Review Article

Diabetic Kidney Disease Update: Pathogenesis and Treatment Overview for Clinicians

Elmukhtar Habas[1], Abdel-Naser Y. Elzouki[1,2,3]

[1]Department of Internal Medicine, Hamad Medical Corporation, [2]Department of Internal Medicine, Hamad General Hospital, College of Medicine, Qatar University, [3]Weill Cornell Medical College, Doha, Qatar

Abstract

Diabetes mellitus is a common cause of chronic kidney disease that progresses to end-stage renal disease (ESRD). Albuminuria (proteinuria) is an early manifestation of diabetic kidney disease (DKD). Although the hemodynamic alterations that occur in diabetics seem the underlying mechanism, others such as metabolic, inflammatory, and hypoxia have a role in DKD pathophysiology. Despite the proven beneficial effects of angiotensin-converting enzyme inhibitors and renin–angiotensin II–aldosterone receptor blockades in proteinuria improvement, their effect to prevent the DKD and to modify its progression to ESRD is not clear enough. New agents such as SLGT2 and autophagy inhibitors and anti-inflammatory are promising agents that may improve proteinuria and inhibit DKD progression. Pathophysiology and new strategies in DKD therapy updates will be reviewed.

Keywords: Diabetes, diabetic kidney disease, pathogenesis, treatment

Introduction

Diabetes mellitus (DM) manifests by polyuria, recurrent urinary tract infection, and albumin loss in the urine (albuminuria/proteinuria). Acute renal failure is not an uncommon complication, however, diabetic nephropathy (DN) or diabetic kidney disease (DKD) has usually a chronic kidney disease (CKD) course, precipitating end-stage renal disease (ESRD), increasing morbidity and mortality.[1,2] The Kidney Disease Outcomes Quality Initiative clinical practice guidelines in 2007 suggested that the DKD term should replace DN to describe kidney involvement in DM, whereas the biopsy-proven kidney disease due to DM is called diabetic glomerulopathy.[3] Understanding of the epidemiology, risk factors, natural history, and pathogenesis of the disease should help practicing physicians recognize the rationale of contemporary clinical practice guidelines and perhaps enhance adhering to them in day-to-day practice. Hence, this narrative review aims to review these aspects concisely.

Materials and Methods

This is a narrative nonsystematic review of the updated literature on pathogenesis and management of CKD. The review aims to provide an updated overview on the epidemiology, pathogenesis, and current and emerging management strategies for DKD.

Nomenclature and Definitions

The DKD stages are as follows: first, glomerular hypertrophy and hyperfiltration, manifesting as enlarged increases in the kidney, and increased glomerular filtration rate (GFR); second, appearance of moderately albuminuria (30–300 mg/day) that later becomes macroalbuminuria (>300 mg/day);[4] third, constant reduction of GFR; and finally, ESRD development.

Appropriate blood sugar control by hypoglycemic agents and hypertension control by the renin–angiotensin–aldosterone system (RAAS) reduce albuminuria prevalence among diabetics.[5] Some patients develop renal function deterioration

Address for correspondence: Dr. Elmukhtar M. Habas, Department of Medicine, Hamad General Hospital, Hamad Medical Corporation, P.O. Box 3050, Doha-Qatar.
E-mail: Habas1962@gmail.com

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without evidence of albuminuria,[6] especially in type 1 diabetic patients.[7] In 2020, the Italian Diabetes Society and the Italian Society of Nephrology addressed in type 2 DM natural history a joint statement that describes two distinctive pathways of DKD: a traditional albuminuric progressive renal impairment and nonalbuminuric renal impairment pathway.[8] The main difference between the two entities is the presence of proteinuria at the beginning of DKD and during its progression to CKD and ESRD. These observations yielded that the nonalbuminuric pathway is due to tubulointerstitial and/or vascular involvement that is mostly controlled by some factors such as dyslipidemia, high blood pressure (BP), obesity, and aging.[8] DKD pathophysiology, new diabetes treatment approaches, and prevention strategies of short- and long-term diabetes-induced kidney complications will be discussed and updated.

