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Diabetic kidney disease: what we know so far – literature review

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Abstract

Diabetic Kidney Disease (DKD) is a major complication of diabetes mellitus, affecting approximately 40% of diabetic patients and representing the leading cause of chronic kidney disease and end-stage renal disease (ESRD). This review delves into the pathogenesis, diagnosis, and therapeutic advancements in DKD. Key pathological mechanisms include hyperglycemia, oxidative stress, and inflammation. Modern treatments, such as SGLT-2 inhibitors and GLP-1 agonists, offer renoprotective benefits by improving endothelial function, reducing inflammation, and mitigating oxidative stress. The review also highlights the importance of timely initiation and optimization of therapies to slow DKD progression and explores new avenues such as epigenetic therapies and autophagy enhancement. Further research is needed to fully understand the long-term benefits and optimal use of these treatments in DKD management.

Keywords: diabetes mellitus, diabetic kidney disease, oxidative stress, SGLT-2 inhibitors, hypergylicemia

Materials and methods

This review was conducted by searching PubMed for articles published in the last six years (2018-2024) using keywords such as “Diabetic kidney disease”, “Diabetes mellitus”, “SGLT-2 inhibitors”, “GLP-1 agonists”, “diabetic nephropathy”

Aim of the study

The aim of this study is to comprehensively review the current understanding of Diabetic Kidney Disease (DKD) by examining its pathogenesis, diagnostic approaches, and therapeutic advancements. The study seeks to elucidate the underlying mechanisms of DKD, including hyperglycemia, oxidative stress, inflammation, and lipid metabolism, and assess current diagnostic criteria and biomarkers. It aims to analyze the efficacy and mechanisms of contemporary treatments, such as SGLT-2 inhibitors and GLP-1 agonists, while exploring emerging therapies like epigenetic modifications and autophagy enhancement. Additionally, the study identifies research gaps to optimize DKD management and improve patient outcomes, emphasizing the need for personalized medicine approaches. By addressing these objectives, the study provides a comprehensive overview of DKD to inform clinical practice and guide future research.

Introduction

Definition

Diabetic kidney disease is the main cause of end-stage renal disease worldwide and one of the most common microvascular complications in diabetic patients. It usually occurs in patients without long-term adequate glycemic control and is one of the main causes of deaths in these patients[1]. The main pathological features of DKD are glomerular sclerosis, podocyte detachment, epithelial-mesenchymal transition (EMT)/endothelial-to-mesenchymal transition (EndMT)/macrophage-myofibroblast transition (MMT), excessive extracellular matrix (ECM) and renal tubular fibrosis. These pathological changes affect glomerular and tubular function, leading to the progression of proteinuria and decreased glomerular filtration capacity[2]. A urinary albumin to creatin ratio higher than 30mg/g used to be the major diagnostic criterion and level of albuminuria was considered the best predictor of loss of kidney function. However, later discovered that DKD progression to End-stage renal disease may follow two distinct pathways, with and without albuminuria, which is more frequent in Type 2 Diabetes. Therefore, DKD as well as chronic kidney disease is currently diagnosed using progressive decrease in the estimated glomerular filtration rate (eGFR) below 60ml/m/1,73m2[3]. Current observations suggest that non-albuminuric pathway may involve processes at the tubulointerstitial and vascular levels, cause by multiple factors, such as hypertension, dyslipidemia, obesity and aging[4].

Epidemiology

In 2021, the International Diabetic Federation predicted that roughly 537 million individuals (20–79 years) are living with diabetes worldwide[5] According to USA data approximately 30% of patients with Type 1 Diabetes and 40% of patients with Type 2 Diabetes develop DKD[6]. The number of patients with DKD is expected to increase due to the rise in global diabetes prevalence, which is estimated to increase by nearly 50% over the next 24 years[7].

Diagnosis

DKD is a clinical diagnosis, which requires establishing diagnosis of diabetes mellitus and demonstrating symptoms of kidney disease based on albuminuria or decrease of eGFR. Albuminuria is traditionally measured over 24h although it is tested most commonly by a random spot urine albumin-to-creatinine ratio. An elevated spot urine albumin-to-creatinine ratio of >30 mg/g is considered significant which should be present in at least 2 or 3 samples over 3–6-month time period. Screening for DKD should be done at least once a year, starting 5 years from diagnosis of Type 1 Diabetes or upon diagnosis of Type 2 diabetes. Biopsy of a kidney is usually not necessary but can be useful in atypical cases[8].

Pathogenesis

Pathogenesis of DKD is not fully understood, however several factors has been proven to contribute to development of renal injury including hyperglycemia, lipid accumulation, oxidative stress, hypoxia, RAAS, ER stress, EMT and programmed cell death.

Hyperglycemia

Due to hyperexpression of glucose transporters high concentration of glucose in extracellular matter will ultimately increase intracellular glucose concentration, which leads to shunting glucose to fructose 6-phosphate and hexosamine metabolic pathways. Therefore, hyperglycemia increases production of advanced glycation end products (AGEs) and reactive oxygen species (ROS), which are associated with the development of DKD. Under these conditions ROS are produced at high levels, and this can lead to other diabetic complications[9]. Also, accumulation of AGEs, causes activation of protein kinase C (PKC)-α, -β, and -δ , and oxidative stress. These changes can damage the renal tubules by disrupting their normal cellular functions, such as ion transport and energy metabolism[10]

Oxidative stress

Oxidative stress is defined as a response to oxidant-antioxidant balance disorder. Upon stimulation due to hyperglycemia, numerous reactive oxygen and nitrogen forms are produced and cannot be completely scavenged by antioxidant defense systems, which leads to physiological and pathological reactions in cells and tissues.

