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Case Reporte

Elmukhtar Habas[1], Amnna Rayani[2], Aml Habas[2], Kalifa Farfar[3], Eshrak Habas[4], Khaled Alarbi[3], Ala Habas[4], Elmehdi Errayes[3], Gamal Alfitori[3]

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Advances in understanding and managing diabetic kidney disease: An updated review

[1]Hamad General Hospital, Open Libyan University, Doha, Qatar
[2]Tripoli Pediatric Hospital, Open Libyan University, Tripoli, Libya
[3]Hamad General Hospital, Doha, Qatar
[4]Tripoli Central Hospital, Tripoli University, Tripoli-Libya

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Abstract. *Chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are common complications of diabetes. Proteinuria is an early indicator of glomerular basement membrane damage caused by diabetes, leading to diabetic kidney disease (DKD). Edema, hypoproteinemia, and proteinuria are common characteristics of DKD. Blood sugar and blood pressure control, along with early detection, are the primary strategies for preventing DKD and slowing its progression.*

This review examines and updates the epidemiology, pathogenesis, and prevention of DKD. Various keywords and phrases are used to search Google, EMBASE, PubMed, Scopus, and Google Scholar for the most recent articles published from January 2023 to December 2024.

Despite advancements in understanding DKD pathogenesis and the development of novel therapies, the disease remains highly prevalent with poor outcomes. The pathophysiology is still not fully understood, leading to gaps in prevention and treatment strategies. Therefore, this review aims to explore these gaps and propose potential new therapies and future research directions.

Keywords: *diabetic kidney disease, diabetic nephropathy, pathogenesis, treatment, prevention.*

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Correspondence should be addressed to Elmukhtar Habas: habas1962@gmail.com

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Ельмухтар Хабас[1], Амнна Райяні[2], Амль Хабас[2], Каліфа Фарфар[3], Ішрак Хабас[4], Халед Алярбі[3], Аля Хабас[4], Ельмехді Еррайєс[3], Гамаль Альфіторі[3]

Сучасний погляд на патогенез та лікування діабетичної хвороби нирок: огляд літератури

[1]Загальний госпіталь Хамад, Відкритий Лівійський університет, Доха, Катар
[2]Дитяча лікарня Тріполі, Відкритий Лівійський університет, Тріполі, Лівія
[3]Загальна лікарня Хамад, Доха, Катар
[4]Центральна лікарня, Університет Тріполі, Тріполі, Лівія

Резюме. *Хронічна хвороба нирок (ХХН) та її термінальна стадія є одними з найпоширеніших і найсерйозніших ускладнень цукрового діабету. Одним із ранніх маркерів ушкодження гломерулярної базальної мембрани, спричиненого гіперглікемією, є протеїнурія, що слугує ключовим предиктором розвитку діабетичної хвороби нирок (ДХН). Основними клінічними ознаками ДХН є набряковий синдром, гіпопротеїнемія та стійка протеїнурія.*

Контроль рівня глікемії та артеріального тиску, а також раннє виявлення ураження нирок залишаються наріжними принципами профілактики ДХН та уповільнення її прогресування.

Цей огляд узагальнює та оновлює сучасні дані щодо епідеміології, патогенезу та стратегії профілактики ДХН. Для аналізу використано найновіші наукові публікації, опубліковані у період із січня 2023 року по грудень 2024 року, шляхом пошуку в базах даних Google, EMBASE, PubMed, Scopus і Google Scholar.

Попри значний прогрес у дослідженні патогенезу ДХН та впровадження новітніх терапевтичних підходів, захворювання зберігає високу поширеність і залишається основною причиною розвитку термінальної ниркової недостатності. Невизначеність деяких аспектів патофізіології ДХН створює прогалини у сучасних методах профілактики та лікування. У цьому контексті даний огляд спрямований на висвітлення цих прогалин та обговорення потенційних терапевтичних стратегій і перспективних напрямів подальших досліджень.