Epidemiology

DM is the major cause of ESRD, for example, In the USA 47% and Malaysia >60% of ESRD is due to DKD.[9] Approximately 23% of intensively treated and 36% of conventionally treated diabetic patients have albuminuria after a mean follow-up of 24 years.[10] Another study noted that 38% developed albuminuria whereas 28% of type 2 diabetic patients had renal impairment after a median of 15 years of follow-up. Furthermore, it was reported that CKD prevalence was <30% to > 80% in diabetic patients,[11] however, DKD prevalence was changing significantly during the past decade.[12]

Diagnosis of Diabetic Kidney Disease

The main problem of diagnosing DKD is proving kidney disease's existence. Clinically, the presence of albuminuria and/or GFR reduction is/are diagnostic for DKD. Recently, urine albumin/creatinine ratio is commonly used to quantify albuminuria, although 24-h urine albumin content is still more informative when the urine is perfectly collected. Two out of three high albumin/creatinine ratios (>30 g/g) of urine spots over 3–6 months are considered diagnostic. Conditions such as vigorous exercise, fever, hematuria, urinary tract infection, and congestive heart failure may cause albuminuria. Hence, 3–6-month period is recommended to confirm diabetes-induced albuminuria in diabetic patients.[13] It is recommended that GFR calculation and proteinuria should be checked at least once per year after 5 years of type 1 DM and at type 2 DM diagnosis.[14] Persistent determined estimated GFR (eGFR) by the CKD epidemiology collaboration equation of <60 mL/min/1.73 m^2 is considered diagnostic for diabetes-induced CKD.

Renal biopsy is not recommended by many authors to diagnose DKD, however, it may be needed if other causes of CKD rather than DKD are suspected. A short history of diabetes, no evidence of diabetic retinopathy, particularly in DM type 2 patients, active urinary sediments, rapidly progressive albuminuria, sudden-onset nephrotic syndrome and/or abrupt GFR reduction, plus other signs and symptoms of other causes of kidney damage are considered as indications for percutaneous renal biopsy in diabetic patients.[14] Approximately 6.5%–94% of renal biopsies that were done for diabetics revealed DKD, and around 3%–83% were non-DKD, whereas 4%–45.5% were both DKD and non-DKD.[15] The varied ranges of biopsy results in diabetic patients can be due to the varied renal biopsy indications and different DM prevalence.

Pathophysiology of Diabetic Kidney Disease

DKD developments occur due to metabolic and/or hemodynamic disturbances. At early DKD stages, the intraglomerular Bp increases, leading to higher GFR. These changes increase the risk of DKD, promoting its progression [Figure 1].

Hemodynamic pathways

Renin releases from granular cells (J-cells) of the renal juxtaglomerular apparatus (JGA) in response to the singular or combined effect of the three factors that are decreased sodium delivery to the distal convoluted tubule (DCT), reduced perfusion pressure that can be detected by the baroreceptors in the afferent arteriole, and the JGA stimulation by the sympathetic system via β1 adrenoreceptors. The main function of the renin hormone is stimulation of angiotensin II formation. Angiotensin II increases the total peripheral resistance, raising the systemic Bp. In the kidneys, angiotensin II increases the vascular tone of both afferent and efferent, but its vasoconstriction effect is more on the afferent arteriole, while it has more smooth muscle content. However, the angiotensin II vasoconstrictor effect on the afferent is minimized by the locally produced prostaglandins-kinins, thromboxane-2, and nitric oxide.

Proximal convoluted tubule (PCT) receives a massive amount of glucose in the filtrate, leading to an increase of

