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Review

Obesity and Chronic Kidney Disease: A Comprehensive Review of Mechanisms, Impact, and Management Strategies

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Abstract

Obesity is a significant public health crisis with increasing rates worldwide. Chronic kidney disease (CKD) has also emerged as a leading cause of death worldwide. This review explores the intricate connection between obesity and CKD, discussing the underlying biological mechanisms, clinical consequences of their coexistence, and strategies for evidence-based management. We conducted an extensive literature review of peer-reviewed studies examining obesity–CKD relationships, including epidemiological studies, mechanistic research, clinical trials, and meta-analyses from major medical databases. Obesity serves as both a risk factor for de novo CKD development and a paradoxical protective factor observed in some studies of advanced CKD, particularly in dialysis populations. This review synthesizes current evidence on obesity-related glomerulopathy, the impact of obesity on CKD progression to end-stage renal disease, and the phenomenon known as the "obesity paradox". Management approaches, including lifestyle interventions, pharmacological treatments, and bariatric surgery, show varying efficacy across different CKD stages. The multifaceted relationship between obesity and CKD necessitates individualized, multidisciplinary approaches to optimize patient outcomes while addressing the unique challenges presented by this complex comorbidity. Early intervention in obese patients may prevent CKD development, while careful management is required in advanced CKD stages where the obesity paradox may confer survival benefits.

Keywords: obesity; chronic kidney disease; obesity-related glomerulopathy; obesity paradox; CKD management

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1. Introduction

Obesity is a substantial public health epidemic in the United States, with its incidence progressively rising in each decade. It is typically defined as having a body mass index (BMI) of 30 or higher [1]. According to the latest data from the Centers for Disease Control (CDC) reported in September 2024, around 40.3% of adults in the United States were classified as obese between August 2021 and August 2023 [2]. They found no significant difference between men and women. Obesity prevalence was slightly higher in adults aged 40–59 than in young adults aged 20–39 years and those 60 years and older.

Chronic kidney disease (CKD) is also a significant global health issue. About 15% of the adult population in the United States is estimated to be affected by CKD, which translates to a huge 37 million adults. Over the last two decades, CKD has become a

prominent cause of death globally. In a recently released report from the World Health Organization (WHO), CKD is now the 9th leading cause of death, rising from 19th in the past, with the number of deaths increasing by an astounding 95% between 2000 and 2021 [3].

Obesity is a known risk factor for chronic kidney disease and its progression, leading to end-stage renal disease (ESRD). A few of the earliest studies on the association between obesity and kidney disease date back to the early 19th century [4]. A systematic review conducted by Garofalo et al. showed obesity as an independent risk factor for the onset of albuminuria without a rise in creatinine level (stage 1 and II CKD) as well as CKD stages III and higher [5], irrespective of other risk factors like diabetes and hypertension [6].

2. Pathogenesis

An increase in adiposity, particularly visceral fat, triggers several metabolic pathways that result in a chronic inflammatory state within the body. In obesity, there is an increase in the number and size of fat cells. These cells release a wide array of biologically active key factors, including cytokines, leptins, adiponectins, and tumor necrosis factor-α (TNF-α), that cause systemic inflammation [7]. These inflammatory mediators released from adipose tissue can damage the endothelium of blood vessels inside the kidney, contributing to endothelial dysfunction. This promotes glomerular hyperfiltration, fibrosis, and worsening of kidney function [7].

Insulin resistance is a common feature of obesity, where the body becomes less responsive to insulin. This produces high levels of circulating insulin in order to maintain blood glucose equilibrium. Insulin induces the proliferation of renal cells and promotes the secretion of insulin-like growth factor 1 (IGF-1) and transforming growth factor beta (TGF-β). It also stimulates mesangial cells to produce more angiotensin II, thus intensifying its harmful effects [8]. It also activates the PI3K/Akt/mTOR pathway [9], leading to glomerular hyperfiltration and podocyte dysfunction. Additionally, the renin–angiotensin–aldosterone system (RAAS) is upregulated in obesity, resulting in increased sodium retention, elevated intraglomerular pressure, and subsequent renal fibrosis.

Inflammation plays a central role in this pathophysiological cascade. Adipose tissue macrophage infiltration leads to overexpression of proinflammatory cytokines such as TNF-α, IL-6, and MCP-1, which activate the NF-κB signaling pathway, promoting tubulointerstitial fibrosis and oxidative stress [10]. The JAK/STAT pathway is also implicated in mediating cytokine-induced inflammation and cellular apoptosis within the renal parenchyma [10].

However, it is not clear if insulin resistance independently influences the increased risk of CKD or its complications. There have been inconsistent associations between the causal effects of insulin resistance and CKD. A cohort study conducted by Schrauben et al. failed to show an independent association of insulin resistance with CKD [11].

