



Chronic kidney disease and obesity – pathomechanisms and treatment – literature review

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Abstract

Introduction and Objective. Chronic kidney disease (CKD) is a major health issue worldwide affecting 10–14% of the globe's population, with a climbing trend. CKD is associated with a variety of factors, including obesity, which has grown increasingly prevalent and adds to the pathogenesis of the disease. The aim of the review is to summarise pathomechanism and current treatment methods of chronic kidney disease. Additionally, using this knowledge, treatment suggestions are provided for different patient groups.

Review Methods. A literature search was conducted in the PubMed database with inclusion criteria 'English language' and 'free full texts', and publications date between 2018 – 2023. A total of 1,172 results were found; 28 publications were ultimately included in the review.

Brief description of the state of knowledge. The pathomechanisms include haemodynamic changes, oxidative stress, adipokine dysregulation, and correlations to insulin resistance and diabetes. Weight loss by proper nutrition and exercise is a beneficial approach to manage CKD in obese patients. Bariatric surgery has proven a realistic alternative due to improvements in kidney function and obesity-related comorbidities. There are several options for pharmacotherapy in CKD and obesity, including SGLT2 inhibitors, GLP-1 analogues, agents targeting the renin-angiotensin-aldosterone system and bardoxolone methyl. Addressing obesity plays an essential role in alleviating CKD risk and progression.

Conclusions. Early intervention involving lifestyle changes, weight reduction strategies, surgical procedures, and medication provides a holistic approach to addressing CKD in obese people. Recognizing the complex interplay of variables that contribute to CKD enables targeted therapy approaches and better patient outcomes.

Key words

obesity, pharmacotherapy, weight loss, adipokines, bariatrics, chronic kidney diseases

INTRODUCTION

The increasing prevalence of obesity and chronic kidney disease (CKD) presents a significant challenge for public health, with both conditions intricately linked through various pathophysiological mechanisms. By comprehensively examining them, a detailed understanding is sought of how obesity contributes to the onset and progression of CKD. Following this exploration, various treatment strategies targeting each identified pathomechanism are investigated. The discussion extends to practical concepts for tailoring treatment plans to individual patients, considering the heterogeneity of those affected by CKD and obesity. These suggestions are intended to complement existing guidelines and inspire further research and innovation. The importance of continuous monitoring of recent literature is underscored, as the field is rapidly evolving with new insights and official guidelines emerging regularly.

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OBJECTIVE

The primary objective of this review is to demystify the complex interplay between CKD and obesity, and to equip healthcare providers with a clear and concise understanding of the diverse treatment approaches for various patient groups. By doing so, the aim is to support more informed clinical decisions, thereby enhancing patient care. The review serves as a consolidated resource summarising current knowledge in a straightforward manner that enhances understanding and clinical application.

REVIEW METHODS

A literature search was conducted in the PubMed database with inclusion of English language, free full texts and publication date between 2018 and 2023. In addition, articles such as meta-analysis, clinical trials, randomised controlled trials and systematic review were included in the first search. The following keywords were used to search the databases: "obesity and chronic kidney disease" (PubMed – 128), "obesity and chronic kidney disease and treatment"

(PubMed – 73), “obesity and chronic kidney disease and surgery” (PubMed – 36), “obesity and chronic kidney disease and pharmacology” (PubMed – 32). Search data is as of 06/01/2024. 28 publications were ultimately included in the review after using these inclusion criteria: date of publication, topic relevance, citation count, and keyword presence in the abstracts. Texts in another language, duplicated, not referring to the title or with an incompatible abstract were excluded.

The references include one study from 2013, conducted by de Zeeuw et al. It was critical to include it since it served as the foundation for subsequent, more recent investigations that we assessed and found significant.