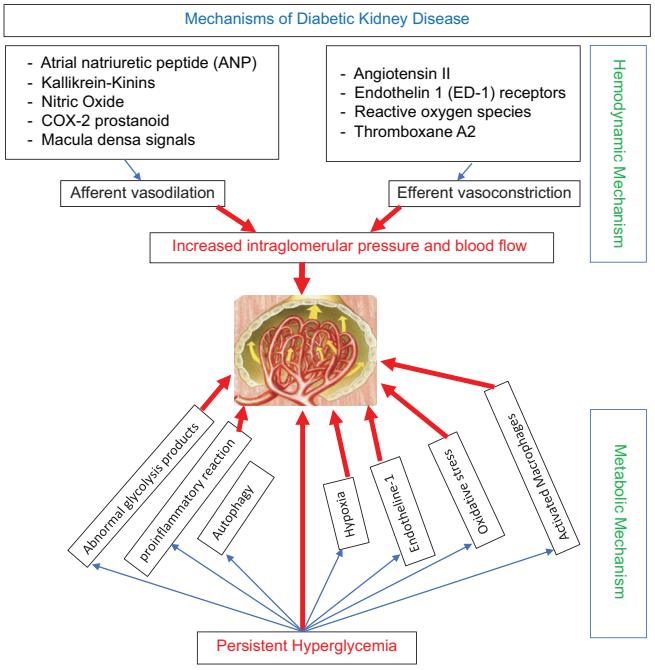

Figure 1: Mechanisms of diabetic kidney disease

PCT reabsorptive power to glucose that couples with sodium reabsorption, reducing sodium concentration into the DCT.[16] The decreased DCT filtrate sodium content and blood flow stimulate the J-cells to excrete the renin hormone, increasing the intraglomerular pressure via the angiotensin II effect.[16,17] Additionally, endothelin-1 (ET-1) serum concentration is high in DM patients. ET-1 A and B receptor stimulation modulates renal vessel tone that affects filtration and blood flow, enhancing DKD pathogenesis.[18] Increased glomerular hyperfiltration may be due to altered autoregulatory responses of the afferent arterioles to the BP fluctuations[19] that are transmitted along to glomerular capillaries, resulting in glomerular sclerosis and peritubular capillaries damage occur because of the persistent rise in intraglomerular BP.[20]

Metabolic pathways

Damage to glomerular basement membrane due to increased intraglomerular BP and DM increases glomerular protein leakage.[20] The presence of proteins in the nephron tubule enhances the formation of pro-inflammatory and profibrotic factors, increasing kidney damage. Furthermore, hyperglycemia leads to the accumulation of reactive oxygen species (ROS),[21] which cause mitochondrial malfunction and defect of pro-oxidant enzymes, such as nicotinamide adenine dinucleotide phosphate oxidase,[22] increasing the risk of kidney damage. Additionally, ROS oxidize proteins, lipids, and nucleic acids, producing metabolites that may ultimately cause significant kidney damage.

Persistent hyperglycemia results in advanced glycation end-product formation and ROS, activating intercellular signaling for pro-inflammatory and profibrotic gene expression, increasing host mediators' formation that causes cell injury. Hyperglycemia causes abnormal glucose metabolism and oxidative stress, leading to the activation of different intracellular signaling pathways, which may have a role in DKD pathogenesis. One of these pathways is a mitogen-activated protein kinase (MAPK). It was reported that MAPK activation stimulates apoptosis and extracellular matrix production by the mesangial cells.[23] Furthermore, hyperglycemia motivates Janus kinase-signal transducers and activators of transcription (JAK-STAT) and nuclear factor-kappa B (NF-κB). These signals are heavily engaged in the initiation of inflammatory reactions. Moreover, NF-κB encourages molecule adhesion and pro-inflammatory cytokine expression (macrophage chemoattractant protein-1, tissue necrosis factor-α, and interleukin-6) that contribute to DKD pathogenesis.[24] The kallikrein–kinin system is also activated by persistent hyperglycemia, encouraging an inflammatory process by generating bradykinins such as kallistatin (an endogenous tissue kallikrein inhibitor), leading to glomerulosclerosis, and tubulointerstitial injury.[25]

Severe hyperglycemia causes a massive amount of glucose delivery to the nephron, requiring more energy and oxygen consumption to reduce glucose loss in urine by upgrading the activity of sodium–glucose cotransport function.[26] Additionally, hyperglycemia stimulates the mitochondrial uncoupling process, increasing the oxidative stress, and the releasing of hypoxia-inducing factor (HIF), increasing oxygen and energy consumption that promotes tubular epithelial cell damage.[27] The oxygen delivery to the kidney tubular system in DKD is decreased mostly due to loss of peritubular capillaries and interstitial fibrosis.[28] However, it is difficult to demonstrate that hypoxia alone precipitates DKD progression. Hence, HIF release inhibition can be claimed as a modality to prevent renal tubular damage and prevent DKD.

