# Obesity-induced diabetic kidney disease-review on pathophysiology and clinical manifestations

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**Abstract**
Obesity is a leading global disease and a major risk factor for diabetes which in turn causes metabolic diseases like chronic kidney disease (CKD) with increased mortality and morbidity. However, the relationship between obesity and diabetic kidney diseases (DKDs) remains unclear. Numerous factors in obesity lead to insulin resistance through adipocyte dysfunction. Insulin resistance is a major player in developing diabetes and promoting kidney disease. Major inflammatory cytokines and adipokines produced by adipocytes in the obese phase have various metabolic effects on the system leading to metabolic diseases. Even though obesity, diabetes, and kidney disease have a well-known correlation, the progression of DKD induced by obesity remains still unclear. In this review, we tried to understand the major pathophysiological mechanism linking obesity and DKDs. In addition, we also try to discuss the clinical manifestations and various effective therapeutics for future treatment.
**Keywords:** Diabetic kidney disease, Cytokines, Obesity, Insulin resistance, Hyperglycemia, Chronic kidney disease, Renin-angiotensin-aldosterone system
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## Introduction

Obesity is an exploding health problem globally. Worldwide 312 million adults were estimated as obese in the 21st century (1) and the number of diabetic patients has increased to 463 million globally in 2019. Diabetes is a multifactorial disease, with obesity being the major contributor to diabetes-related insulin resistance and hyperglycemia. The rapid rise of obesity-induced type 2 diabetes is significantly seen in developed and developing countries. Obesity contributes to type 2 diabetes in approximately 90% of cases. Additionally, 197 million people worldwide suffer from impaired glucose tolerance, most frequently as a result of obesity and related metabolic syndrome (2). Although obesity is the main driving force behind the increasing prevalence of type 2 diabetes, other factors, including genetic and environmental factors, have a significant contribution to the development of diabetic disease as well. There is growing evidence that the incidence of chronic kidney disease (CKD) is rising in part due to the markedly high prevalence of type 2 diabetes and obesity (3). "Diabesity" is a term that has been coined to describe the interdependence of diabetes and obesity. The progression from obesity to diabetes is promoted by increased insulin resistance coupled with

progressive defects in insulin secretion. Insulin resistance and inadequate insulin secretion emerge very early in the course of obesity-related diabetes patients. Tumor necrosis factor (TNF) and interleukin-6 (IL-6) plasma concentrations are increased in the insulin-resistant states of obesity and type 2 diabetes, explicating the linking mechanisms underlying inflammation in these two conditions (4). These pathophysiological links between type 2 diabetes and obesity are directing strong evidence. Patients with diabetes mellitus are often known to exhibit high mortality and morbidity causing diabetic kidney disease (DKD). Renal fibrosis, along with altered renal hemodynamics, oxidative stress, inflammation, hypoxia, and an overactive renin-angiotensin-aldosterone system (RAAS), is a key factor in the pathogenesis of DKD (5). Obesity-related kidney disease however is linked to physiological, anatomical, and pathological changes in the kidney, like diabetes-related kidney disease. Obese people with diabetes have a higher risk of developing CKDs than normal people. This is a significant factor in the higher cumulative incidence of CKD in type 2 diabetes than in type 1 diabetes (6). In this review, we aim to provide insights into the mechanisms that may lead to DKD as a result of obesity, its pathophysiology, and

clinical manifestations from existing literature. Further, we discussed the potential therapeutics for obesity-related DKD which can be used for targeted therapies in near future.

### Epidemiology of obesity and diabetes

As a global disease burden, DKD needs immediate attention. However, the number of individuals with diabetes who develop CKD during any given period has decreased as a result of improvements in diabetes management. The study revealed the prevalence of DKD in India to be 34.4% (7) and a multicentre study conducted in India, showed that 62.3% of people had diabetic CKD (8). Further, a study by Deng et al revealed that type 2 diabetes has ascended to the position of the second leading cause of CDK and CDK-related deaths (9). The prevalence of obesity was found to be 38.4% for men and 36.2% for women among the Indian population (10). In 2015, it was estimated that 609 million adults were obese, representing 39% of the world population. Obesity has become more prevalent among people of all ages and genders, regardless of location, ethnicity, or socioeconomic status, though it tends to be more prevalent in the elderly and women (11). Numerous studies have demonstrated that the significant increase in type 2 diabetes prevalence and obesity is linked to the emergence of CKD and end-stage kidney disease (ESKD) (12). The study, which included 74,986 prehypertensive participants in the Nord-Trondelag in Norway, found that obesity significantly raises the risk of CKD (13).