Later in our work, we have chosen to reference several review papers. We utilised citation-rich sources that offer comprehensive summaries of current research, enabling us to identify significant trends. Referencing these reviews allows us to present a broad perspective and clarify the complexity of the issues for our readers. These review papers provide valuable context and background, which are crucial for understanding the development and current state of research in our focus areas. We specifically cite these reviews in our discussion on chronic kidney disease (CKD) (1, 3), obesity (4,5), and pathomechanisms (1, 4, 5, 12, 14, 16). By integrating insights from these review papers, we can more effectively highlight the interconnectedness of various factors and the multifaceted nature of these conditions. Additionally, we found that some summarising conclusions were valuable for discussing collective data (1, 4, 16, 21). These conclusions help to synthesise diverse findings and offer a coherent narrative that supports our analysis.

DESCRIPTION OF THE STATE OF KNOWLEDGE – REPOSITIONED FROM OBJECTIVE

Chronic kidney disease (CKD). In 2012, CKD was described in Kidney Disease Improving Global Outcomes (KDIGO) as abnormalities of kidney function or structure, presenting for more than three months and causing implications for health. It is classified based on cause, glomerular filtration rate (GFR) category and albuminuria category (CGA). Criteria include albuminuria >30 mg/24 hours, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology or structural abnormalities detected by imaging and history of kidney transplantation. Diagnostic rate of the GFR is <60 ml/min/1.73 m², further qualified as mildly to moderately decreased (G3a) – GFR rate between 59 and 45, moderately to severely decreased (G3b) – GFR rate between 44 and 30, severely decreased (G4) – GFR rate between 29 and 15 and kidney failure (G5) – GFR rate <15. [KDIGO 2012]

Roughly 10–14% of the world’s population suffer from CKD, meaning that approximately 845 million people are affected globally. The percentage prevalence rate has been stable since the beginning of the 21st century; however, since then the world population has dramatically increased. Therefore, the absolute number of CKD cases is in fact much higher today than 20 years ago. Due to this significant increase in the last few years, it is anticipated that the number of patients affected by this condition will continue to rise. Also, in 2013, CKD surged from the 19th position to the 12th rank as the leading cause of death. According to the forecast, by

2040 CKD will rank 5th among the world’s major causes of death. The disease more frequently affects women, elderly patients (older than 60), people in low-income countries, and individuals with family history of CKD or comorbidities, such as diabetes, heart failure, hypertension and obesity [1–3]. Management of CKD is based on controlling the primary cause by mostly symptomatic treatment. Early identification of modifiable risk factors and maintenance of a health-conscious lifestyle are critical for prevention.

Obesity. Obesity is the over-accumulation of fatty acids in white adipose tissue. [4, 5]. A body mass index (BMI) is recommended for diagnosing obesity. According to the WHO, a BMI between 25 and 30 kg/m² is considered overweight, while a BMI above 30 kg/m² is considered obese [6,7]. Additionally, waist-to-hip ratio, waist-to-circumference, and waist-to-height ratio (WHtR) may also be useful in making a diagnosis. Liu et al. showed that WHtR could be a more accurate predictor of CKD than other markers [8, 9]. Unfortunately, the prevalence of obesity continues to rise, and according to the WHO European Regional Obesity Report 2022, it can affect up to 59% of adults, compared to an estimated 23% in the European region. [7, 10, 11].

This is a significant problem because obesity can be linked to a variety of diseases including: metabolic syndrome, dyslipidemia, hypertension, type-2 diabetes mellitus (T2DM) cardiovascular diseases, non-alcoholic fatty liver disease, asthma, obstructive sleep apnea, osteoarthritis, depression, some cancers, and may also lead to CKD [4, 7, 10]. The pathophysiology of obesity involves a variety of factors, including biological, psychological, environmental, and behavioural factors, genetic predisposition, family history, unhealthy eating habits and overeating, excessive drinking of alcohol, smoking, insufficient physical activity, depression or socio-economic status [7, 10].

The review investigates the correlation between obesity and CKD, focusing on the processes by which obesity affects renal function.