Hyperinsulinemia, almost inadvertently associated with insulin resistance, leads to increased glomerular hyperfiltration and increased vascular permeability [12]. Hyperinsulinemia also promotes salt and water retention in renal tubules, causing uncontrolled hypertension. This results in altered endothelial cell function, causing tubulointerstitial ischemia and hypoxic injury. Hyperinsulinemia also causes renal tubular cell proliferation that induces remodeling of the tubular interstitium. This is considered one of the key pathophysiologic mechanisms of diabetic kidney disease, as demonstrated by animal studies [13].

2.1. Obesity Related Glomerulopathy

Dating back to the early 1970s, an association was identified between obesity and severe proteinuria, leading to the identification of a distinct clinical entity known as obesity-related glomerulopathy (ORG) [14]. ORG is diagnosed based on two main criteria: (1) clinical obesity, which is defined as a body mass index (BMI) of $\geq$30 kg/m^2 for Western populations and $\geq$25 kg/m^2 for Asian populations, and (2) kidney biopsy evidence of glomerulomegaly, with or without signs of focal segmental glomerulosclerosis (FSGS) [14]. Up to 40% of individuals may be affected by ORG, regardless of their glomerular filtration rate or degree of albuminuria. About 10% of those with ORG may progress to end-stage kidney disease [14]. Studies have reported severe adverse renal outcomes, such as progression to ESRD or CKD-related mortality, in people with a BMI $\geq$ 25 kg/m^2 [15–17]. The risk increases significantly in individuals with a BMI over 30 [18].

2.2. Glomerular Hemodynamic Changes

Obesity causes dilation of the afferent arterioles, resulting in higher renal plasma flow and an increased glomerular filtration rate (GFR) [14]. Glomerular hyperfiltration leads to higher sodium reabsorption at the proximal convoluted tubules in individuals with obesity. Subsequently, less sodium delivered to the distal convoluted tubules leads to activation of tubuloglomerular feedback, whereby the macula densa secretes vasoactive substances, causing vasodilation of the afferent arteriole and raising GFR. This creates a vicious cycle of increased sodium reabsorption at the proximal convoluted tubules and ongoing glomerular hyperfiltration [12].

2.3. Ectopic Renal Fat Deposits

Ectopic fat deposition in the kidney promotes insulin resistance in podocytes, increases the release of proinflammatory factors, and alters their response to mechanical forces associated with glomerular hyperfiltration. This leads to podocyte injury, proteinuria, progressive renal damage, and fibrosis. Ectopic renal fat can mechanically compress the renal vasculature, resulting in increased hydrostatic pressure and reduced tubular outflow, which in turn activates more of the renin–angiotensin–aldosterone system (RAAS) [12]. Obesity is linked to decreased secretion of adiponectin by adipose tissue, a hormone known for its anti-inflammatory effects. Additionally, adipose tissue secretes leptin and resistin, which are known to promote proinflammatory pathways.

2.4. Chronic Inflammatory State in Obesity

Studies have highlighted a chronic state of inflammation in patients with obesity, which causes damage to vascular endothelial cells and worsens glomerular injury [14,19,20]. ORG results from the interplay between cells involved in inflammation (including macrophages, lymphocytes, and mast cells) and a range of inflammatory mediators (tumor necrosis factor α, interleukin 6, monocyte chemoattractant protein 1 (MCP-1), chemokines, plasminogen activator inhibitor [14]. Figure 1 illustrates the complex interplay of key pathophysiological mechanisms in ORG.

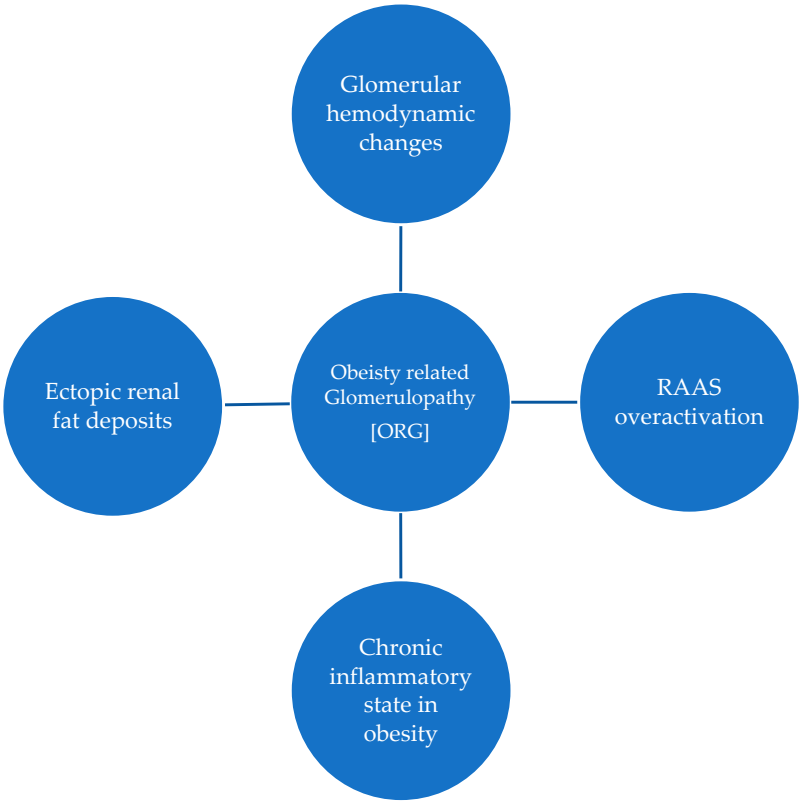

Figure 1. Principal pathophysiological mechanisms underlying obesity-related glomerulopathy (ORG). RAAS: Renin–angiotensin–aldosterone system.