### Pathophysiological pathways of obesity-induced DKD
#### Adipokine imbalance

Adipokines, the bioactive polypeptides reported to be abundant in human blood which is secreted by adipose tissue, and have been linked to the occurrence and progression of numerous diseases, including diabetes mellitus, renal insufficiency, obesity, and metabolic syndrome. By changing the glomerular filtration rate (GFR) and possibly modulating renal tubule function, adipokines such as adiponectin, leptin, resistin, and visfatin increase the risk of developing albuminuria. Via activating matrix metalloproteinase (MMP)-9 and nuclear factor kappa B (NF-κB) in monocytes and human endothelial cells, visfatin's pro-inflammatory mediator activity is crucial for the pathophysiology of vascular inflammation in obesity and type 2 diabetes (14). Follistatin-like 1 (FSTL1) is a proinflammatory cytokine, secreted by adipocytes that promote adipogenesis and could activate the NF-κB and C-Jun N-terminal kinase (JNK) signalling pathways in adipocytes and macrophages, which are crucial in obesity-induced inflammation and insulin resistance (15). Thus, the adipokine imbalance due to obesity has been known to promote insulin resistance, and vascular inflammation which in turn contributes to metabolic syndrome, and kidney diseases.

### Obesity, diabetes and glomerulopathy

Glomerulopathy is a common condition that affects the glomerulus, the impairment of which can cause haematuria or proteinuria. This impairment is brought about as a result of injury or dysfunction of the endothelium, glomerular filtration barrier, or podocytes. Adiponectin maintains the integrity of podocytes by binding to its receptor and the signalling pathways controlled by the 5 AMP-activated protein kinase. The glomerular barrier becomes more vulnerable as a result of decreased adiponectin secretion caused by increased body mass index (BMI), resulting in podocyte reduction and proteinuria (16). The dysfunction or the reduction of the podocytes leads to glomerulopathy.

### Insulin imbalance in DKD

Insulin resistance as a result of adiposity is a significant pathway that is linked to the pathogenesis of obesity-related kidney disease (17). Insulin-AKT signalling controls adipose tissue metabolism by enhancing lipogenesis, protein synthesis, and glucose uptake. Obesity-induced chronic low-grade inflammation triggers the JNK pathway, which phosphorylates IRS 1 and 2 at Ser/Thr residues and dephosphorylates IRS 1 at Tyr residues to halt IRS from activating down the signalling pathway. As a result, the PI3K/AKT insulin signalling is inhibited, which lowers the sensitivity of target cells to insulin. The accumulation of high glucose in the blood will stimulate the body to produce more insulin to reduce the excess glucose. The excess of insulin synthesis will result in hyperinsulinemia which leads to hyperproliferation. Thus, there is a link between JNK activity to insulin resistance during obesity (18). The insulin imbalance leads to insulin resistance which has a strong correlation to the development of DKD.

### Obesity, diabetes and albuminuria

Microalbuminuria (30-300 mg/d) is the first clinical sign of obesity and diabetes-related renal injury, and it can eventually progress to overt proteinuria (300-3000 mg/d). Increases in urine albumin excretion strongly correlate with increases in body weight and other markers of obesity, such as BMI, waist circumference, and waist-to-hip ratio, based on the studies conducted in overweight diabetic and nondiabetic individuals (19). Inflammation and oxidative stress associated with hyperglycaemia are known to cause glomerular filtration barrier damage,

which leads to protein leakage across the membrane, resulting in albuminuria (20).

## Overactivation of the renin-angiotensin-aldosterone system

Obesity is associated with both systemic and adipose RAAS overactivation. The RAAS is well known for regulating blood pressure, fluid homeostasis, and electrolyte balance. An increase in plasma angiotensinogen (Agt), renin, angiotensin-converting enzyme (ACE), and angiotensin (Ang II) are linked to obesity. Increases in Ang II may enhance aldosterone secretion, further which promotes insulin resistance and stimulating factors derived from adipocytes (21). By stimulating the release of chemokines, increasing oxidative stress, and inhibiting the secretion of adiponectin, Ang II can cause inflammation. In response to hyperglycemia and sodium retention, the neurohormonal RAAS pathway is primarily activated in diabetes. According to a study, hyperglycemia increases oxidative stress, the RAS, and epithelial-mesenchymal transition in the system and contributes to kidney fibrosis (22).