Ключові слова: *діабетична хвороба нирок, діабетична нефропатія, патогенез, лікування, профілактика.*

Introduction. Diabetic nephropathy or diabetic kidney disease (DKD) represents the predominant etiology of nephrotic syndrome (NS) in adults [1]. DKD is a clinical syndrome delineated by persistent albuminuria (>300 mg/day or >200 μg/min) confirmed on a minimum of two occasions of 3 to 6 months apart, gradual reduction in glomerular filtration rate (GFR), increased intraglomerular hydrostatic pressure [2]. Proteinuria was initially identified in diabetes mellitus (DM) in the late 18th century. In the 1930s, the characteristic nodular glomerulosclerosis lesions linked to DM were characterized and connected with proteinuria and hypertension (HTN). By the 1950s, kidney involvement was recognized as a prevalent complication of DM, affecting up to 50% of people with diabetes with DM for > 20 years. Recent studies have highlighted atypical presentations of DKD, characterized by a dissociation between proteinuria and decreased kidney function. However, it is important to note that microalbuminuria does not consistently predict DKD [3]. Most cases of DKD exhibit proteinuria, which worsens as the disease advances and is consistently linked to HTN.

Elmukhtar Habas
habas1962@gmail.com

DKD is presently the primary etiology of CKD in the USA. and other Western societies. It represents a major long-term complication regarding coexisting diseases and death in diabetics. DKD represents the predominant etiology of end-stage kidney disease (ESKD) in different parts of the world [4]. It represents approximately 80% of ESKD's underlying causes in the USA. The prevalence of renal failure (RF) is approximately a sequence of DM-associated injury in 40% in type 1, and 20 to 30% in type 2 DM patients. However, these estimates may be underestimated [5].

RF in diabetics is notably prevalent among specific ethnic groups, including Black individuals, Mexican Americans, Polynesians, and Pima Indians. Risk factors include hyperglycemia severity and chronicity, HTN, and dyslipidemia, including elevated serum cholesterol and triglycerides [1]. Cigarette consumption, renin-angiotensin-aldosterone system (RAAS) dysregulation, strong family history of DM, and genetic factors associated with reduced glomerular count are other risk factors for RF in diabetics. Type 2 DM frequently remains undiagnosed for several years, leading to DKD within less than 10 years post-diagnosis [6]. Additionally, ESKD typically requires at least 10 years following the onset of nephropathy for its development [7]. DKD pathophysiology is a multifactorial and complex process, including metabolic, hemodynamic mechanisms, dysbiosis, vascular, molecular, and inflammatory intermediates and reactions [8]. DKD prevention or at least

delaying its occurrence by good control of arterial blood pressure and blood sugar are the typical measures [9].

In this concise review, we will review the epidemiology, pathophysiology, prevention, and management plans to prevent or minimize DKD occurring to improve the outcomes, explore the gaps of all the mentioned topics, and propose solutions and prospective research projects. EMBASE, Google, Scopus, Google Scholar, and PubMed were searched with different phrases and keywords, such as diabetic nephropathy, DM renal or kidney complication, DM and kidney, proteinuria in DM, novel DKD therapies, and pathogenesis of DKD. We concise the search period for published reviews and original articles between January 2022 and 31 December 2024.

Epidemiology of DKD. DKD increases steeply in correlation with the rapid increase of DM incidence worldwide [6], especially in underdeveloped countries where resources are limited [10]. Diabetes represents a significant global health challenge. In 2021, 10% of adults (537 million) were diagnosed with diabetes, with projections indicating an increase to 783 million by 2045, representing a 46% rise [1], although approximately 50% of individuals with diabetes remain undiagnosed [11].