3. Obesity and Chronic Kidney Disease Progression

3.1. Risk Factors and Epidemiological Evidence

Multiple large-scale studies have shown obesity to be a significant risk factor for CKD development and progression to ESRD [15,17]. A landmark study by Hsu et al. [16], which followed 320,252 adult patients from 1964 to 1985, concluded that elevated BMI independently predicted ESRD development, with high BMI being a strong and independent risk factor for ESRD. This underscores the critical importance of weight management in preventing progression to end-stage disease [16]. Epidemiological data reveal that the rate of BMI increase in the incident ESRD population is about twice as high as that of the general U.S. population across all age groups. Waist circumference has proven to be a more reliable predictor of ESRD risk compared to BMI alone, suggesting that central adiposity patterns may be especially important in predicting renal outcomes.

3.2. Obesity as a Prognostic Factor

Data from a large meta-analysis [5] indicated that obesity, but not overweight status, has been linked to a decline in kidney function, specifically reduced estimated glomerular filtration rate (eGFR < 60 mL/min/1.73 m^2) and higher prevalence of albuminuria. Individuals with a body mass index (BMI) above 30 kg/m^2 had a higher relative risk of 36% of these consequences when compared to individuals with lower BMI values [5]. A dose–response effect, with each 1 kg/m^2 increase in BMI leading to an additional 2% risk of progression to eGFR < 60 mL/min/1.73 m^2, was exhibited in another study [21].

Report from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014 showed that 44.1% of individuals with CKD also had obesity (BMI > 30 kg/m^2), compared with an overall obesity prevalence of about 38% in the same study group [22]. It is known that globally, CKD affects roughly 10% of the population; however, the exact

proportion affected by obesity is not certain. Regardless, lifetime risk models suggest that adults with obesity do have a higher probability of developing CKD across all stages (41.0% vs. 32.5% in normal-weight individuals) [22]. In addition to its role in CKD, obesity has been consistently linked to an elevated risk of kidney malignancies [22]. Figure 2 illustrates how various risk factors associated with obesity may contribute to the development of CKD [23]. Some of these factors act directly on the kidneys, while others influence kidney health more indirectly through changes in blood pressure, metabolism, or inflammation. The figure also outlines current and potential treatment options aimed at interrupting these harmful pathways, offering a clearer picture of how we might better prevent or manage kidney disease in people living with obesity.

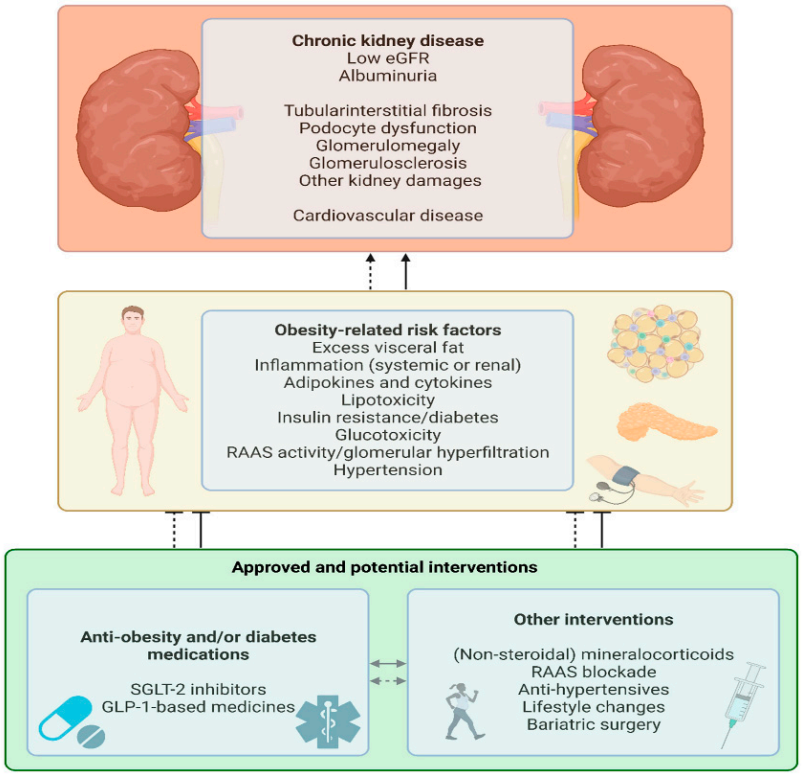

Figure 2. Pathophysiological associations and therapeutic options in obesity-related kidney disease. This figure shows the known or suspected obesity-related risk factors (yellow box) directly or indirectly implicated in the development of chronic kidney disease (CKD). Reproduced from Kreiner, F.F. et al. [23]. This article is published under the Creative Commons Attribution (CC BY 4.0) license, which permits reproduction with proper attribution.