## Oxidative stress

Reactive oxygen species (ROS) are generated in the cells by various intracellular organelles, including the mitochondria, endoplasmic reticulum, peroxisomes, and enzyme clusters like NADPH oxidases. Oxidative stress promotes adipocytes to produce more leptin, MCP-1, IL-6, and TNF while inhibiting the production of adiponectin (23). With the high level of intracellular glucose, an increased proton gradient and the excess of NADH, FADH2 production in the inner mitochondrial membrane leads to electron leakage at complex III and the production of superoxide. Superoxide radical production is increased by NOX enzyme activation,

which catalyses the reduction of oxygen by using NADPH (24). Increased hormone levels in the renin-angiotensin system are related to obesity and increased angiotensin II levels through NOX activation, $H_2O_2$ production, and $O_2$ radical formation have been linked to oxidative stress in the vasculature. Oxidative stress causes progressive renal damage, which can result in renal ischemia, lesions to the glomeruli, cell death, and apoptosis, aggravating the severe inflammatory processes (25). Figure 1 shows the pathophysiological pathways of obesity-induced DKD.

## The role of gut microbe in DKD and obesity

Obesity, type 1 and type 2 diabetes have been linked to dysregulation in the microbiota that causes a shortage of short-chain fatty acids (SCFA), such as acetate, propionate, and butyrate. The SCFA produced by the gut microbiota enters the bloodstream and reaches the liver, adipose tissues, and kidneys through G-protein coupled receptors. Recent research has demonstrated that by promoting histone deacetylation, SCFAs from the microbiota facilitate the histones for post-translational modification in the colon. Diabetes and CKDs both have been linked to SCFA-induced epigenetic changes (26). DKD patients had lower concentrations of butyrate-producing bacteria, such as *Roseburia intestinalis* and *Faecalibacterium prausnitzii*, than the general population and had *Enterobacteriaceae* and *Proteobacteriaceae* which may increase the production of pro-inflammatory compounds. The population of *L. acidophilus, L. gasseri, L. salivarius,* and *L. amylovorus* were increased, whereas that of *L. amylovorus* was decreased in T2DM patients, indicating a significant diversity in the functional effects of bacteria on the host metabolism (27). Lipopolysaccharides (LPS), which are produced by bacteria and absorbed by the intestines, cause metabolic endotoxemia, which results in inflammation and oxidative stress. Obesity is associated with metabolic
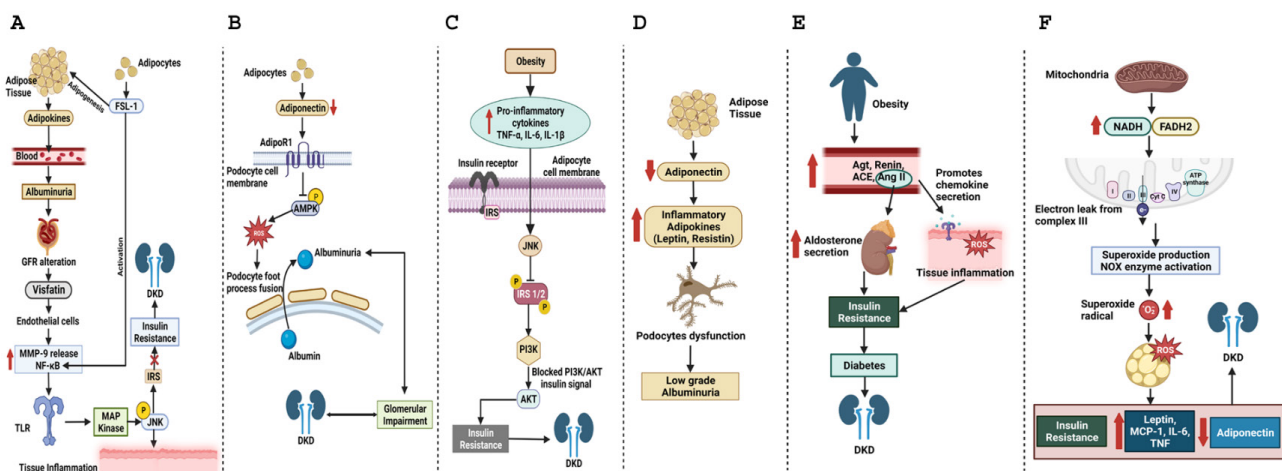


**Figure 1.** The different pathophysiological pathways of obesity-induced DKD. (A) Adipokine imbalance; (B) Obesity, Diabetes, and Glomerulopathy; (C) Insulin imbalance in DKD; (D) Obesity, diabetes, and albuminuria; (E) Overactivation of RAAS; and (F) Oxidative stress.

dysfunction caused by the induction of pro-inflammatory cytokines like IL-6 and TNF-α. Enhanced absorption of nutrients, production of SCFA, lipogenesis, inflammation, and intestinal permeability are the potential causes giving rise to DKD (28).