Autophagy (self-killing) process abnormality is also reported in DKD pathogenesis.[29] Autophagy is a body self-mechanism by which the damaged proteins and organelles are cleared, and it recycles intracellular resources in response to conditions such as nutrient deficiency.[29] Mammalian target of rapamycin complex 1 (mTORC1) has a role, by inhibiting Unc-51-like kinase 1 activity that stimulates autophagy in diabetics.[30,31] It is noted that inhibition of mTORC1 by rapamycin decreases the risk of DKD in diabetic mice.[31] Additionally, DKD epigenetic modifications affect gene expression without alteration of DNA sequence. DM induces epigenetic variations such as DNA methylation, histone modification, chromatin conformational changes, and altered expressions of noncoding RNAs.[32] It is reported that in a mouse study, an aberrant DNA methylation in the mesangial cells of type 2 diabetic mice was combined with an increase of transforming growth factor-β (TGF-β) expression and formation.[33] Interestingly, it was documented that epigenetic changes act as "metabolic memory," mediating the persistent long-term expression of diabetes-related genes and phenotypes that were induced by hyperglycemia, which might persist even after hyperglycemia control,[32] increasing the risk of DKD.

The main histological feature of the DKD is mesangial cell hypertrophy and matrix accumulation that is mediated by the TGF-β system.[34] TGF-β production is increased in high blood sugar and angiotensin II milieu by the mesangial cell, increasing glomerular extracellular mesangial matrix production and reducing the production of matrix metalloproteinases which controls extracellular matrix normal structure via old tissue lysis.[34]

Hyperglycemia causes glucose catabolism via nonglycolytic pathways such as the polyol pathway, increasing oxidative stress via protein kinase C (PKC) activation. The activated PKC lowers endothelial nitric oxide synthase (eNOS) formation and increases ET-1 and vascular endothelial growth factor (VEGF) levels, encouraging endothelial instability and cytokine production. The high VEGF and low eNOS stimulate vascular proliferation and endothelial permeability in DND.[35] A balance between angiopoietins 1 and 2 is essential to control the endothelial function, preventing endothelial proliferation in DKD.[36]

Macrophages are activated by hyperglycemic stress, high angiotensin II, oxidized low-density lipoproteins, and other glycolysis end-products in DM. Furthermore, macrophage

migration increases into the glomeruli and the kidney interstitium in diabetic patients. These changes have a significant link with DND progression.[37] Furthermore, the activated macrophages produce tumor necrosis factor-alpha, a pleiotropic cytokine that promotes more damage and DKD progression.[37] TGF-beta and plasminogen activator inhibitor 1 production increases due to the metabolism of the excess glucose by the hexosamine pathway.[38] Injury of PCT by abnormal glycolysis end-products, albuminuria, increased TGF-beta, and high angiotensin II cause pericyte conversion into myofibroblasts, producing more collagen and fibronectin deposition in the kidney interstitium.[19] Inhibition of these pathways can reduce and prevent DKD development.

Therapeutic Strategies of Diabetic Kidney Disease

DKD is a progressive disease, but good control of blood sugar targeting normal glycated hemoglobin and Bp control targeting ≤120/80 mmHg are essential to limit the DND development and progression. Furthermore, hyperlipidemia, cardiovascular (CV), and cerebrovascular complications of DM must be addressed and treated promptly to improve the long-term DM outcome [Table 1].

