LDL (oxLDL)], CRP, adiponectin, leptin, and paraoxonase 1 activity. In diabetic and obese patients ( $n=45$ ) they observed the lowest values for adiponectin vs. the normoponderal patients ( $n=81$ ) (75). Yaturu *et al* studied 43 subjects with CKD and 34 control subjects and evaluated plasma and urinary levels of adiponectin. In patients with CKD, the plasma levels of adiponectin were not decreased compared with the controls. The study revealed a negative correlation between urinary adiponectin levels and GFR ( $r=-0.4$ ;  $P<0.05$ ) and a positive correlation with plasma adiponectin levels ( $r=0.9$ ;  $P<0.0001$ ) (76). Moreover, increased consumption of sugars was found to lead to obesity (77) and further to a decreased level of adiponectin (72).

Regarding anti-inflammatory effects, adiponectin was found to suppress IL-6 and TNF- $\alpha$  expression, which are activated by NF- $\kappa$ B. Adiponectin was found to bind to its two receptors and to activate adaptor protein containing a pleckstrin homology domain 1 (APPL1) (78). Once activated, APPL1 was found to further activate peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ) and phosphorylation of 5'activated protein kinase (AMPK), and mitogen-activated protein kinase (p38-MAPK) was found to occur (78). Phospho-AMPK downstream was found to phosphorylate acetyl-CoA carboxylase (ACC), promote fatty acid oxidation, and inhibit lipogenesis. Phosphorylation of endothelial nitric oxide synthase (eNOS) by AMP was found to stimulate NO production, which results in vasodilation (78). In inflammation, adiponectin presents a cytoprotective effect, activates AMP, suppresses mammalian target for rapamycin (mTOR) and the inhibitor of nuclear factor  $\kappa$ B kinase subunit  $\gamma$ -phosphatase and tensin homology (IKK-NF- $\kappa$ B-PTEN) signaling pathways (78). The

phosphatidylinositol 3-kinase-protein kinase B (PI3K-AKT) signaling pathway controls the metabolic effects of insulin, which is involved in glycogen synthesis, increases glucose uptake, inhibits lipolysis also being involved in other physiological processes such as motility (78). Adiponectin may activate insulin receptor substrate  $\frac{1}{2}$  (IRS1/2) increasing insulin sensitivity (78).

Hypoadiponectinemia is associated with CKD. A potential mechanism for this was identified in mice presenting with hypoadiponectinemia. These mice exhibit podocyte fusion with adiponectin treatment improving the glomerular podocyte foot processes via activation of AMPK, which downregulates podocyte NADPH oxidase (Nox)4. Importantly, these mice exhibit albuminuria, clearly demonstrating a link between hypoadiponectinemia and kidney dysfunction (79). Moreover, podocytes present AdipoR1, an alteration of the receptor that may lead to obesity-related dysfunction. Increased urinary levels of both the low- and high-molecular-weight isoforms of adiponectin were detected in patients with established kidney disease and patients with type 2 diabetes (79). *In vivo*, it has been observed that only a week of consuming a high-fat diet, contributes to kidney inflammation, which is associated with albuminuria, and further triggers urinary excretion of monocyte chemotactic protein (MCP-1) and H<sub>2</sub>O<sub>2</sub> (79).

## 5. Leptin and CKD

Leptin is a small peptide hormone, secreted mainly by visceral, subcutaneous, and pericardial adipose compartments, but can be produced even by normal human osteoblasts, subchondral osteoblasts, placental syncytiotrophoblasts, and the gastric epithelium. This hormone regulates bone metabolism and food intake after it binds to its receptors in the hypothalamus (80). Moreover, leptin exhibits additional important metabolic effects on peripheral tissues of liver, skeletal muscle, and bone marrow. In CKD patients, serum levels of leptin are increased with a decline in GFR. Leptin may be implicated in patients with CKD in hematopoiesis, nutrition, and bone metabolism. Increased leptin levels seem to be a risk factor for CKD development (80).

Shankar *et al* conducted a large cross-sectional study which included 5,000 patients, and revealed that the risk of CKD development significantly increases as blood levels of leptin rise (81). Leptin may be involved in CKD pathogenesis and progression through two mechanism. First, by stimulating the sympathetic nervous system, it promotes renal sodium reabsorption and increases blood pressure. Second, leptin may induce renal injury by stimulating renal endothelial cell proliferation, increased mesangial cell production, which leads to renal scarring by collagen type I and IV production, renal fibrosis, and proteinuria (81-84).

Canpolat *et al* studied CKD patients divided into four groups (patients with non-dialysis, dialysis, kidney transplant and control group) and evaluated levels of leptin. Plasma levels of leptin did not differ at all in the four mentioned groups (85). Noor and co-researchers conducted a cross-sectional study at the Nephrology Department of Jinnah Post Graduate Medical Center from January 2014 to September 2014, which included CKD patients divided by GFR values in II, III, and IV stages. The study excluded CKD patients with DM, steroid therapy