Pathomechanisms. Increased BMI can lead to impaired kidney function through several mechanisms. Haemodynamic changes induced by obesity, such as elevated cardiac output and blood volume, have a major impact on the renal circulation. One factor accelerating the kidney’s consumption? is the elevated renal flow itself. Even more crucial is the imbalance in many blood components, which occurs in obese patients. When these compounds enter the kidney in such abnormal amounts, they could cause injury [6, 12].

Obesity increases oxidative stress in the whole organism, even in metabolically healthy obese patients [6]. One of the mechanisms responsible for the increase is the greater volume of triglyceride (TG) storing adipose tissue, compared to individuals with normal BMI. Adipocytes, apart from their primary function, act as a secretory organ with endocrine, paracrine, and autocrine functions. Secreted substances, adipokines and cytokines, are involved in body weight regulation and local inflammation. In obese patients, the endocrine function is highly dysregulated [4, 5, 12–14]. According to studies, various levels of adiponectin, whether high or low in CKD, have different impacts on mortality and incidence of cardiovascular disease, which is sometimes called the ‘adiponectin paradox’ [5, 13]. Hypertrophic

adipocytes over-produce pro-inflammatory cytokines, promoting insulin resistance and recruiting immune cells, leading to irreversible kidney injury [4, 5, 12–15]. On the one hand, in CKD the concentration of adiponectin can be increased two to three times. On the other hand, reduction of the level, which may also occur in obesity, decreases the protective effect on the kidneys and may lead to renal fibrosis and oxidative stress. As for leptin, the progression of CKD is also due to the high concentration of adiponectin [5, 13].

Elevated leptin blood levels can be related to both obesity and increased production of adipokine, as well as CKD and impaired adipokine degradation. The result can be hypertension, vascular endothelial dysfunction, glomerulosclerosis, proteinuria, and renin-angiotensin-aldosterone system (RAAS) activation, all of which can eventually lead to renal damage [4, 5]. Also, the relationship between higher leptin levels and CKD progression has been proven [5].

Moreover, obesity is commonly related to dyslipidemia in both metabolically healthy and unhealthy obese patients [2]. Studies show that higher levels of TG and low-density cholesterol can also cause kidney damage because accumulation of lipids damages the podocytes and tubular cells [1].

Ghrelin also plays a key role in renal pathology and function, particularly as it relates to obesity and related diseases, and its receptors have been found in podocytes. In studies, the effect of the hormone on the kidneys varies, in one of which it may act as a preventative against oxidative stress, inflammation, renal fibrosis or obstructive nephropathy, and in others it may stimulate glomerular sclerosis, interstitial fibrosis, podocyte damage or increase the incidence of angiotensin-II-induced hypertension [4].

Obese individuals often simultaneously suffer from insulin resistance or diabetes. There are several mechanisms responsible for kidney damage in patients with dysregulated insulin and glucose levels. Increased level of insulin induces oxidative stress inside podocytes and promotes the synthesis of collagen IV, transforming growth factor (TGF) beta-1, which may result in tubulointerstitial fibrosis [16]. Thirdly, insulin interferes with sodium channels and aggravates the effects of angiotensin II, resulting in increased production of inflammatory cytokines and proteinuria, both of which contribute to kidney injury [17]. It is worth noting that, according to studies, obesity may even be a protective factor in end-stage renal disease (ESRD) [6]. However, ESRD severely limits treatment options, therefore this paradox is not very significant from a clinical standpoint. For patients, it is critical to begin prevention and therapy as soon as possible. Now that many of the components involved in pathophysiology have been identified, there are multiple possibilities for initiating treatment. Every previously discussed factor that contributes to kidney damage in obese patients can be targeted as a therapy foothold.