Abdominal fat accumulation has been linked to chronic inflammation and protein–energy wasting, in patients undergoing hemodialysis, both of which contribute significantly to increased mortality risk [24]. Abdominal fat accumulation has also been associated with sarcopenia, defined as progressive loss of skeletal muscle mass and strength. Sarcopenia is especially prevalent among elderly individuals receiving long-term hemodialysis and is closely linked with frailty, disability, and protein–energy wasting [25,26].

Obesity is a risk factor due to surgical challenges like prolonged operative time, delayed wound healing, higher venous thromboembolism risk, nerve injury, and cardiac events. Bariatric surgery before renal transplantation is safe, feasible, and improves access and outcomes in severely obese patients.

4. The Obesity Paradox in Chronic Kidney Disease

While obesity is a well-established risk factor for the onset of chronic kidney disease, accumulating evidence suggests that it may provide a survival benefit in individuals with advanced disease stages [27], as illustrated in Figure 3. This phenomenon, commonly referred to as the obesity paradox, is considered a classic example of "reverse epidemiology." Similar paradoxical patterns have been observed for other cardiovascular risk factors such as lipid levels, blood pressure, uric acid, homocysteine, and adiponectin. These findings stand in contrast to their established adverse roles in the general population.

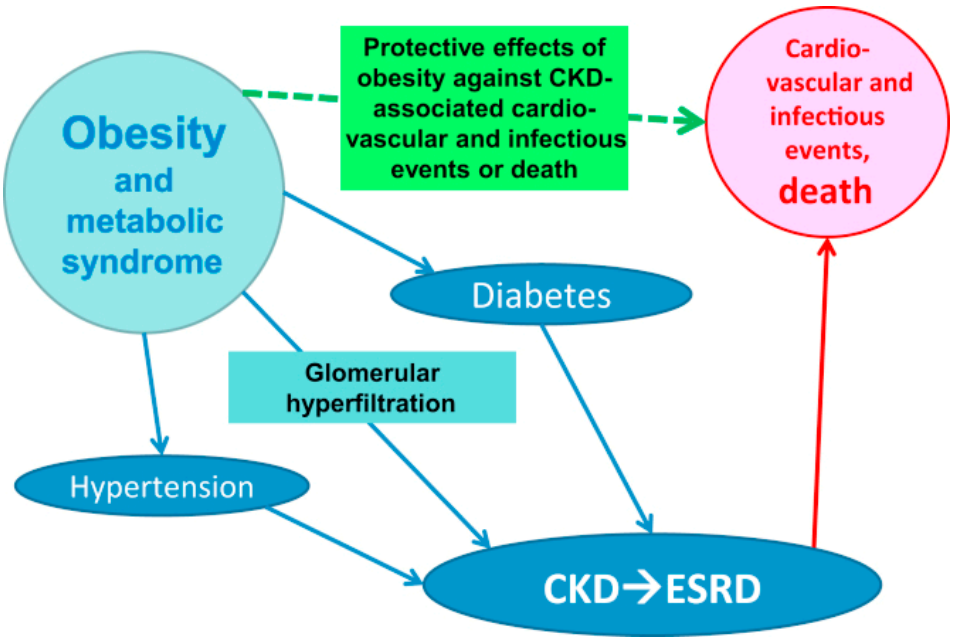

Figure 3. Illustration of the obesity paradox. Obesity is a risk factor for chronic kidney disease (CKD), yet it protects against CKD-associated death. ESRD, end-stage renal disease. Reproduced from Kalantar-Zadeh, K. et al. [27]. This article is available under the Creative Commons CC BY-NC-ND 4.0 license, which permits non-commercial reproduction without modification, provided full attribution is given.

Besides CKD, the obesity paradox has also been observed in other chronic conditions like heart failure, chronic obstructive pulmonary disease, cirrhosis of the liver, cancer, and among elderly patients. In these settings, malnutrition and inflammation strongly predict poor outcomes. Increased muscle mass and higher body fat seem to offer protective benefits, while low body weight and weight loss are linked to higher mortality. When considering protective factors, individuals with greater skeletal mass relative to fat mass have a better survival advantage.

Several mechanisms have been proposed to explain this paradox. One such hypothesis is that overnutrition leads to long-term complications, whereas undernutrition contributes to short-term mortality. Other presented protective effects of obesity include improved hemodynamic stability, enhanced lipoprotein binding to circulating endotoxins, favorable cytokine profiles, sequestration of toxins by adipose tissue, and antioxidative functions of muscle [27,28].