Oxidative stress response may be activated by many pathways including hexosamine pathway and polyol pathway. In the hexosamine pathway approximately 2-5% of glucose-6-phosphate is converted to fructosoe-6phosphate (F6P) and then enters the hexosamine pathway. At states of prolonged hyperglycemia F6P is undergoing several enzymatic reactions using glutamine fructose-6-phosphate aminotransferase (GFAT) which in state of overexpression increases NF-κB promoter activity and TNF-α expression in mesangial cells and stimulates the production of TGF-β1 and PAI-1, inducing inflammatory response, extracellular matrix (ECM) accumulation and diabetic glomerulosclerosis.

Another pathway is polyol pathway in which glucose is reduced to sorbitol under the actions of aldose reductase (AR) and nicotinamide adenine dinucleotide phosphate and then oxidized to fructose in presence of sorbitol dehydrogenase (SDH) and nicotinamide adenine dinucleotide. In states of hyperglycemia AR is activated, causing increased production of sorbitol. Due to the consistent SDH activity, the produced sorbitols are accumulated in cells, which causes an increase in cell membrane permeability, resulting in exudation of intracellular matters such as inositol and reduced glutathione (GSH) and eventually oxidative stress response. During this metabolic process, the activation of AR is dependent on NADPH, while the metabolism of excessive glucose consumes large amounts of NADPH, leading to reduced GSH production and ROS scavenging capacity, eventually resulting in redox balance disorder *in vivo*.

The last-mentioned pathway is the AGEs pathway. AGEs are a highly reactive, end products of non-enzymatic reactions between glucuronyl and free amino groups. Prolonged hyperglycemia accelerates AGEs production which causes an increase of ROS production. A large body of research suggested that receptor for AGEs (RAGE) is increasingly expressed by glomerular epithelial cells, mesangial cells, endothelial cells, and podocytes upon hyperglycemia stimulation. The RAGE binding to AGEs activates NADPH oxidase to increase ROS production in endothelial cells, which disturbed molecular conformation and altered enzyme activity, inducing oxidative stress responses. Therefore, the activated oxidative stress mediates the downstream signaling pathways (e.g., NF-κB, TNF-β, JNK, and p38-MAPK to increase the release of adhesion molecules, vascular endothelial factors and inflammatory factors leading to multiple mechanisms that contribute to renal injury, such as renal interstitial fibrosis and mesangial expansion[11].

Lipid accumulation

Lipid accumulation is a common feature in the tubular cells of patients with DKD. Lipid accumulation is most likely caused by increased lipid synthesis and uptake, decreased β-oxidation and cholesterol efflux. In the course of DKD, downregulation of energy metabolism genes occurs leading to suppressed AMP kinase signaling, followed by downregulation of fatty acid oxidation genes. Lipotoxicity in renal tubular epithelial cells is associated with inflammation, oxidative stress, mitochondrial dysfunction and cell death. Hypercholesterolemia also results in creating lipid deposition in kidney tissue affecting oxygen delivery through diffusion. Furthermore, lipid deposition in renal arteries increases their stiffness making them less responsive via dilation which reduces blood flow and causing hypoxia.

Ischemia and hypoxia

The blood supply to tubular epithelial cells originates from efferent arterioles of the glomeruli, reaching veins surrounding renal tubules. Hypoxia is a crucial factor causing the onset and progression of DKD. Hemodynamic changes, metabolic factors, and immune responses can directly damage vascular endothelial cells, leading to the local activation of the RAS or a decrease in NO levels. This results in renal vasoconstriction and reduced oxygen delivery. As oxygen transport decreases, kidney perfusion is disrupted, worsening renal hypoxia.

Consequently, renal tubular epithelial cells suffer from mitochondrial dysfunction and impaired oxygen use, leading to cellular degeneration, atrophy, damage to periductal capillaries, and a further reduction in blood supply. These cascading effects contribute to interstitial fibrosis and a decline in kidney function[13].

Mitochondrial dysfunction

Mitochondrial dysfunction plays a significant role in the progression of diabetic kidney disease (DKD). The mitochondria are critical for cellular energy production and homeostasis, and their dysfunction in DKD contributes to several pathogenic processes. In DKD, high glucose levels and other metabolic disturbances lead to the overproduction of reactive oxygen species (ROS) within the mitochondria. This oxidative stress damages mitochondrial DNA, proteins, and lipids, impairing their function and triggering inflammatory pathways. Mitochondrial ROS has been linked to the activation of the NLRP3 inflammasome, a key driver of inflammation in DKD. Diabetic conditions induce metabolic reprogramming in kidney cells, shifting energy production from oxidative phosphorylation to glycolysis, a less efficient process. This shift reduces ATP production, exacerbating cellular stress and energy deficits in renal cells. Metabolic changes also affect the balance of NADH and NAD+, affecting mitochondrial function and promoting further metabolic disturbances. The balance between mitochondrial biogenesis and mitophagy (the removal of damaged mitochondria) is disrupted in DKD. Factors like PGC-1α, a master regulator of mitochondrial biogenesis, are downregulated, leading to reduced mitochondrial content and function. Additionally, impaired mitophagy results in the accumulation of dysfunctional mitochondria, further contributing to cellular damage and kidney dysfunction.