Weight loss through diet and exercise. It is generally known that a diet for obese people is beneficial both metabolically and nutritionally. Previous studies have already shown that healthy lifestyle interventions, in combination or alone, are a good choice for improving metabolic health in this group. Ikizler et al. in a study of 111 patients with moderate to severe CKD, noted that dietary calorie restriction resulted in loss of weight and fat mass, while aerobic exercise reduced

inflammatory reaction and oxidative stress. In addition, participants found it more difficult to keep up with the exercise interventions than the diet, as shown by the percentage of sessions completed [15].

Additionally, studies have shown the beneficial effects of a healthy and nutritious diet on both the prevention and progression of CKD. Robin Lo et al. recommended including the following products: vegetables, fruit, legumes, whole grains, nuts, and fish, as well as consuming less sodium, red and processed meat, and high-sugar drinks [1]. Another study tested Very Low Carb Ketogenic Diets (VLCKD) in patients with obesity and CKD. This key component in this diet is its low daily carbohydrate intake of less than 20g. Although it is not usually recommended for people with reduced kidney filtration, many positive outcomes have been observed, such as weight and fat mass loss in less than three months. Bruci et al. also observed improvements in glucose and lipid metabolism, a reduction in blood pressure and triglyceride levels without affecting the body's water-electrolyte balance. Importantly, conclusions were drawn on the potential improvement of renal function due to decreased uric acid level [18]. In a similar small study, metabolic improvements were also observed after a 12-week long strict low-calorie ketogenic diet in obese participants with advanced diabetic nephropathy [13].

Aydemir et al. in a randomised clinical trial involving 111 participants noted that dietary caloric restriction increased adipokine levels without affecting leptin levels, implying an effect on metabolism improvement in patients with stage 3–4 CKD [13]. However, low-calorie diets can affect people with diabetes and cause electrolyte disturbances, fluid overload, constipation, uremia, and blood glucose disturbances. Regardless of the type of diet, it is crucial that it remains under medical supervision [18, 19].

Surgical management of weight loss – bariatric surgery. Bariatric surgery (BS) is one of the treatment methods recommended for people with CKD and obesity. In general, it is possible to remove part of the stomach in a laparoscopic sleeve gastrectomy (LSG), or to connect the stomach to the digestive system by bypassing the proximal part of the small intestine in a gastric bypass called Roux-en-Y (RYGB) [4]. According to the National Institutes of Health (NIH), patients with a BMI over 40 kg/m², and individuals with a BMI of more than 35 kg/m² with comorbid metabolic disease, are qualified to undergo bariatric surgery [20]. It is proven that BS not only helps in weight loss, increases life expectancy, and reduces obesity-related comorbidities, but is also linked to slower eGFR decline and remission of albuminuria and proteinuria [20–23].

A randomised study 100 patients with T2DM, obesity and CKD at different stages, were placed into two groups: RYGB and medical care. Cohen et al. observed better remission of CKD and albuminuria after one year in patients following RYGB, than medical care alone, although the difference between the two was not significant after five years. [21, 23]. In another study, Kassam et al. showed that LSG may be beneficial in ESRD when a kidney transplant is not possible due to obesity. Also, its effect on reducing the incidence of hypertension has been demonstrated [20]. Nevertheless, BS may involve side-effects, including band erosion, gastric leak, nephrolithiasis, oxalate nephropathy, nutrient deficiencies due to a restrictive diet after BS, and acute kidney injury

(AKI), when compared with the non-CKD population [19, 22].

Pharmacotherapy of obesity and CKD. Many pharmaceutical drugs used in diabetes have proven useful in the treatment of systemic diseases. Some of them may be used in obese patients with CKD, not only to improve and protect the kidney function directly, but also to support weight loss.