A large retrospective cohort study [29] by Wang et al. included about 4.5 million people from the United Kingdom database, showing that being overweight or obese is an independent risk factor for a higher incidence of CKD, regardless of associated metabolic abnormalities. A similar large-scale study conducted in the United States [30] examined over 3 million veterans with obesity and normal kidney function (eGFR > 60 mL/min/1.73 m^2),

and it observed increased kidney function loss in patients over 40 years old. Patients with a BMI between 25 and 30 were found to have the best clinical outcomes [30]. These findings highlight that obesity contributes to new-onset CKD and accelerates its progression in individuals with initially normal kidney function.

However, after the development of CKD, the picture changes. Multiple meta-analyses have shown that overweight and obesity are linked to better survival in patients with advanced CKD (eGFR < 30 mL/min/1.73 m^2) and those on dialysis [31–33]. The obesity paradox is strongly evident in the dialysis population, especially among patients undergoing maintenance hemodialysis [34]. However, in kidney transplant recipients, higher BMI before transplantation is associated with worse outcomes, including higher mortality [33].

Considering everything, obesity should be regarded as an important risk factor for the onset of CKD. Yet, paradoxically, in patients with advanced CKD, especially those on hemodialysis, higher BMI seems to have a survival advantage. This reverse epidemiology points out the complexity of obesity's role in kidney disease and suggests that its impact depends strongly on the stage of CKD and the clinical context [34,35].

5. Management and Treatment Strategies for Obesity in CKD

Obesity and CKD frequently coexist and exacerbate each other because of complex pathophysiologic mechanisms of related co-morbidities described earlier. Weight loss achieved through lifestyle and behavioral modifications, or that achieved through medications or surgical options, reduces albuminuria and, in many cases, slows the decline in eGFR [36]. Thus, the latest Kidney Disease: Improving Global Outcomes (KDIGO) 2024 guidelines for CKD treatment emphasize the importance of regular physical exercise, diet, and lifestyle modifications to attain and maintain a healthy BMI in overweight or obese patients with CKD [37]. There is, however, a lack of standardized methods to follow for weight loss in this population. A one-size-fits-all approach is ineffective for these patients, and management strategies typically require a personalized plan to meet each individual's specific needs, potentially slowing disease progression, improving kidney function, and reducing the risk of complications [38].

5.1. Lifestyle Interventions

Intensive lifestyle interventions like a calorie-restricted diet and physical exercise are an integral part of the management strategy for obese patients with CKD, as there is strong evidence to support it [39,40]. A meta-analysis conducted by Navaneethan et al. in 2009 [41] looked at the benefits of intentional weight loss in patients with non-dialysis dependent CKD and found that non-surgical weight loss interventions significantly reduced proteinuria and blood pressure and seemed to slow the progression of kidney disease. Another meta-analysis, published in Kidney Medicine by Neale et al., found that lifestyle interventions positively affected certain risk factors for the progression of CKD, including a decline in albuminuria, improvement in blood pressure, and weight [42].

5.1.1. Dietary Interventions

Due to the complexity of this condition, it is essential to exercise extreme caution when recommending dietary changes for these patients. It involves a complex modification of nutritional calories, protein, fat content, carbohydrates (as the majority of this patient population is insulin-resistant and has diabetes), sodium, phosphorus, and potassium restriction [43]. This warrants consultation with a renal dietitian who specializes in this patient population and understands its intricacies [37].

Plant-Based Diets

Plant-based diets (PBDs), generally low in protein, can be an essential tool to consider, especially in patients with obesity and advanced CKD [44]. The KDIGO 2024 guidelines place a strong emphasis on plant-based diets [37], highlighting their low acid load, along with personalized recommendations for protein intake (based on individual needs, other metabolic comorbidities, and CKD stage) and reduced consumption of ultra-processed foods. They emphasize the need to incorporate fresh fruits, vegetables, whole grains, eliminate trans fats, processed meat, and sugary drinks, and restrict high sodium, phosphorus, and potassium, especially at the advanced stages of CKD [45]. 2020 update of the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline for nutrition in CKD [46] recommend CKD 3–5 metabolically stable patients should have a low protein diet 0.55–0.6 g/kg body weight/day or 0.28–0.43 g/kg body weight/day along with supplementation of keto acid and amino acid analogs to meet nutritional needs—grade 1A recommendation. Experts recommend this kind of approach as there is very strong evidence regarding its ability to reduce risk for end-stage renal disease and death.

Very Low-Calorie Diet

Very low-calorie (<800 kcal/day) or ketogenic diets have gained popularity over the last decade. They are increasingly used to promote weight loss, although they have not been extensively studied in patients with moderate to severe stages of CKD. An observational prospective study conducted by Bruci et al. enrolled 92 patients and assigned them a very low-calorie diet for three months to evaluate its effectiveness and safety [47]. Of the 92 patients enrolled, 38 had mild kidney disease (GFR 89–60 mL/min/1.73 m^2). The study assessed the safety and effectiveness of this diet for weight loss and found it to be relatively safe, with no differences in liver and kidney function between those with mild CKD and those with normal kidney function. The patients experienced a 20% reduction in weight, with 80% of the weight loss coming from fat. Approximately 30% of patients with mild CKD showed improvement in their kidney function by the end of the study.