Mitochondrial dysfunction leads to cell death through apoptosis and necrosis pathways. Damaged mitochondria release pro-apoptotic factors like cytochrome c, initiating cell death cascades. This cell loss, particularly in renal tubular epithelial cells, contributes to tubulointerstitial fibrosis, a hallmark of DKD. Fibrosis impairs kidney function by replacing functional tissue with scar tissue .[14]

Inflammation

Inflammation plays a key role in the development and progression of DKD. The pro-inflammatory and pro-fibrotic processes result in metabolic alterations, hyperfiltration, ROS, immune and inflammation activation and subsequent fibrosis. Although DKD usually is classified as a non-inflammatory glomerular disease, genome-wide transcriptome analysis studies strongly indicate presence of inflammatory signaling pathways. Diabetic kidney had an approximate 7- to 8-fold increase in leukocytes compared to controls, and among total 347 immune cells consisted of 49% T cells, 21% B cells, 23% monocytes, and 7% plasma cells.

Key mechanisms of inflammation in DKD include:

Nuclear Factor Kappa B (NF-κB): Hyperglycemia and oxidative stress activate NF-κB, a transcription factor that induces the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These cytokines play a pivotal role in promoting inflammation within the kidneys.

Inflammasomes: Specifically, the NLRP3 inflammasome is activated in response to metabolic stress, leading to the release of IL-1β and IL-18. These cytokines further drive the inflammatory process, contributing to tissue damage.

Macrophages: Both resident and infiltrating macrophages in the kidney increase in number during DKD. These macrophages can adopt different activation states, with a shift toward the M1-like pro-inflammatory phenotype being predominant. This polarization amplifies the inflammatory response and exacerbates kidney damage.
Gene Expression Changes: Single-cell transcriptomic analyses reveal that macrophages in DKD exhibit heightened expression of both pro-inflammatory and anti-inflammatory genes. This dynamic gene expression reflects the complex and evolving nature of inflammation in DKD.
Cytokines: Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β are elevated in DKD. These cytokines contribute to endothelial dysfunction, increased vascular permeability, and fibrosis. Their presence correlates with disease severity and progression.
Advanced Glycation End Products (AGEs): AGEs accumulate in diabetic conditions and interact with the receptor for AGE (RAGE) on renal cells. This interaction activates NF-κB and other inflammatory pathways, further promoting inflammation and kidney damage.
Chronic Inflammation: Persistent activation of inflammatory pathways leads to sustained inflammation, which causes progressive damage to the glomeruli and tubulointerstitium. This results in glomerulosclerosis and tubulointerstitial fibrosis, hallmark features of DKD.
Fibrosis: Inflammatory cytokines and mediators promote the activation of fibroblasts and the deposition of extracellular matrix proteins, leading to renal fibrosis. Fibrosis impairs kidney function and contributes to the progression of DKD to end-stage renal disease.
These interconnected processes highlight the critical role of inflammation in DKD, from initial metabolic alterations and immune activation to chronic inflammation and fibrosis, ultimately driving the disease towards end-stage renal failure[15].
Renin-angiotensin-aldosterone system

The pathogenesis of diabetic kidney disease (DKD) involves intricate metabolic and inflammatory mechanisms, with significant contributions from the renin-angiotensin-aldosterone system (RAAS) and sodium-glucose cotransporter 2 (SGLT2). Angiotensin II, a critical bioactive component of RAAS, is elevated in DKD and promotes reactive oxygen species (ROS) production, leading to podocyte damage through calcium influx and subsequent renal injury and glomerular hypertension. This hypertension contributes to kidney enlargement due to increased single nephron glomerular filtration rate (GFR).
Aldosterone, another RAAS component, plays a crucial role in DKD by increasing extracellular matrix protein production, which is essential in the disease's pathogenesis. Under high-glucose conditions, aldosterone induces the expression of TGF-β1 and the type IV collagen gene in cultured mesangial cells, promoting macrophage infiltration in the glomerulus and tubulointerstitium. It also stimulates pro-fibrotic molecules such as connective tissue growth factor (CTGF) and plasminogen activator inhibitor-1 (PAI-1) and exacerbates inflammation via ROS. Aldosterone's effects culminate in vascular dysfunction, fibrosis, cardiac hypertrophy, and renal inflammation. Furthermore, aldosterone inhibits regulatory T (Treg) lymphocytes, which suppress immune responses, leading to further dysregulated inflammation and fibrosis[16,17].

Role of vasopressin in pathogenesis of DKD

Vasopressin, or antidiuretic hormone (ADH), is primarily known for its role in regulating the body's water balance by promoting water reabsorption in the kidneys. In the context of DKD, vasopressin's effects on kidney function become more pronounced. The hormone acts on the renal collecting ducts and tubules through its receptors, particularly the V2 receptors, to enhance water reabsorption. However, in DKD, this mechanism can become maladaptive. Increased vasopressin activity can lead to excessive water reabsorption, contributing to fluid overload. This condition exacerbates hypertension and increases the risk of heart failure, which are common comorbidities in diabetic patients with kidney disease. The altered water reabsorption can disturb electrolyte balance, causing issues such as hyponatremia (low sodium levels) or hyperkalemia (high potassium levels), which further complicates the management of DKD.