SGLT2 inhibitors (SGLT2i) are a group of medications that prevent the kidneys from absorbing glucose, which increases its excretion and results in a daily loss of about 300 kcal. This caloric loss is associated with an average weight reduction of 2–3 kg in clinical trials. According to the most recent guidelines, SGLT2i may be used to treat individuals who have both T2DM and obesity, with an intermediate function that it plays in encouraging weight loss. The advantages of SGLT2i in managing heart failure, improving cardiovascular outcomes, and lowering hospitalisation rates are highlighted by the available data. In 2019, Perkovic et al. published the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE trial), a study conducted on 4,401 patients suffering from both T2DM and CKD. The study produced astounding results over the course of more than 2.5 years. The main outcome was a significant reduction of the incidence of combined ESRD, doubling of serum creatinine, and death from renal or cardiovascular causes (by 30% when compared to placebo). The risk of particular renal issues, such as ESRD and elevated creatinine levels, was 32% lower in the canagliflozin group and the risk of kidney failure alone was decreased by 34%. Patients taking canagliflozin additionally had lower risk of cardiovascular mortality and hospitalisation for heart failure. Glycated haemoglobin levels, blood pressure, weight-loss and the urine albumin-to-creatinine ratio also improved as a result of the treatment. [24]. Treating patients with T2DM and CKD could be greatly aided by this data, but given the several similar pathomechanisms between obesity and T2DM, canagliflozin may also prove highly beneficial for obese patients with CKD who are not diabetic.

In 2020, a similar study was published which evaluated the effect of dapagliflozin on both T2DM and non-T2DM patients. The Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) study demonstrated a remarkable decrease in the risk of kidney failure in general, including ESRD. Regardless of whether or not the individuals had T2DM, dapagliflozin provided close advantages [25]. This suggests that irrespective of the aetiology or diabetes status, SGLT2i are positioned as a pivotal disease-modifying therapy for chronic renal disease. The current opinion is that the absolute benefits outweigh the hazards, notwithstanding a relative increase in the likelihood of some adverse responses (such as lower limb amputation, urinary tract infections, and mycotic vaginal infections). When comparing SGLT2i to a placebo, many meta-analyses show a consistent favourable result in terms of weight reduction [16].

GLP-1 analogues (GLP-1a) have been approved for treating T2DM as well as obesity. They cause a moderate to high degree of weight reduction by increasing the feeling of fullness, decreasing hunger, and suppressing glucagon in a glucose-dependent way. The existing data suggests that GLP-1a have benefits in decreasing renal and/or cardiovascular issues in individuals who suffer from T2DM, especially those who have

experienced a cardiovascular event in the past or are at risk for developing one. [16]. The treatment has also proven to slow down the course of albuminuria. It has no major impact on retinopathy, hypoglycaemia, and unfavourable pancreatic events. Additionally, GLP-1a seem to contribute more to weight reduction than SGLT2 inhibitors (SGLT2i) [16].

As previously established, obesity may cause hyperactivation of the RAAS. This system is also a target for pharmaceutical treatment. Trials investigating the efficacy of RAAS-targeting medications on T2DM patients found a significant decrease (16% – 20%) of combined mortality, creatinine levels and risk of developing kidney failure. Additionally, urine protein levels in those with obesity-related glomerulopathy were found to have declined by 30% – 80% from baseline. This data comes from collective analysis of a few different studies [1]. This data was collected independent of the lowering of blood pressure, therefore the treatment proves useful in patients who do not suffer from hypertension.

Bardoxolone methyl is a novel medication that has shown particularly promising results in CKD patients. It improves mitochondrial activity, suppresses pro-inflammatory signals, and amplifies the protective antioxidant reaction. [26]. The most important study so far was published in 2013 (Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes [BEACON]: The Occurrence of Renal Events) evaluated 2,185 participants with stage 4 CKD and T2DM. Although the study had to be discontinued due to safety concerns, the findings were quite fascinating. Compared to the placebo group, the bardoxolone methyl group presented a substantial increase in kidney function and blood pressure, as well as significant decrease in body weight [27]. Since then, a few articles have analysed that data, undertaking a more cautious selection of participant (excluding patients with fluid retention due to heart failure) in an attempt to reduce adverse effects. A *post-hoc* analysis from 2018 revealed the possible benefits of bardoxolone methyl in protecting kidney function [26]. Another study, also published in 2018, investigated effects of the drug in obese patients. The findings revealed substantial decreases in body weight (proportional to baseline BMI) and waist circumference, as well as improvements in glycaemic control, particularly in individuals with glycated haemoglobin levels exceeding clinical practice guideline, suggested objectives at baseline. The decrease in weight was not caused by muscle wasting, since 24-hour urine creatinine excretion remained constant. The trend of gains in eGFR after therapy diverged from that of weight loss, demonstrating actual improvements in measured GFR. Overall, bardoxolone methyl may be a beneficial therapy for obesity in people with T2DM and CKD, provided the risk of symptomatic heart failure is reduced by dosage titration or other measures [28].