Table 1: Current and emerging therapeutic strategies for diabetic kidney disease

ACE inhibitors and ARBs
SGLT2 inhibitors
GLP-1 receptor agonists
Anti-inflammatory agents
Anti-oxidate
ASK-1 inhibitor
ET-1 receptor antagonists
Other agents with therapeutic potentials

ACE: Angiotensin-converting enzyme, ARB: Angiotensin II receptor blocker, SGLT2: Sodium–glucose cotransporter-2, GLP-1: Glucagon-like peptide-1, ASK-1: Apoptosis signal-regulating kinase, ET-1: Endothelin-1

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

Renin–angiotensin–aldosterone system inhibitors (RAASis) are recently the most common agents are used to control the Bp in diabetic patients. The RAASis reduce intraglomerular pressure and glomerular hyperfiltration.[39] Furthermore, they amend the oxidative stress of angiotensin II, inflammation, and fibrosis,[40] hence hypothetically, RAASis may completely pause the DKD progression to ESRD.

The decent effectiveness of the RAASis was proven in the management of DKD by various randomized studies such as the Collaborative (captopril), RENAAL (losartan), and IDNT (irbesartan) studies which reported that serum creatinine doubling, ESRD, and mortality rates are decreased.[21] However, it was observed that the kidney outcome improvement is beyond to be attributed only to the RAASis lowering Bp effect.[21]

Dual angiotensin-converting enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARB) therapies were proven more effective than a singular group agent in controlling the Bp, and in the prevention of proteinuria deterioration. However, the long-term DKN outcome was not changed, and the risk of acute renal failure and hyperkalemia is increased.[41] The nonsteroidal mineralocorticoid receptor antagonists such as apararenone, esaxerenone, and finerenone are potent and selective to inhibit mineralocorticoid receptors than the steroidal mineralocorticoid receptor antagonists (spironolactone and eplerenone), decreasing the risk of hyperkalemia when they are used with RAASis.[42] It was reported that in type 2 DM patients, adding esaxerenone to ACEi or ARB significantly decreases the proteinuria,[43] but the combination is initially associated with dose-dependent eGFR reduction, which is improved during 12 weeks of the treatment.[43] It is reported that adding finerenone to ACEi or ARBs improves proteinuria, and decreases the risk of a long-term eGFR decline, ESRD, and death from renal diabetic-related diseases.[44]

Sodium–glucose cotransporter-2 inhibitors

Sodium–glucose cotransporter-2 (SGLT2) proteins are present in the PCT of the kidneys. The SGLT2 proteins are transporters that concern with 90% of the filtered glucose reabsorption in PCT, therefore, inhibiting this mechanism by SGLT2 inhibitors will effectively help in DM control.[45] SGLT2 inhibitors reduce and even may prevent ESRD.[46] It was noted that empagliflozin reduces cardiovascular system (CVS) morbidity and mortality in type 2 diabetes,[47] and decreases the risk of DKD and its progression to ESRD.[48] A similar effect was reported with canagliflozin,[48] and dapagliflozin.[49]

Although the exact mechanisms of SGLT2 inhibitors' effect to prevent DKD and its progression are not clearly understood, their sodium reabsorption inhibitory effect in the PCT, which increases filtrate sodium content into the densa macula, activating a feedback mechanism. The tubule-interstitial feedback mechanism causes afferent renal arteriole vasoconstriction which reduces renal blood flow, and the intraglomerular Bp.[50] This hypothetical assumption is supported by the significant reduction of eGFR in type 1 diabetics who are treated with empagliflozin.[51]

PCT cell needs more energy and oxygen consumption in hyperglycemic status. SGLT2 inhibitors modulate the oxygen and energy requirements by inhibiting the sodium–glucose cotransport system, producing better renoprotection. The possible explanation of the renoprotective effect is due to oxygen demand reduction that is resulted from the mitochondrial uncoupling process impairment by SGLT2 in the PCT epithelial cells. Furthermore, empagliflozin's renoprotective role in both proteinuric and nonproteinuric DKD patients may be due to its promoting effect on the production of ketone bodies, which block the mTORC1 pathway in PCT cells,[52] reducing the autophagy. Additionally,

it was reported that chronic SGLT2 inhibitor (ipragliflozin) administration reduces significantly the accumulation of Krebs cycle intermediates, and also impairs the increased oxidative stress in the kidneys of diabetic patients.[53] Moreover, SGLT2 reduces oxidative stress, improves cortical hypoxia, and promotes vascular remodeling via attenuation of renal capillary injury and fibrosis by a VEGF-dependent pathway in diabetic mice.[53,54] Furthermore, recently, it is reported that type 2 DM patients had atherosclerotic CV disease, ertugliflozin minimizes the risk for the prespecified renal vascular DM effects, and it preserves the eGFR and decreases urine albumin creatinine ratio.[55]