Vasopressin also has significant metabolic effects beyond its role in fluid balance. The paper emphasizes how dysregulation of vasopressin impacts metabolic pathways in the context of DKD. Vasopressin can influence glucose metabolism, potentially worsening insulin resistance and hyperglycemia. Elevated vasopressin levels might interfere with normal glucose homeostasis, exacerbating the metabolic disturbances seen in diabetic patients. The hormone affects renal metabolic processes, including those involved in the production and excretion of metabolic byproducts. Dysregulation can lead to further renal impairment and contribute to the overall progression of kidney disease. Both excessive and insufficient vasopressin activity can adversely affect kidney health. Increased vasopressin levels can lead to persistent fluid retention and hypertension, which aggravate renal damage and accelerate disease progression. This excessive activity is often associated with more severe kidney dysfunction and complications in DKD patients. On the other hand, insufficient vasopressin activity can lead to inadequate fluid reabsorption, resulting in dehydration and imbalances that stress the renal system further. This condition might also contribute to a worsening of kidney function over time[18].

Autophagy dysfunction

In diabetic kidney disease, autophagy dysfunction plays a pivotal role in disease progression. Normally, autophagy degrades and recycles damaged organelles and proteins, maintaining cellular homeostasis. However, hyperglycemia and associated oxidative stress impair autophagic processes in DKD. This impairment leads to the accumulation of damaged cellular components, increased oxidative stress, and heightened inflammation, contributing to renal cell injury and fibrosis. Specific mechanisms include reduced expression of autophagy-related genes and proteins, and impaired autophagosome formation and clearance.

Autophagy in podocytes: podocytes are specialized cells in the glomerulus crucial for maintaining the kidney’s filtration barrier. Autophagy is essential for podocyte health and function, as it helps in the clearance of damaged mitochondria and misfolded proteins. In DKD, autophagy in podocytes is impaired, leading to the accumulation of these damaged components. This impairment contributes to podocyte injury, detachment, and loss, which in turn disrupts the glomerular filtration barrier, leading to proteinuria and progressive kidney damage. Key factors contributing to autophagy dysfunction in podocytes include hyperglycemia-induced oxidative stress and inflammation, which downregulate autophagy-related genes and pathways[19].

Treatment of DKD

SGLT-2 inhibitors

SGLT2 inhibitors have revolutionized the treatment of diabetic kidney disease by offering multiple benefits that extend beyond glycemic control. According to Lytvyn et al. (2020), these inhibitors work by blocking the sodium-glucose cotransporter-2 in the proximal tubules of the kidney, leading to increased glucose excretion and subsequently lowering blood glucose levels. This action not only improves glycemic control but also reduces hyperfiltration and glomerular hypertension, key factors in the progression of DKD. Additionally, SGLT2 inhibitors have been shown to decrease albuminuria, a marker of kidney damage, and slow the decline in glomerular filtration rate (GFR), thereby preserving kidney function over time[20].

The anti-inflammatory and antioxidant properties of SGLT2 inhibitors further contribute to their renoprotective effects. As highlighted by Winiarska et al. (2021), inflammation and oxidative stress play critical roles in the pathogenesis of DKD. By mitigating these processes, SGLT2 inhibitors help protect renal tissues from damage. This is supported by evidence showing reduced levels of pro-inflammatory cytokines and markers of oxidative stress in patients treated with these drugs. Additionally, SGLT2 inhibitors improve renal metabolic health by enhancing mitochondrial function and reducing renal hypoxia, which are crucial in preventing the progression of DKD[21].By inhibiting SGLT2, these drugs reduce the infiltration of inflammatory cells into the kidneys and lower the expression of inflammatory cytokines, contributing to a less inflammatory renal environment. Additionally, the study discusses the potential of SGLT2 inhibitors to improve renal fibrosis by reducing the activity of fibrotic pathways, thereby preserving kidney structure and function.

Moreover, Dai et al. (2023) point out that SGLT2 inhibitors improve renal hemodynamics by restoring tubuloglomerular feedback, a mechanism that helps regulate glomerular filtration rate and renal blood flow. This effect is particularly beneficial in preventing hyperfiltration injury that is commonly observed in early stages of DKD. The study also emphasizes the role of SGLT2 inhibitors in enhancing autophagy, a cellular process that removes damaged proteins and organelles, which helps in maintaining cellular health and function in the kidneys.

Moreover, SGLT2 inhibitors have demonstrated cardiovascular benefits, which are particularly important for patients with DKD who are at high risk of cardiovascular events. Clinical trials have shown that these inhibitors reduce the risk of heart failure and other major cardiovascular events, further emphasizing their comprehensive benefits in managing DKD.

In summary, SGLT2 inhibitors represent a significant advancement in the treatment of DKD by addressing multiple pathophysiological aspects of the disease, including hyperglycemia, hyperfiltration, inflammation, and oxidative stress. Their ability to improve both renal and cardiovascular outcomes makes them a cornerstone in the management of patients with DKD.

Research has also indicated that SGLT2 inhibitors exert protective effects on kidney morphology. Histopathological studies in diabetic models show that these drugs can reduce glomerular hypertrophy and fibrosis, two key pathological features of DKD. By mitigating these structural changes, SGLT2 inhibitors help preserve the integrity and function of renal tissues, further highlighting their role in slowing the progression of DKD.