European nations have striking epidemiologic disparities, ranging from Greece to 29/million population in Ukraine [12]. European nations, notably Germany, have more renal replacement treatment patients than the US. DM was present in 59% of renal replacement treatment patients in southwest Germany in 1995, with 90% having type 2 DM [13]. Even Denmark and Australia, which have low rates of type 2 DM, have seen a rise in ESKD. Asia has lower occurrence rates and prevalence of published data. Netherlands's research suggested DKD is underdiagnosed. It was noted that histopathologic changes consistent with DKD in 106 of 168 individuals who have type 1 or 2 DM were confirmed by renal tissue examination from autopsies. In 20 of 106 individuals, DKD was not noted [14].

In 2021, the prevalence of diabetes among adults in the Middle East and North Africa (MENA) region was 73 million, with projections indicating an increase to 136 million by 2045, representing an 87% rise [11]. A study in Saudi Arabia reported that DKD prevalence among Type 1 DM patients in Taif City was 23.7%, higher than the Saudi Arabian cohort average of 20.59%, which can be reduced by sugar and blood pressure control [15]. In Qatar, DM prevalence is expected to rise from 17.8% in 2023 to 29.5% by 2050 among adults aged 20–79 [16], and obesity causes 57.5% of Qatar's DM pandemic [17]. The increased rate of DM is associated with an increase in DKD risk, CKD, and ESKD, increasing healthcare costs by more than a third of the national health budget by 2050 [17].

In retrospective Chinese research, type 2 diabetics with renal damage had a significant frequency of nondiabetic renal illness. Renal biopsy revealed that 72.73% of 88 type 2 diabetics had non-diabetic renal disease (NDRD), compared to 20.46% for DKD and 6.82% for complex NDRD. Most NDRDs were membranous, IgA, and focal segmental glomerulosclerosis [18]. In The Gulf Cooperation Council countries, more than 30% of diabetics develop kidney disease, making DKD a cause in 41% of dialysis-dependent ESKD [19].

The average age of ESKD linked to DM is 60 years. Although DKD is more common in elderlies who have had type 2 DM for a longer time, the significance of age in DKD development is uncertain. Early-onset type 2 diabetes among Pima Indians was connected with an increased incidence of ESKD [20]. Furthermore, Blacks, Mexican Americans, and Pima Indians with type 2 DM had a 3- 6-fold greater rate of DKD than Whites [4]. The significant prevalence of DKD in these genetically diverse groups shows that socioeconomic variables, including nutrition, poor hyperglycemia balance, HTN, and obesity, are key to its development. It also suggests family grouping in certain people. Around 50% of Pima Indians with diabetes develop DKD by age 20, and 15% get ESKD. A systematic review of 32 studies from 16 nations [21]. Urban environments dominated the research (90.6%). The assessment and classification of CKD varied greatly. Most studies (62.5%) assessed kidney injury using urine protein. CKD prevalence ranged from 11% to 83.7%. Proteinuria caused 94.9% of incidents at 10 years, ESKD 34.7% at 5 years, and nephropathy mortality 18.4% at 20 years. Diabetes duration, blood pressure, age, obesity, and poor glucose management often impact renal damage [21]. Another review reported that in Africa, the CKD prevalence varied from 2% to 41%, and among diabetics, it was 11 to 90%, and CKD is 11–20% prevalent in North Africa [22].

Type 1 diabetes seldom causes DKD before 10 years. Overt nephropathy affects 3% of newly diagnosed type 2 DM. Peak incidence (3%/year) occurs in people with DM for 10-20 years, then falls. Patients without proteinuria after 20-25 years had a 1%-year chance of renal disease [4].

Pathophysiology of DKD. The pathophysiology of DKD involves a complex interplay mainly between metabolic, molecular, and hemodynamic mechanisms that lead to kidney damage [23]. DKD pathogenesis is still unspecific due to its complicated etiology, and understanding the pathophysiology helps tailor DKD therapy [24]. Different pathways and mediators contribute to DKD development [25]. Renal hemodynamic changes, overactive RAAS, inflammation processes, gut microbiota, and oxidative stress are the main mechanisms of DKD and kidney tissue fibrosis [25, 26]. Hyperglycemia releases vasoactive mediators that dilate afferent arteriolar walls, while high local angiotensin II levels constrict efferent arterioles, causing glomerular hypertension and kidney injury [27]. RAAS activation alters intraglomerular hemodynamics and glomerulus and tubulointerstitium structure [28]. Oxidative stress damages kidney cells and activates im-

munological pathways like inflammation and immune reactions, causing proteinuria, faster tubulointerstitial fibrosis, and ESKD [28]. The possible mechanisms of interplay in DKD are represented in Figure 1.