## Synergy of low nephron number and obesity

The number of human nephrons is essential for gaining access to the pathology of CKD because it is closely correlated to the adaptive responses of the kidneys in terms of their function and pathological states. Human nephron number fluctuates up to 13-fold with numerous factors on kidney development, such as inherited body size and ethnicity, maternal health and nutrition, gestational diabetes, and other environmental factors (29). It is hypothesized that the nephron count decreases with the advancement of kidney diseases. Birth weight is significantly correlated with nephron numbers, low birth weight individuals are more likely to develop metabolic syndrome and obesity in the future (30). It was noticed that the hemodynamic changes remain consistent with the glomerular hyperperfusion and hyperfiltration in obese patients. Additionally, it was noted that the only factor associated with the progression of renal disease due to a decreased nephron count in a study on 54 patients with unilateral renal agenesis or remnant kidneys was being overweight (31).

## Clinical manifestations

### Obesity as an independent risk factor of DKD

Obesity is known to be the main contributing factor to metabolic diseases. Leptin, cytokines, adiponectin, proinflammatory substances, and glycerol are secreted by the adipose tissues and have an impact on metabolism indicating the association of obesity with kidney disease. Insulin resistance is well-known to be influenced by obesity which is a clinical feature of both metabolic kidney diseases and diabetes. Based on the study conducted by Hill et al, a strong association between obesity with DKD was found in the English diabetes population (32). However, this association varies according to ethnicity, gender, and differences in odds of obesity. Additionally, a secondary analysis of the Look Action for Health in Diabetes (AHEAD) randomized clinical trial recommends weight loss as a complementary therapy for obese patients to halt the progression of DKD (33).

## Promotion of nephrolithiasis due to obesity

The rising incidence of nephrolithiasis in recent years has been attributed to a major part of obesity. The lithogenic urinary profile, insulin resistance, and dietary factors are thought to be connected to the underlying pathophysiology of calcium oxalate and uric acid stone formation in obese patients. A Study demonstrates that the proportion of uric acid rises with BMI (34). The renal acid-base metabolism is thought to be altered by insulin resistance, lowering the urine pH and increasing the possibility of uric acid stone formation. In obese patients, increased oxalate excretion is a major risk factor in developing calcium oxalate stones, and a positive correlation between the excretion of calcium oxalate, body weight, and body surface area was stated (35). Weight loss seems to be the primary treatment for obesity-related nephrolithiasis, but it is important to understand the complications that can arise to avoid developing serious medical issues.

## Increased risk of end-stage kidney disease in kidney donors due to obesity

End-stage kidney disease is a chronic long-term kidney disease. Indicators of central fat distribution, such as waist-to-hip ratio or visceral fat are more closely associated with the high incidence of ESKD than BMI (36). After accounting for several risk factors, such as baseline eGFR and hypertension, ethnicity, age of kidney donation, and sex, obesity was the only independent factor associated with a higher risk of developing ESKD after donation. It was predicted that 40 non-obese and 94 obese living donors per 10,000 individuals would develop ESKD within 20 years of kidney donation. The study showed male and female donors of African, American, and Caucasians with a range of baseline estimated GFRs had similar effects of obesity on ESKD risk (37).

## Role of obesity to the risk of delayed graft function in kidney transplant recipients

Kidney transplantation is the preferred course of treatment for ESKD, the end stage of last-term kidney disease. Patients receiving organ transplants from deceased donors highly experience delayed graft function (DGF). Obesity is caused by a variety of etiopathologies in renal transplant patients, and many of the factors that have an impact on the transplant are prevalent in the general population and the uremic status of the patients, general health, and their immunosuppression therapy are additional variables that are more directly associated with transplant (38). Obesity and overweight are extremely prevalent at the time of transplant. Poor clinical outcomes, including death with graft function and graft failure, have been linked to DGF. Chronic graft dysfunction, which may ultimately shorten graft longevity, may be facilitated by DGF (39). The prevalence of obesity and overweight has been rising at an alarming rate globally and the risk of obesity is progressive with increasing BMI from class I to III. Additionally, the study revealed that recipients who were pre-obese and overweight had higher risks of having kidney transplant failure than healthy recipients (40).