Additionally, the metabolic benefits of SGLT2 inhibitors extend to improving lipid profiles and reducing body weight, both of which are beneficial for patients with DKD who often struggle with metabolic syndrome. These effects are partly attributed to the caloric loss associated with glycosuria and the subsequent utilization of fat stores, which contribute to weight loss and improved metabolic health.

Overall, the comprehensive benefits of SGLT2 inhibitors in managing DKD make them an essential therapy in the arsenal against this debilitating condition. Their multifaceted mechanisms of action not only address the glycemic aspects of diabetes but also provide substantial renal and cardiovascular protection, which are critical for improving the long-term outcomes of patients with DKD[22,23,24,25].

GLP-1 agonists

GLP-1 agonists play a pivotal role in the management of diabetic kidney disease (DKD) by targeting multiple pathological mechanisms integral to disease progression. These agents extend their benefits beyond glycemic control, offering significant renoprotective effects through the improvement of endothelial function and the reduction of inflammation and oxidative stress within the renal microvasculature. GLP-1 agonists achieve these effects both directly, by enhancing the health of the kidneys' filtering units, and indirectly, by promoting systemic improvements such as better glucose control, reduced blood pressure, and weight loss. This dual action helps mitigate the multifactorial damage seen in DKD.

These agents exert their beneficial effects by modulating key molecular pathways involved in inflammation and oxidative stress. They inhibit NF-κB, a pivotal regulator of inflammatory responses, and enhance Nrf2 activity, which is crucial for the antioxidant defense system. These molecular actions help to reduce renal inflammation and oxidative damage, key contributors to DKD progression.

Additionally, recent insights into the molecular mechanisms of DKD highlight that GLP-1 agonists also affect pathways related to cellular stress responses and fibrosis. These agonists can reduce the activity of transforming growth factor-beta (TGF-β), a critical mediator of fibrosis in DKD. This reduction in TGF-β activity helps to mitigate the progression of kidney fibrosis, a common and detrimental complication of DKD. Furthermore, GLP-1 agonists are shown to improve autophagy, a cellular process involved in the degradation and recycling of cellular components, which is often impaired in DKD.

Moreover, GLP-1 agonists are compared with SGLT2 inhibitors, another class of therapeutic agents used in DKD management. While both drug classes demonstrate significant renoprotective effects, they do so via distinct mechanisms. GLP-1 agonists primarily exert their benefits by reducing inflammation and oxidative stress, whereas SGLT2 inhibitors primarily improve renal outcomes through hemodynamic changes, such as reducing hyperfiltration and preserving renal function.

The comprehensive benefits of GLP-1 agonists, including their anti-inflammatory, antioxidant, antifibrotic, and metabolic effects, make them a promising therapeutic option for slowing the progression of DKD. However, there is a need for further extensive clinical trials to better understand the long-term benefits, mechanisms of action, and optimal use of GLP-1 agonists in the DKD patient population. Overall, these findings underscore the potential of GLP-1 agonists to significantly impact the management and progression of DKD through their multifaceted therapeutic actions[16,20,21].

DPP-4 inhibitors

DPP-4 inhibitors play a significant role in the management of diabetic kidney disease (DKD) by targeting key pathological mechanisms involved in the disease's progression. These agents primarily improve glycemic control, which indirectly benefits renal function. By inhibiting the DPP-4 enzyme, these drugs increase the levels of incretin hormones, such as GLP-1, thereby enhancing insulin secretion and reducing glucagon levels, which helps to manage blood glucose levels more effectively.

In addition to their glycemic effects, DPP-4 inhibitors offer direct renoprotective benefits. They help reduce renal inflammation and oxidative stress, two critical factors in the progression of DKD. By modulating the activity of the NF-κB pathway, DPP-4 inhibitors reduce the inflammatory responses within the kidneys. Moreover, these agents enhance the activity of antioxidant pathways, such as Nrf2, helping to mitigate oxidative damage in renal tissues.

Recent advances in the understanding of DKD mechanisms reveal that DPP-4 inhibitors also impact cellular stress responses and fibrosis. These inhibitors can reduce the activity of transforming growth factor-beta (TGF-β), a key mediator of fibrosis in DKD. Lowering TGF-β activity helps to prevent the progression of kidney fibrosis, a common and severe complication of DKD. Furthermore, DPP-4 inhibitors improve autophagy, a crucial cellular process for degrading and recycling cellular components, which is often impaired in DKD.

When comparing DPP-4 inhibitors to other classes of diabetes medications, such as SGLT2 inhibitors and GLP-1 agonists, it is evident that while each class has unique mechanisms of action, they all offer renoprotective benefits. DPP-4 inhibitors mainly provide their benefits through metabolic control and anti-inflammatory effects. In contrast, SGLT2 inhibitors primarily work by reducing hyperfiltration and providing hemodynamic benefits, and GLP-1 agonists exert their effects by reducing inflammation, oxidative stress, and fibrosis.

The multifaceted benefits of DPP-4 inhibitors, including their glycemic, anti-inflammatory, antioxidant, and antifibrotic effects, make them a promising therapeutic option for managing DKD. However, further clinical trials are needed to better understand the long-term benefits, specific mechanisms of action, and optimal use of DPP-4 inhibitors in the DKD patient population. Overall, these findings highlight the potential of DPP-4 inhibitors to significantly impact the management and progression of DKD through their comprehensive therapeutic actions.