It has been claimed recently that there is not a significant protective effect of dapagliflozin on the renal and CV with advanced CKD. The U.S. Food and Drug Administration (FDA) on May 3 approved dapagliflozin (Farxiga) oral tablets to reduce the risk of kidney function decline, kidney failure, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease (CKD) who are at risk of disease progression. This announcement comes after the FDA approved dapagliflozin oral tablets in 2020 for adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization for heart failure.

FDA approval was based on results from the DAPA-CKD trial, which involved 4,304 participants and showed that dapagliflozin results in salutary effects on renal function and mortality among patients with CKD, irrespective of diabetes mellitus status.

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) stimulates insulin secretion following food intake. Analogs of GLP-1 such as liraglutide and semaglutide are utilized for type 2 DM therapy. Liraglutide therapy is followed by lower rates of DND development and progression than placebo.[56] Another study reported that in type 2 diabetic patients who had moderate-to-severe CKD and had been treated with dulaglutide, eGFR decreased significantly compared with insulin glargine over 52 weeks.[57] A randomized controlled trial of semaglutide is at present being conducted to assess its long-term effects on eGFR decline rate, development of ESRD, and death from kidney or CV events.

Anti-inflammatory agents

Pentoxifylline is a methylxanthine derivative that has a nonspecific phosphodiesterase inhibitor with anti-inflammatory and antiproteinuric effects.[58] The combined therapy of RAAS blockades and pentoxifylline therapy for 2 years revealed a reduction in albuminuria and eGFR decline in type 2 diabetic patients with Stage III and IV CKD.[59] More randomized clinical trials are at present being performed to clarify the benefits of adding pentoxifylline to delay the ESRD, and diminution of death risks that are related to the renal cause.

JAK-STAT pathway activation that associates with the transmission of signals via cytokines and chemokines, promoting different ranges of cellular damage responses in DKD patients.[60] A selective JAK-1 and JAK-2 inhibitor (baricitimab) therapy decreases albuminuria and inflammatory biomarkers.[61] Furthermore, it was reported that C–C chemokine receptor type 2 inhibitor reduces proteinuria in type 2 diabetics.[62] New research projects are required to assess the effects of these agents in delaying and/or pausing the DKD progression.

It was suggested that several innate immune pathways have roles in DKD pathogenesis, and alteration of these pathways may be a novel therapeutic method.[63] Complement C5a deposits were detected in DKD patients' renal biopsy tissues; additionally, the usage of C5a inhibitor decreases glomerular and tubulointerstitial damage in db/db mice.[64] Toll-like receptor 4 is activated by lipid and glucose metabolism intermediate products, causing an inflammatory reaction via NF-κB signaling.[65] Hence, blocking these pathways can affect the outcome of DKD pathogenesis and progression of DKD theoretically, therefore, new research projects are urged to investigate this assumption.