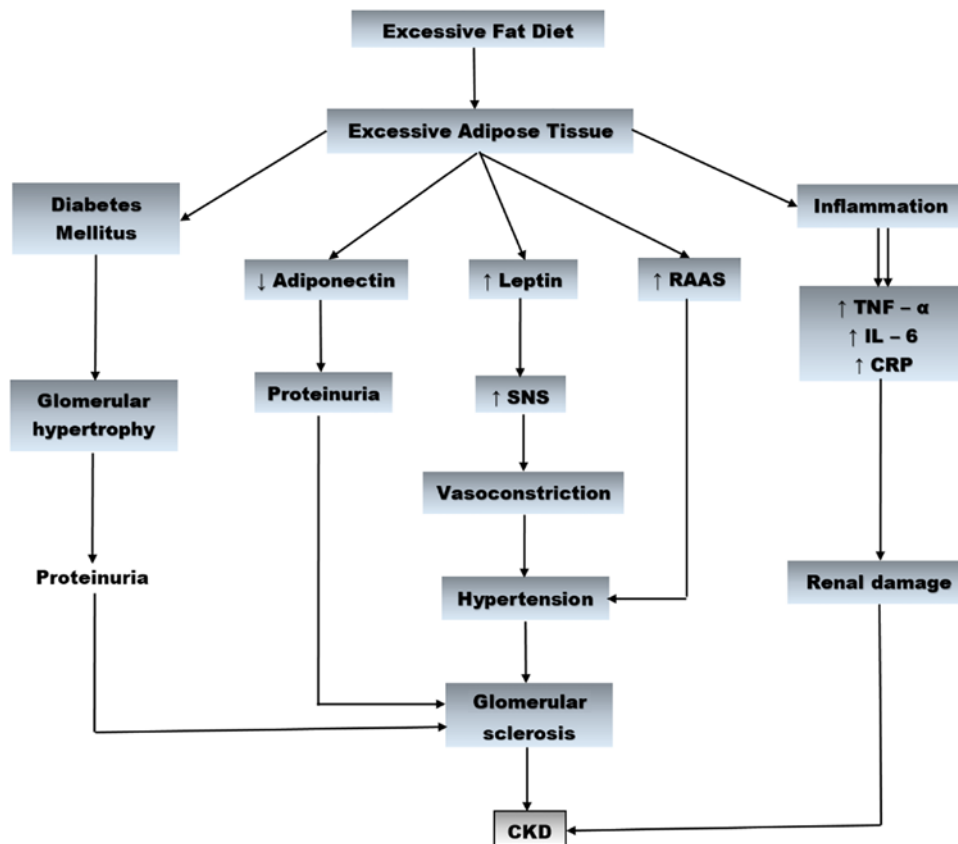


Figure 1. The involvement of obesity in the pathophysiology of CKD [image adapted from Silva and Matos (92)]. CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system; TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; SNS, sympathetic nervous system.

and any inflammatory disease. Serum leptin, CRP, and lipid profile (HDL, LDL) were measured. The serum levels of leptin and CRP were increased with CKD progression. The control group presented increased HDL/LDL ratio vs. the CKD group ( $P < 0.001$ ). Leptin presented a positive correlation with CRP ( $r = 0.994$ ;  $P < 0.001$ ), suggesting that inflammation contributes to hyperleptinemia, and a negative correlation with HDL/LDL ratio ( $r = -0.403$ ;  $P < 0.001$ ) was also observed (86).

Studies performed *in-vitro* and in animals have demonstrated that leptin and adiponectin may mediate pathological and functional changes in renal parenchyma (87,88). Elevated leptin levels have also been detected in diabetic and obese non-diabetic CKD patients (89,90). Korczyńska *et al* reported that leptin gene expression from subcutaneous adipose tissue of patients with CKD contributes to elevated serum leptin levels. In patients with CKD, serum levels of leptin were three times higher both in men and women, compared with healthy controls. In CKD women, serum leptin levels were two times higher than in men. The study also revealed that the mRNA level for leptin gene expression from subcutaneous adipose tissue of CKD patients was three times higher compared with that noted in the controls. In addition, total saturated fatty acids (SFA) and monounsaturated FA (MUFA) presented higher serum levels in CKD patients vs. the control group. Serum levels of total n-3 polyunsaturated FAs (n-3PUFAs) and n-6 polyunsaturated (n-6 PUFAs) were decreased in patients with CKD vs. healthy controls. To test whether the serum FA has an impact on adipose leptin gene expression, 3T3-L1 adipocyte cells were treated with various FAs; such as

SFA (palmitic acid 16:0; PA), MUFA (oleic acid 18:1, OA), n-3 PUFA (docosahexaenoic acid 22:6 n-3 DHA) and n-6 PUFA (arachidonic acid 20:4 n-6 AA) at different concentrations. After 48 h of incubation with PA and OA, it was observed that FAs, which were increased in serum CKD patients, contributed to elevated leptin gene expression. Instead, DHA and AA FAs, which were decreased in the serum of patients with CKD, had decreased expression of the leptin gene (91). Collectively, inflammation, OS, RAAS activation, changes in leptin and adiponectin levels, increased secretion of insulin and insulin resistance, contribute to CKD development (Fig. 1).

## 6. Conclusions

Diabetic and hypertensive overweight and obese patients present an increased risk to develop CKD. Higher amounts of fat in diet leads to renal fat accumulation, which is associated with hypertension. Obesity affects renal hemodynamic by increasing blood pressure, pulse rate, and RAAS activity, by reducing GFR and by inducing histological perturbations. Decreased adiponectin level, increased leptin level, increased secretions of proinflammatory cytokines and activation of RAAS, result in the development of glomerulopathy. Chronic obesity is involved in glomerular hyperfiltration, glomerular hypertrophy, promotes proteinuria, glomerulomegaly and focal and segmental glomerulosclerosis. Weight loss has beneficial effects on the entire body, including renal functions, which are associated even with the improvement in glomerular hemodynamics.

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## Availability of data and materials

All information in this review is documented by relevant references.

## Authors' contributions

DM, DGB, AT, OS, IAV, DAM, CCP, ME, ASN, AEN and CS designed the study, performed the literature search and selected the included studies and wrote the manuscript. DM, DGB, AT, OS, IAV, DAM, CCP, ME, ASN, AEN and CS critically revised the manuscript. All authors read and approved the final manuscript. The contributions of all the authors on this review are greatly valued and appreciated.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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