RAAS inhibitors

RAAS inhibitors primarily function by lowering blood pressure and reducing proteinuria, both of which are critical in slowing the progression of DKD. By blocking the effects of angiotensin II, these drugs decrease vasoconstriction and aldosterone secretion, leading to reduced blood pressure and less strain on the kidneys' filtering units. Additionally, RAAS inhibitors have been shown to reduce the permeability of the glomerular basement membrane, thereby lowering protein excretion in the urine, which is a marker of kidney damage.

Beyond their hemodynamic effects, RAAS inhibitors also exhibit anti-inflammatory and antifibrotic properties. These agents help to reduce inflammation within the renal microvasculature, which is a significant contributor to the progression of DKD. By modulating the activity of pro-inflammatory cytokines and inhibiting pathways such as NF-κB, RAAS inhibitors mitigate inflammatory responses in the kidneys.

Moreover, they reduce the activity of transforming growth factor-beta (TGF-β), a crucial mediator of renal fibrosis. Lowering TGF-β activity helps prevent the progression of kidney fibrosis, a common and detrimental complication of DKD.

Recent insights into DKD mechanisms, as highlighted in Gembillo et al. (2021), emphasize the importance of addressing therapeutic inertia in the management of DKD. Therapeutic inertia, the failure to initiate or intensify therapy when indicated, is a significant barrier to effective DKD management. The paper underscores the need for timely initiation and optimization of RAAS inhibitor therapy to achieve better renal outcomes. It also highlights the potential of combining RAAS inhibitors with other therapeutic agents, such as SGLT2 inhibitors and GLP-1 agonists, to enhance renoprotective effects through complementary mechanisms.

When comparing RAAS inhibitors to other classes of diabetes medications, such as SGLT2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors, it is evident that while each class has unique mechanisms of action, they all contribute to renal protection in DKD. RAAS inhibitors mainly provide benefits through hemodynamic control, anti-inflammatory, and antifibrotic effects. In contrast, SGLT2 inhibitors reduce hyperfiltration and oxidative stress, GLP-1 agonists reduce inflammation, oxidative stress, and fibrosis, and DPP-4 inhibitors offer metabolic and anti-inflammatory benefits[26].

New opportunities in managing DKD

Recent research into diabetic kidney disease (DKD) highlights several promising avenues for advancing treatment and understanding of the condition. The study by Akhouri et al. (2023) emphasizes the potential of targeting DNA methylation in DKD. By focusing on the role of DNA methylation, researchers can explore the development of epigenetic therapies aimed at correcting aberrant methylation patterns associated with the disease. This approach could lead to the creation of DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis), which might restore normal gene function and offer new diagnostic biomarkers. Techniques such as CRISPR-based epigenome editing could also be employed to precisely modify methylation patterns linked to DKD, potentially offering groundbreaking therapeutic options.

In the realm of precision medicine, Tye et al. (2021) highlights the benefits of tailoring DKD treatments to individual genetic and molecular profiles. This approach could revolutionize treatment by integrating various types of omics data to develop comprehensive, personalized treatment strategies. Pharmacogenomics could optimize drug therapies based on genetic profiles, while nutrigenomics could personalize dietary recommendations to influence metabolic pathways involved in DKD. Predictive modeling using artificial intelligence (AI) and machine learning (ML) could enhance risk assessment and treatment outcomes. Additionally, integrating multi-omics data could lead to a more holistic understanding of DKD, enabling the development of network medicine approaches that identify novel therapeutic targets.

The identification of novel biomarkers for DKD progression, as discussed by Swaminathan et al. (2023), offers significant potential for early disease detection and improved patient management. New biomarkers could lead to the development of non-invasive tests, such as blood or urine assays, that detect DKD at its earliest stages.

High-sensitivity assays could improve early diagnosis, while longitudinal studies tracking biomarker levels could help monitor disease progression and adjust treatments accordingly. Dynamic biomarker panels could provide real-time insights into disease status, and integrating biomarker data into clinical decision support systems could enhance risk stratification and personalized treatment planning.

The research by Bian and Ren (2022) explores the role of the sirtuin family in DKD, revealing opportunities for innovative therapeutic interventions. Targeting specific sirtuins, such as SIRT1 activators, could mitigate DKD-related damage by addressing oxidative stress and inflammation. Additionally, targeting SIRT3 might improve mitochondrial function in kidney cells. Combining sirtuin modulators with other therapies could enhance overall treatment efficacy. Further research into the molecular pathways and interacting proteins related to sirtuins could uncover additional therapeutic targets. Nutraceuticals like resveratrol, which activate SIRT1, may also be investigated as complementary treatments for DKD.

Conclusions

Diabetic Kidney Disease presents a complex interplay of metabolic, inflammatory, and oxidative stress pathways, making it a critical area of concern for managing diabetes mellitus. This review highlights the multifaceted nature of DKD pathogenesis, emphasizing hyperglycemia-induced damage, lipid accumulation, and mitochondrial dysfunction as central contributors to renal injury. The role of inflammation, particularly through pathways involving NF-κB and inflammasomes, underscores the inflammatory milieu's significance in DKD progression.