Delete: Based on the collected data, the authors of the current review provide suggestions for individualised plans for the prevention and treatment of obesity and CKD.

CONCLUSIONS

To prevent obesity-related chronic kidney disease, the most effective strategy appears to be to lose weight promptly and adopt healthier eating habits before any kidney symptoms develop. For overweight patients without comorbidities or CKD risk factors, weight reduction through diet and exercise

has significant advantages. VLCKD and GLP-1a are options for individuals in this category who have a BMI approaching obesity. For patients with a BMI over 40 kg/m², or 35 kg/m² with comorbidities, bariatric surgery is a viable option. More importantly, the current findings show benefits in incorporating GLP-1a, VLCKD, and/or bardoxolone methyl in this group. For those at high risk of CKD and with mild to moderate CKD, a healthy and nutritious diet and exercise can be very beneficial. Additionally, in this category, all aforementioned treatment methods could be considered in various combinations, tailored to the patient's individual history and needs, noting that VLCKD is an appropriate option only to be proposed for patients without diabetes. For those with end-stage renal failure who are not eligible for transplantation, LSG may be offered to assist with weight reduction. For patients with severe CKD, findings do not support incorporating VLCKD or diet and exercise as previously described, because lifestyle adjustments must be carefully aligned with renal function and dialysis requirements. Canagliflozin and dapagliflozin are primarily recommended for patients with T2DM, but they might also be effective for those with CKD only. GLP-1a can be highly beneficial for obese patients, with or without T2DM, and with or without CKD. RAAS-targeting medications might be used in obese patients with CKD, regardless of whether or not they have hypertension. Bardoxolone methyl appears to be highly effective across nearly all patient groups, but is not typically recommended solely for treating overweight. Table 1 summarises the recommended treatment methods for the various patient groups.

Treatment method	Comorbidities					
	Overweight	Obesity	Obesity with high risk of CKD	Obesity with mild to moderate CKD	Obesity with severe CKD	Obesity with CKD and T2DM
Diet and exercise	+	+	+	+	-	+
Bariatric surgery	-	+/-	+	+	+	+
Very Low Carb Ketogenic Diet (VLCKD)	+/-	+	+	+	-	-
SGLT2i	-	+/-	+	+	+/-	+
GLP-1a	+/-	+	+	+	+	+
RAAS - targeting medications	-	-	+	+	+/-	+/-
Bardoxolone methyl	-	+	+	+	+	+

Table 1. Effectiveness of mentioned treatment methods in groups of patients with different comorbidities (+) – effective; (+/-) – effectiveness differs significantly among patients in the same group; (-) – ineffective or contraindicated

It is important to note that because this work is not a meta-analysis or a systematic review, our findings were not intended to be viewed as a gold standard. These only serve as concepts for physicians to consider while working with patients, as well as for future researchers to investigate further.

The increasing worldwide prevalence of obesity is concerning due to the associated dangers, which include an increased risk of developing CKD. The pathomechanism underlying the connection between the two conditions is complex and involves several processes. It is crucial to recognise and understand these mechanisms in order to develop novel therapeutic approaches for obese patients,

reduce their risk of developing CKD, and lessen the severity of the condition once it does develop. An individualised comprehensive treatment plan, based on the relationship between the two diseases, should be provided for those patients.

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