## Management and therapeutic strategies for the treatment of obesity-related DKD

New potential therapeutic strategies have been

implemented like protein kinase C (PKC), which is crucial in many intracellular signalling pathways. These signalling molecules are involved in the pathogenesis of DKD and can be activated through glucose. The elevated PKC can participate in the pathophysiology of DKD. It is seen that the PKC inhibitor, ruboxistaurin reduces the albuminuria rate and increases the eGFR rate in patients in clinical trials, thus, identifying it to be a novel drug (41). The mainstay of DKD therapy has been RAAS inhibitors. Esaxerenone is a novel non-steroidal mineralocorticoid receptor identified in clinical trials which are used for the treatment of type 2 diabetes with microalbuminuria (42). This inhibitor can be a potent candidate due to its safety and efficacy. Adiponectin improves insulin sensitivity in obesity-related metabolic disorders, like DM by inhibiting hepatic gluconeogenesis and enhancing glucose transporter-4 (GLUT)-mediated glucose uptake in muscle and adipose tissue (43). The adiponectin receptor agonist AdipoRon is another possible drug candidate and it is shown to ameliorate diabetes associated with obesity. In DKD, the JAK/STAT pathway is highly activated, which participates in the signalling of cytokines and chemokines that cause a range of cellular responses in obesity-induced DKD. Baricitimab, a JAK-1 and JAK-2 inhibitor, and anti-inflammatory drug, had an intriguing decrease in albuminuria and inflammatory biomarkers in phase 2 clinical trials (44). Novel adipokine, FSTL1 mediates adipogenesis, inflammation, and insulin resistance. The need for future cohort studies to gather more proof of the link between FSTL1 and metabolic disorders is required. Apart from it, microRNAs are potential targets for novel therapeutics, but it may be difficult to deliver them selectively and prevent side effects. Table 1 lists the possible therapeutics which could be used against obesity-induced DKD.

## Conclusion

Obesity related DKD is a global health issue with high prevalence and poor diagnosis. The severity of obesity influences the prevalence of DKD, ESKD, and, nephrolithiasis. We reviewed obesity and diabetes diseases regarding the several pathophysiological mechanisms which are causing DKD. Several studies explicitly the underlying mechanisms of obesity-induced diabetes, but still the mechanism of obesity-induced DKD is unclear. In particular, we have little understanding of the relative contribution of the signaling pathways which modulate kidney diseases via insulin resistance. The management strategies discussed may serve and can be utilized as a future treatment. For a better understanding of the pathophysiology that contributes to the onset of obesity-induced DKD, further research into the underlying pathway is obliged. This will assist in the discovery and development of new targeted therapies.

## Future perspectives

Regular systematic screening for obesity-induced DKD is required for early diagnosis and to reduce the prevalence earlier. To reduce obesity- and diabetes-related renal disease morbidity and mortality, novel therapeutic approaches are needed. Significant biomarkers for early identification should be investigated to improve the prognostic and diagnostic precision which could be incorporated into standard clinical care. Understanding the mentioned techniques might pave way for personalized treatment and help improve patient outcomes.

### Authors' contribution

**Conceptualization:** Gnanasambandan Ramanathan.
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**Formal analysis:** Harini Ravi and Soumik Das.
**Investigation:** Ramprasad Elumalai.
**Methodology:** Harini Ravi and Soumik Das.
**Project administration:** Gnanasambandan Ramanathan.
**Resources:** Ramprasad Elumalai.
**Supervision:** Gnanasambandan Ramanathan.
**Validation:** Harini Ravi and Soumik Das.
**Visualization:** Gnanasambandan Ramanathan.
**Writing-original draft:** Ramprasad Elumalai.

### Conflicts of interest

Authors declare no conflict of interests.

**Table 1.** List of therapeutics and their effect on obesity-induced DKD

| Possible therapeutics | Effects | References |
|---|---|---|
| Exercise | Exercise improves insulin sensitivity and glucose tolerance along with fat mass reduction | (45) |
| GLP-1 RA | Reduction in hypertension and albuminuria | (46) |
| Melatonin | Eliminates the free radicals produced by mitochondria, inhibits the NF-κB and reduces proinflammatory mediators | (47) |
| SGLT2 inhibitor | Activate glomerular feedback and decreases the GFR | (48) |
| Lorcaserin | It is a Selective serotonin 2C receptor agonist and reduces appetite | (49) |
| Pyridoxamine (Vitamin B6 derivative) | Specific AGE inhibitor. Inhibits mild vascular dysfunction and reduces the lipid content of the liver. | (49) |
| Ruboxistaurin | Specific PKCβ inhibitor. Reduces albuminuria and expression of TGF-β | (50) |

GLP-1 RA: Glucagon-like peptide – Receptor Agonist; SGLT2: Sodium-glucose cotransporter-2; NF-κB: Nuclear factor-κB; GFR: Growth factor receptor; PKCβ: Protein kinase C beta; TGF-β: Transforming growth factor beta.

## Ethical issues

The authors have completely observed ethical issues (including plagiarism, data fabrication, and double publication).

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