Patients with moderate to severe CKD should avoid using a very low-calorie diet as the evidence is lacking and there is potential for serious adverse effects like life-threatening hyperkalemia and severe dehydration, especially in the initial phase [48]. The 2020 update of the KDOQI guidelines for nutrition in CKD patients included a strong (1C) recommendation to prescribe 25–35 kcal/kg/day in metabolically stable CKD patients of all stages (stages 1–5D), aiming to maintain nutrition while promoting weight control [46]. Very-low energy intake is associated with a higher risk of cardiovascular death in patients with CKD. A cross-sectional study was conducted using the National Health and Nutrition Examination Survey (NHANES) database, where 4264 CKD patients were enrolled between 2009 and 2018, and their nutritional intake data were analyzed to evaluate the association of energy intake and cardiovascular mortality [49]. Results revealed that patients whose total energy intake was <25 kcal/kg/day had a 41% increased risk of cardiovascular mortality. This makes a strong case to avoid such extreme calorie restriction in patients with CKD.

Low-Energy Diet

Low-energy diets (LED), consisting of 800–1200 kcal/day, are the latest development in the CKD realm, claimed to aid in weight loss and considered a relatively safe option. A recently published feasibility multi-center randomized controlled trial (RCT): SLOW-CKD [50], randomized 49 patients with stage 1–3b CKD into LED and usual care. The participants in the LED group received meal replacements three to four times a day, consisting of 800–900 kcal/day, along with regularly scheduled sessions with a dietician at two-week intervals, as well as as-needed communication via telephone or text messages.

They conducted this intense protocol for the initial 3 months, followed by another 3 months of a 'maintenance' phase, during which support for diet and exercise was available, and the patients were transitioned off the LED in a stepwise manner. The results were impressive, with 46% of patients in the LED group achieving a weight loss of more than 10 kg. The treatment was relatively safe, with only two patients developing serious adverse effects (SAEs)—acute kidney injury (AKI) and hypoglycemia—which were comparable to the control group, where two patients also developed SAEs (hypoglycemia). This feasibility study demonstrated that LED under expert dietitian guidance is safe and feasible for weight loss in obese patients with mild to moderate CKD (Stages 1–3B).

Mediterranean Diet

The Mediterranean/Dietary Approaches to Stop Hypertension (DASH) diet, which includes whole grains, legumes, fresh fruits and vegetables, fish, and poultry, and lower processed meat and other ultra-processed foods, is increasingly recommended for patients with CKD. A large randomized controlled trial enrolled 6719 obese/overweight adults between September 2013 and December 2016, across 23 centers and randomly assigned them to an intensive weight loss lifestyle intervention group with energy-restricted Mediterranean diet (30% calorie restriction), physical activity (walking 45 min/day) and behavioral support and the other group received usual care with advice to adhere to regular Mediterranean diet [51]. At the end of one year, results revealed this intervention preserved kidney function in patients with CKD and slowed the decline in eGFR in the intervention group compared to standard care.

5.1.2. Exercise Interventions

Regular physical exercise complements dietary changes in obese patients with CKD and helps improve the metabolic parameters and reduce inflammation and oxidative stress. A randomized controlled trial published in the Journal of the American Society of Nephrology enrolled 122 patients with obesity and moderate to severe CKD (stages 3 and 4) [40]. They were randomized to receive a calorie-restricted diet with aerobic exercise, a calorie-restricted diet alone, aerobic exercise alone, or usual care. At the end of a four-month study period, the group receiving the combined intervention had a statistically significant decrease in body weight and body fat percentage. This intervention also led to a significant reduction in inflammatory and oxidative stress markers, including F2-isoprostane and interleukin-6 (IL-6) concentrations. This indicates that combining a calorie-restricted diet with aerobic exercise yields significantly better outcomes for reducing both body fat percentage and inflammation.

5.2. Pharmacologic Interventions

Although lifestyle interventions, such as calorie-restricted diets and regular physical activity, are the cornerstone of weight-loss strategies, maintaining the lost weight has been difficult for most patients who initially achieved weight loss through these interventions. Therefore, clinical guidelines suggest using adjunctive pharmacotherapy for adults with a BMI of >30 or >27 along with co-morbidities like type 2 diabetes, CKD, and cardiovascular disease [52].

5.2.1. Glucagon-like Peptide-1 Receptor Agonists

The latest, most effective, and relatively safe options in this field are glucagon-like peptide-1 (GLP-1) receptor agonists. Since their introduction for weight loss in 2021 with the STEP-1 trial, multiple studies have assessed the safety and effectiveness of GLP-1 agonists in promoting weight loss, as well as their potential to slow the progression of kidney disease and reduce the need for dialysis. A landmark multi-nation trial by Perkovic

et al. (FLOW trial) randomized 3533 participants with type 2 diabetes and CKD to receive subcutaneous semaglutide 1 mg weekly or placebo and studied the effects of semaglutide on kidney outcomes [53]. The trial was terminated early because semaglutide significantly reduced the risk of major kidney disease events (including dialysis, transplant, or decrease in eGFR to <15 mL/min/1.73 m^2), 50% or greater reduction in eGFR from baseline, and death from kidney-related or cardiovascular causes. Although this trial did not evaluate weight loss benefits, most participants were obese patients with CKD and had an average BMI of 32. This highlights the potential of these medications to lower the risk of kidney failure and decrease the need for dialysis.