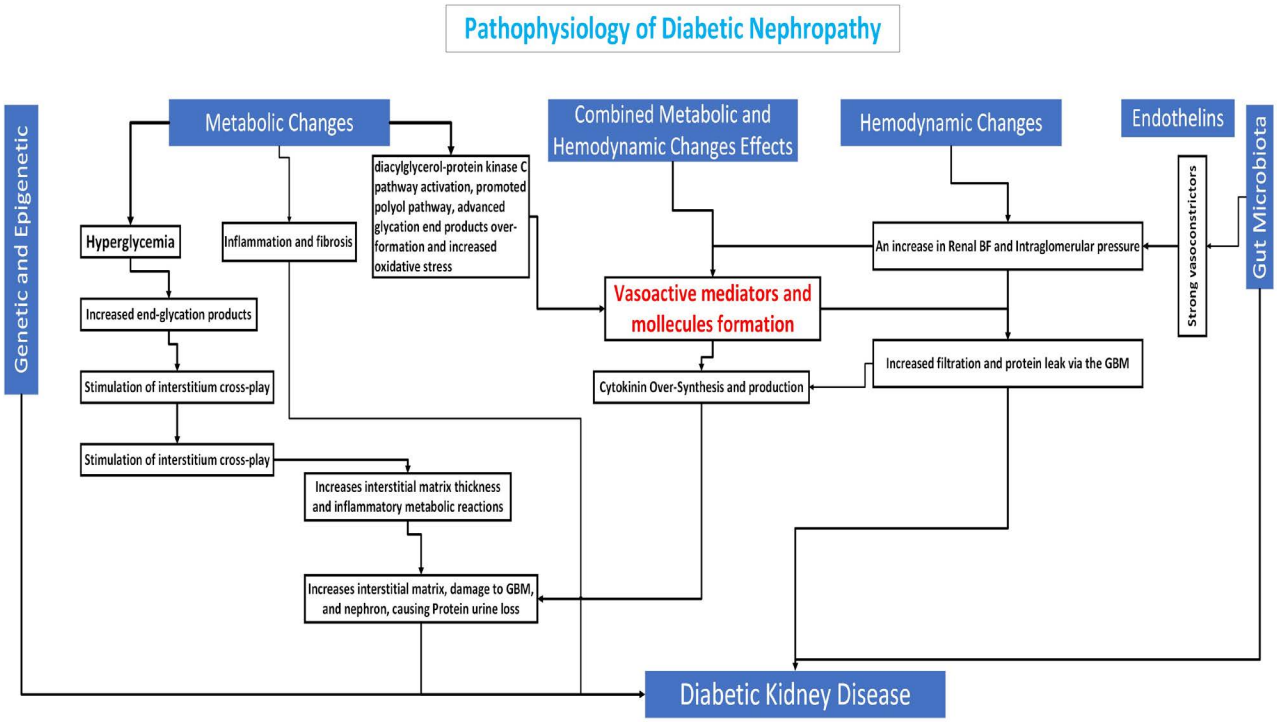

Fig. 1. Pathophysiological mechanisms of DKD. Abbreviation: GBM, glomerular basement membrane.