Anti-oxidant

Activation of cellular anti-oxidant pathways such as NF-erythroid-2-related factor 2 (Nrf-2). Nrf-2 is a transcription factor that regulates the expression of several antioxidant and cytoprotective genes that can inhibit the oxidation stress due to hyperglycemia and hypoxia. Modulating the Nrf-2 effect seems a reasonable therapeutic option to prevent and/or delay DKD development. During the oxidative stress, the Kelch-like ECH-associated protein 1 (Keap-1) structure changes, dissociating Nrf-2 from the Keap-1/Nrf-2 complex. The free Nrf-2 translocates into the nucleus, inducing targeted genes transcription, and the free Keap-1 negatively regulates the NF-κB kinase subunit β inhibitor, inactivating the NF-κB pathway. Bardoxolone methyl stimulates the change of Keap-1 and simultaneously acts as Nrf-2 inducer and NF-κB inhibitor.[66] It was observed that bardoxolone methyl increases the eGFR in type 2 DM and CKD Stage IIIb and Stage IV patients,[67] however, it was reported that bardoxolone methyl administration in type 2 DM patients increases the CV event risk.[68] Nevertheless, re-analysis revealed that the risk of CV event is more in patients admitted with heart failure with high baseline B-type natriuretic peptide (BNP), and the increased risk of CV events is not significantly related bardoxolone methyl therapy.[69] Another study reported that bardoxolone methyl therapy in type 2 DM patients had Stage III and IV CKD, and they had not significant evidence of heart failure (BNP <200 pg/mL) for 16 weeks did not result in serious adverse CV events.[70]

Apoptosis signal-regulating kinase inhibitor

Sustained oxidative stress leads to activation of ASK, inducing apoptosis, inflammation, and fibrosis through downstream signaling pathway activation in DKD patients.[71] Preliminary data reported that a selective ASK-1 inhibitor (selonsertib) decreases eGFR during the first 4 weeks, however, the eGFR drop is less during the 44 weeks of the therapy.[72] Further

studies are urged to investigate this agent more to evaluate its safety and efficacy in preventing DKD.

Endothelin-1 receptors antagonists

It is reported that combining ET-1 A-receptor antagonists (avosentan and atrasentan) with standard ARB regimens reduces proteinuria in DKD patients, but the fluid retention side effect on long-term therapy increases the risk of CV events.[73] Despite the contradictory reports, adding a low dose of ET-1 antagonists was recommended by some authors. Further research is needed to investigate the ET-1 receptor antagonists' efficacy and safety in DKD therapy and prevention. However, it appears that fluid retention is the major issue, and it must be closely monitored.

Other agents with therapeutic potentials

DKD progression is a manifestation of continuous kidney fibrosis, hence, stopping the fibrosis reduces or even prevents ESRD development. Administration of antifibrotic such as pirfenidone decreases TGF-β expression, amends mesangial matrix expansion, and improves eGFR in diabetic db/db mice.[74,75] However, further human clinical studies are required to prove the safety and efficacy of this drug in diabetic patients with DKD.

Targeting the HIF is another modality that can be suggested. Administration of cobalt nitrate as an activator for HIF improves albuminuria and tubulointerstitial damage in diabetic rats.[27] HIF stabilizers are also known as HIF prolyl hydroxylase inhibitors (enarodustat) are used for CKD-associated anemia therapy,[76] and some of them have illustrated a defensive property against DKD in preclinical studies. It was illustrated that enarodustat offsets the renal metabolic changes, inducing fatty acid and amino acid metabolism upregulation in the diabetic kidneys. This upregulation reduces glutathione disulfide accumulation, leading to an increase of glutathione/glutathione disulfide ratio, and glomerular hypertrophy improvement.[77]

Epigenetics has an essential role in the pathogenesis of DKD. It was noted that administration of GSK-J4 (a histone demethylase) inhibitor reduces proteinuria, and ameliorates glomerular expansion and tubulointerstitial injury in type 2 diabetic animals' model.[78] Finally, microRNAs are also likely novel therapeutics, but selective delivery and avoidance of off-objective effects may be challenging issues.[79] Therefore, research projects are needed to determine the efficacy and safety of these agents.

Conclusions

RAAS blockades are the preferred treatment for DKD, but their effects are not well proven to prevent DKD from progressing to ESRD, even with the addition of newly available agents. However, it appears that advances in our knowledge of DKD pathophysiology have illuminated several points and given rise to new expectations for new therapies and preventive measures. SGLT2 inhibitors, which have renoprotective effects, are one of the proven promising agents. Other agents, such as antioxidatives, anti-inflammatory agents, HIF stabilizers, and others, are promising novel therapeutic agents; however, before they are approved for DKD therapy, further globalized human studies are needed to determine their effects, benefits, and protection abilities.

Authors' contributions

Equal.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No ethical approval is required for review articles type of study.

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