Therapeutically, significant strides have been made with the advent of Sodium-Glucose Cotransporter-2 inhibitors and Glucagon-Like Peptide-1 agonists. These agents have demonstrated not only glycemic control but also substantial renoprotective effects by reducing albuminuria, preserving glomerular filtration rate, and mitigating oxidative stress and inflammation. The dual benefits of these therapies underscore the importance of early and aggressive management of DKD to slow disease progression and prevent complications.

Furthermore, emerging research into the roles of autophagy and epigenetic modifications offers promising new avenues for DKD treatment. Autophagy enhancement could potentially mitigate cellular damage by promoting the clearance of damaged organelles and proteins, while epigenetic therapies might offer ways to modify disease progression at a molecular level.

Despite these advances, challenges remain. The variability in patient responses to current treatments and the need for personalized medicine approaches highlight the necessity for ongoing research. Long-term studies are essential to fully understand the durability and safety of these new therapies. Additionally, a deeper exploration into the mechanisms driving DKD in different patient populations, including those without significant albuminuria, is crucial.

In conclusion, while substantial progress has been made in understanding and managing DKD, it remains a leading cause of morbidity in diabetic patients. The integration of novel therapies with established treatment regimens, alongside a focus on personalized medicine, holds promise for improving outcomes. Ongoing research and clinical trials will be vital in refining these approaches and ultimately reducing the burden of DKD.

Disclosure

Author's contribution

Conceptualization: Piotr Kuczyński and Anna Marszałek; Methodology: Weronika Zofia Marzec; Software: Aleksandra Wydra-Rojek; Check: Paulina Wasiewicz- Ciach and Katarzyna Kutyła; Formal analysis: Marcelina Teresa Marzec and Wojciech Jan Mokot; Investigation: Paulina Wasiewicz-Ciach Resources: Aleksandra Łakoma; Data curation: Weronika Zofia Marzec; Writing - rough preparation: Anna Marszałek and Piotr Kuczyński; Writing - review and editing: Aleksandra Wydra-Rojek and Paulina Wasiewicz-Ciach; Visualization: Maciej Choiński Supervision: Maciej Choiński; Project administration: Marcelina Teresa Marzec and Aleksandra Wydra-Rojek; Receiving funding - no specific funding.

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References:

1. Lin YC, Chang YH, Yang SY, Wu KD, Chu TS. Update of pathophysiology and management of diabetic kidney disease. J Formos Med Assoc. 2018 Aug;117(8):662-675. doi: 10.1016/j.jfma.2018.02.007. Epub 2018 Mar 2. PMID: 29486908.
2. Liu Z, Liu J, Wang W, An X, Luo L, Yu D, Sun W. Epigenetic modification in diabetic kidney disease. Front Endocrinol (Lausanne). 2023 Jun 30;14:1133970. doi: 10.3389/fendo.2023.1133970. PMID: 37455912; PMCID: PMC10348754.
3. Ahmad AA, Draves SO, Rosca M. Mitochondria in Diabetic Kidney Disease. Cells. 2021 Oct 29;10(11):2945. doi: 10.3390/cells10112945. PMID: 34831168; PMCID: PMC8616075.
4. Sugahara M, Pak WLW, Tanaka T, Tang SCW, Nangaku M. Update on diagnosis, pathophysiology, and management of diabetic kidney disease. Nephrology (Carlton). 2021 Jun;26(6):491-500. doi: 10.1111/nep.13860. Epub 2021 Feb 17. PMID: 33550672.
5. Sindhu D, Sharma GS, Kumbala D. Management of diabetic kidney disease: where do we stand?: A narrative review. Medicine (Baltimore). 2023 Mar 31;102(13):e33366. doi: 10.1097/MD.0000000000033366. PMID: 37000108; PMCID: PMC10063294.