Another observational study evaluated semaglutide in obese patients on dialysis who wished to undergo transplant [54]. Obesity, abdominal adiposity in particular, is a relative contraindication for kidney transplant, as the risk of potential surgical complications in terms of wound healing and graft loss is high in patients with central obesity [22]. Researchers from Austria conducted an open-label, prospective trial with 13 patients with ESRD on dialysis who were not listed for a kidney transplant due to obesity [54]. These patients had an average BMI of 37 kg/m^2. Although there was a high incidence of side effects, mainly gastrointestinal issues leading to drug discontinuation, three patients achieved significant weight loss, enough to be considered for kidney transplant listing. Although conducted on a small sample size, this study gives hope for many similar patients who are currently denied a kidney transplant solely because of their weight.

A similar study published in Nature randomized 101 obese patients with non-diabetic CKD (eGFR > 25 and UACR > 30 and <3500 mg/g) and BMI > 27 kg/m^2 to semaglutide 2.4 mg per week or placebo for 6 months and looked at the percentage reduction in urine albumin creatinine ratio at 24 weeks as a primary end point [55]. Participants in the semaglutide group experienced a 52.1% reduction in albuminuria compared to the placebo group, indicating the potential to slow the progression of kidney disease.

5.2.2. Dual Glucose-Dependent Insulinotropic Polypeptide and GLP-1 Receptor Agonists

Tirzepatide—a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist has demonstrated similar benefits. A meta-analysis examined the renal effects and safety of tirzepatide in patients with and without diabetes. They used data from 15 RCTs involving over 14,000 participants. The study revealed that tirzepatide demonstrated a significantly better reduction in the urine albumin-creatinine ratio compared to placebo, insulin, or the highest dose of semaglutide (2.4 mg subcutaneously, administered weekly) [56]. It was also safe, with no significant increase in the risk of adverse effects. This study highlights the potential of these weight loss medications to improve kidney disease outcomes in patients with obesity and CKD.

5.2.3. Sodium-Glucose Co-Transporter 2 Inhibitors

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have gained recent popularity in CKD and heart failure patients, with and without diabetes, because of their cardiovascular and renal benefits. These medications have been shown to reduce albuminuria, preserve kidney function, and delay the need for dialysis in patients with CKD [57]. They can also promote weight loss in patients with CKD, primarily by increasing the excretion of glucose in urine through the inhibition of its reabsorption in the proximal convoluted tubules of nephrons. This glucosuria leads to calorie loss, which in turn aids in weight loss.

A cross-sectional study conducted by Gerlanc et al. used a questionnaire on a sample of 205 patients with type 2 diabetes who were prescribed canagliflozin [58]. Results showed that over 66% of patients reported weight loss after starting canagliflozin, although the amount of weight lost varied significantly depending on whether the patients were

engaged in other weight-loss programs for at least 6 months. Patients involved in such efforts reported losing more than 10 pounds and had better diabetes control, suggesting a synergistic effect of SGLT2 Inhibitors when combined with lifestyle interventions.

5.2.4. Phentermine

Phentermine, one of the earliest anti-obesity medications still in use, functions as an appetite suppressant. While it can still be used in the treatment of obesity in patients with CKD, it has not been well studied in this population, and there is a lack of robust RCTs to assess its safety [59]. The kidneys primarily metabolize it, so clinicians should exercise caution when prescribing it [36]. Common side effects include increased heart rate and blood pressure, which can be problematic in patients with CKD, especially those with hypertension. Caution is advised when administering it to patients with moderate to advanced CKD.

5.2.5. Orlistat

Orlistat, a lipase inhibitor that reduces the absorption of dietary fat, can be an effective obesity treatment. However, in patients with CKD, it can potentially worsen kidney function due to its potential for causing hyperoxaluria. It binds to dietary calcium, leaving oxalate free to be absorbed into the bloodstream, which can lead to hyperoxaluria and, in turn, acute kidney injury [60]. There have been several case reports suggesting a higher risk of AKI with orlistat use [61], particularly in those with underlying CKD. In a drug-benefits database study conducted in Canada, Weir et al. identified over 950 patients who filled a prescription for orlistat between 1 January 2002 and 31 March 2008 [62]. They identified the incidence of AKI occurring 12 months before and after the prescription and found a significantly higher incidence of AKI after starting orlistat (18 versus 5, $p = 0.01$). It should thus be used with extreme caution, with close monitoring of kidney function, and, if possible, should be avoided, as there are many other pharmacological options with a better efficacy and safety profile.