6. Ahmad AA, Draves SO, Rosca M. Mitochondria in Diabetic Kidney Disease. Cells. 2021 Oct 29;10(11):2945. doi: 10.3390/cells10112945. PMID: 34831168; PMCID: PMC8616075.
7. Tuttle KR, Agarwal R, Alpers CE, Bakris GL, Brosius FC, Kolkhof P, Uribarri J. Molecular mechanisms and therapeutic targets for diabetic kidney disease. Kidney Int. 2022 Aug;102(2):248-260. doi: 10.1016/j.kint.2022.05.012. Epub 2022 Jun 3. PMID: 35661785.
8. Sugahara M, Pak WLW, Tanaka T, Tang SCW, Nangaku M. Update on diagnosis, pathophysiology, and management of diabetic kidney disease. *Nephrology*. 2021; 26: 491–500
9. Hung PH, Hsu YC, Chen TH, Lin CL. Recent Advances in Diabetic Kidney Diseases: From Kidney Injury to Kidney Fibrosis. Int J Mol Sci. 2021 Nov 1;22(21):11857. doi: 10.3390/ijms222111857. PMID: 34769288; PMCID: PMC8584225.
10. Wang Y, Jin M, Cheng CK, Li Q. Tubular injury in diabetic kidney disease: molecular mechanisms and potential therapeutic perspectives. Front Endocrinol (Lausanne). 2023 Aug 2;14:1238927. doi: 10.3389/fendo.2023.1238927. PMID: 37600689; PMCID: PMC10433744.
11. Ma X, Ma J, Leng T, Yuan Z, Hu T, Liu Q, Shen T. Advances in oxidative stress in pathogenesis of diabetic kidney disease and efficacy of TCM intervention. Ren Fail. 2023 Dec;45(1):2146512. doi: 10.1080/0886022X.2022.2146512. PMID: 36762989; PMCID: PMC9930779.
12. Wang Y, Jin M, Cheng CK, Li Q. Tubular injury in diabetic kidney disease: molecular mechanisms and potential therapeutic perspectives. Front Endocrinol (Lausanne). 2023 Aug 2;14:1238927. doi: 10.3389/fendo.2023.1238927. PMID: 37600689; PMCID: PMC10433744.
13. Xu C, Ha X, Yang S, Tian X, Jiang H. Advances in understanding and treating diabetic kidney disease: focus on tubulointerstitial inflammation mechanisms. Front Endocrinol (Lausanne). 2023 Oct 4;14:1232790. doi: 10.3389/fendo.2023.1232790. PMID: 37859992; PMCID: PMC10583558.
14. Ahmad AA, Draves SO, Rosca M. Mitochondria in Diabetic Kidney Disease. Cells. 2021 Oct 29;10(11):2945. doi: 10.3390/cells10112945. PMID: 34831168; PMCID: PMC8616075.
15. Jung SW, Moon JY. The role of inflammation in diabetic kidney disease. Korean J Intern Med. 2021 Jul;36(4):753-766. doi: 10.3904/kjim.2021.174. Epub 2021 Jul 1. PMID: 34237822; PMCID: PMC8273831.
16. Watanabe K, Sato E, Mishima E, Miyazaki M, Tanaka T. What's New in the Molecular Mechanisms of Diabetic Kidney Disease: Recent Advances. Int J Mol Sci. 2022 Dec 29;24(1):570. doi: 10.3390/ijms24010570. PMID: 36614011; PMCID: PMC9820354.
17. Rico-Fontalvo J, Aroca G, Cabrales J, Daza-Arnedo R, Yánez-Rodríguez T, Martínez-Ávila MC, Uparella-Gulfo I, Raad-Sarabia M. Molecular Mechanisms of Diabetic Kidney Disease. Int J Mol Sci. 2022 Aug 4;23(15):8668. doi: 10.3390/ijms23158668. PMID: 35955802; PMCID: PMC9369345.

18. Lebedeva S, Margaryan A, Smolyarchuk E, Nedorubov A, Materenchuk M, Tonevitsky A, Mutig K. Metabolic effects of vasopressin in pathophysiology of diabetic kidney disease. Front Endocrinol (Lausanne). 2023 Sep 18;14:1176199. doi: 10.3389/fendo.2023.1176199. PMID: 37790608; PMCID: PMC10545091.
19. Gonzalez CD, Carro Negueruela MP, Nicora Santamarina C, Resnik R, Vaccaro MI. Autophagy Dysregulation in Diabetic Kidney Disease: From Pathophysiology to Pharmacological Interventions. Cells. 2021 Sep 21;10(9):2497. doi: 10.3390/cells10092497. PMID: 34572148; PMCID: PMC8469825.
20. Lytvyn Y, Bjornstad P, van Raalte DH, Heerspink HL, Cherney DZI. The New Biology of Diabetic Kidney Disease-Mechanisms and Therapeutic Implications. Endocr Rev. 2020 Apr 1;41(2):202–31. doi: 10.1210/endrev/bnz010. PMID: 31633153; PMCID: PMC7156849.
21. Winiarska A, Knysak M, Nabrdalik K, Gumprecht J, Stompór T. Inflammation and Oxidative Stress in Diabetic Kidney Disease: The Targets for SGLT2 Inhibitors and GLP-1 Receptor Agonists. Int J Mol Sci. 2021 Oct 6;22(19):10822. doi: 10.3390/ijms221910822. PMID: 34639160; PMCID: PMC8509708.
22. Lu, YP., Zhang, ZY., Wu, HW. *et al.* SGLT2 inhibitors improve kidney function and morphology by regulating renal metabolic reprogramming in mice with diabetic kidney disease. *J Transl Med* **20**, 420 (2022).
23. Song J, Li X, Ni J. A Role for Sodium-Glucose Cotransporter 2 Inhibitors in the Treatment of Chronic Kidney Disease: A Mini Review. Kidney Blood Press Res. 2023;48(1):599-610. doi: 10.1159/000534174. Epub 2023 Sep 16. PMID: 37717569; PMCID: PMC10614480.
24. Radica Z. Alicic, Joshua J. Neumiller, Emily J. Johnson, Brad Dieter, Katherine R. Tuttle; Sodium–Glucose Cotransporter 2 Inhibition and Diabetic Kidney Disease. *Diabetes* 1 February 2019; 68 (2): 248–257.
25. Dai ZC, Chen JX, Zou R, Liang XB, Tang JX, Yao CW. Role and mechanisms of SGLT-2 inhibitors in the treatment of diabetic kidney disease. Front Immunol. 2023 Sep 21;14:1213473. doi: 10.3389/fimmu.2023.1213473. PMID: 37809091; PMCID: PMC10552262.
26. Gembillo G, Ingrasciotta Y, Crisafulli S, Luxi N, Siligato R, Santoro D, Trifirò G. Kidney Disease in Diabetic Patients: From Pathophysiology to Pharmacological Aspects with a Focus on Therapeutic Inertia. Int J Mol Sci. 2021 May 1;22(9):4824. doi: 10.3390/ijms22094824. PMID: 34062938; PMCID: PMC8124790.