5.3. Surgical Interventions

Bariatric surgery can be an effective option for weight loss in obese patients with CKD who do not respond to maximum lifestyle interventions and medical therapy [63]. Evidence from several cohort studies and recent RCTs shows that weight loss is associated with improved blood pressure, diabetes management, and metabolic control, and has been shown to reduce albuminuria and slow the progression of kidney disease [64].

Bariatric surgery can also benefit those with ESRD who are unable to receive a kidney transplant due to severe obesity. For these patients, bariatric surgery can lead to rapid weight loss and help them qualify for a kidney transplant, potentially eliminating the need for dialysis [65].

A retrospective cohort study conducted by Sheetz et al. evaluated whether bariatric surgery is associated with a survival benefit in patients with obesity and ESRD [66]. They used data from the United States Renal Data System (USRDS) registry from 2006 to 2015 to assess differences in outcomes for patients who received bariatric surgery ($n = 1597$). They compared these to a matched cohort of patients who did not undergo bariatric surgery ($n = 4750$) but received standard care. Results revealed that bariatric surgery was associated with lower all-cause mortality compared to usual care (cumulative incidence, 25.6% vs. 39.8%; hazard ratio, 0.69, 95% CI, 0.60–0.78) and also showed that bariatric surgery was linked to an increase in kidney transplant at 5 years (cumulative incidence, 33.0% vs. 20.4%; hazard ratio, 1.82; 95% CI, 1.58–2.09). Bariatric surgery can thus be used as a powerful tool to avoid the initiation of dialysis, or for those already on dialysis, it can serve as a

bridge until a transplant, as patients are more likely to be successful in obtaining a kidney transplant and surviving after the surgery.

5.4. Integrated Care Models

Obesity management in patients with kidney disease is a complex task. It is best addressed through a multidisciplinary approach [67], with nephrologists playing a central role by incorporating medications such as SGLT2i and GLP-1 receptor agonists to promote weight loss. Simultaneously, consulting and referring to a renal nutritionist and an exercise physiologist for diet and lifestyle interventions can help achieve better outcomes. Assistance from endocrinologists and our bariatric surgery colleagues is also essential in certain populations where diet, exercise, and medications fail to produce the desired results.

5.5. Emerging Treatments

New pharmacological and surgical approaches for managing obesity in CKD patients continue to emerge, with dual and triple incretin receptor agonists showing particular promise [68]. In a phase 2 trial, 338 obese participants with at least one weight-related condition were enrolled and received 12 mg of retatrutide versus a placebo. Patients receiving retatrutide, a triple-hormone combination (an agonist of glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors), had 18% weight loss at 24 weeks (1.6% for placebo) and 24% over 48 weeks [68].

Targeting mitochondrial function represents a potential new strategy for obesity-related glomerulopathy therapy [69]. Recent research provides additional clarity on risk factors, including the impact of monoallelic variants [70]. These advances support targeted testing, especially for individuals of African descent, and open the door for genotype-guided treatments in obesity-related kidney disease, where APOL1-related FSGS/ORG overlap is suspected. Recent advances in metabolomics and proteomics may offer insights into diagnosis and identify new therapeutic targets for obesity-related kidney disease.

Precision nephrology is progressing: APOL1 risk variants significantly affect CKD risk and presentation. an APOL1 inhibitor, inaxaplin (VX-147), achieved approximately 48% reduction in proteinuria in a phase 2a APOL1-mediated kidney disease (AMKD) study [71], with a relatively mild to moderate side effect profile; none of this led to the discontinuation of the drug in study participants

6. Conclusions

The relationship between obesity and chronic kidney disease is a complex clinical challenge that requires a thorough understanding of underlying pathophysiological mechanisms and evidence-based management strategies. Effective management strategies must address the multifaceted nature of this relationship through personalized, multidisciplinary approaches. Early intervention in obese patients to prevent CKD development, combined with careful management of established CKD patients with obesity, represents the optimal approach for improving patient outcomes. Management options include lifestyle modifications, medications such as GLP-1 receptor agonists and SGLT2 inhibitors, and bariatric surgery when appropriate.

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Abbreviations

The following abbreviations are used in this manuscript:

CKD	Chronic kidney disease
BMI	Body mass index
CDC	Centers for Disease Control
WHO	World Health Organization
ESRD	End stage renal disease
TNF	Tumor necrosis factor
IGF-1	Insulin like growth factor-1
TGF	Transforming growth factor
ORG	Obesity related glomerulopathy
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
RASS	Renin–angiotensin–aldosterone system
MCP-1	Monocyte chemoattractant protein-1
NHANES	National Health and Nutrition Examination Survey
KDIGO	Kidney Disease: Improving Global Outcomes
PBD	Plant-based diets
KDOQI	Kidney Disease Outcomes Quality Initiative
LED	Low-energy diets
RCT	Randomized controlled trial
SAEs	Serious adverse events
AKI	Acute kidney injury
DASH	Dietary Approaches to Stop Hypertension
IL-6	Interleukin-6
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulinotropic polypeptide
SGLT-2i	Sodium-glucose co-transporter 2 inhibitors
USRDS	United States Renal Data System
AMKD	APOL1-mediated kidney disease

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