Metabolic mechanism for DKD. For a while, it has been known that hyperglycemia induces glomerular hyperfiltration, resulting in increased pressure and subsequent injury to the glomeruli concept, which is accepted as the primary mechanism of DKD. The accumulation of advanced glycation end products and activation of the RAAS exacerbates the DKD process [23]. The pathophysiology is intricate, encompassing protein glycosylation, hormonally regulated cytokine formation and release (e.g., transforming growth factor-beta), mesangial matrix deposition, and changes in glomerular hemodynamics, causing small vessel disease [23]. Hyperfiltration is the earliest functional abnormality that can serve as a predictor for DKD progression to CKD and ESKD [29].

Hyperglycemia induces glycosylation of glomerular proteins, potentially leading to mesangial cell proliferation, vascular endothelial damage, and matrix expansion [30]. The glomerular basement membrane typically exhibits thickening. Lesions associated with diffuse or nodular intercapillary glomerulosclerosis are characterized by their distinct morphology; the nodular glomerulosclerosis regions are commonly termed Kimmelstiel-Wilson lesions [23, 31]. Marked hyalinosis is observed in afferent and efferent arterioles, accompanied by arteriosclerosis with extracapillary hypercellularity and podocyte phenotype significant loss plus severe podocyte-foot processes effacement [32]. Additionally, tubular atrophy and interstitial fibrosis may be present. Mesangial matrix expansion is the sole factor that correlates with the progression to ESKD, severe proteinuria, and poor outcome [33].

Hemodynamic consequences of DM compromise of increased intraglomerular and systematic blood pressure [34], causing hyperfiltration [35]. Although the mechanism is unknown, glomerular hyperfiltration is the initial step in DKD, leading to increasing albuminuria, falling GFR, CKD, and ESKD. The possible mechanism is an increased efferent arteriole and decreased afferent arteriole tone that raises the intraglomerular hydrostatic pressure, mostly due to RAAS activation [23].

Hemodynamic mechanisms for DKD. These mechanisms of DKD depend mainly upon the regional and systemic RAAS activation [36].

Renin-angiotensin-aldosterone system (RAAS) activation and intraglomerular pressure. The RAAS activation strongly affects intrarenal hemodynamic function. Furthermore, RAAS activation increases oxidative stress, and inflammation [23]. In early DKD, these mechanisms cause glomerular hypertrophy and mechanical stress, which starts a profibrotic cascade [37]. RAAS inhibition was reported to slow DKD development and progression [38]. The activated local renin system in the kidneys or enhanced intrarenal angiotensin II (AngII) sensitivity may cause glomeruli hyperperfusion and increased intraglomerular hydrostatic pressure [39].

DKD experimental models consistently show higher RAAS activation than confined paracrine RAAS activation, including all cascade constituents and phases. Juxtaglomerular cells produce prorenin, which stimulates renin to activate the RAAS cascade, activating angiotensinogen conversion to AngI and then to AngII by angiotensin-converting enzyme. RAAS blocking was reported to improve DM-induced renal injury outcomes, mostly due to its impact on systemic blood pressure and intraglomerular hydrostatic pressure [23]. It is documented that dual blockade is potentially more effective than single blockage since angiotensin-converting enzyme inhibitors (ACEis) and ARBs operate on distinct RAAS sites [23]. Early research revealed ACEis and ARB may help DKD [23]; however, hyperkalemia and AKI make this combination risky [23].

AngII stimulates an inhibitory G protein to activate the luminal membrane Na+/H+ antiporter and increases phosphatidylinositol turnover [23]. The adrenal cortex secretes more aldosterone, which boosts salt transport by the renal cortex collecting ducts. In the proximal convoluted tubule (PCT), AngII decreases proteinase activity and increases mesangial cell size by reducing the plasminogen activator. Additionally, AngII increases vascular endothelial (ET) growth factor and TGF-β1 release from the glomeruli epithelial and mesangial cells, producing mesangial matrix expansion [23]. Renal fibroblasts have AngII type 1 (ATI) receptors and react to stimulation by proliferating, extending the matrix, and manufacturing fibronectin, predominantly via TGF-β [23].

In DKD, AngII directly stimulates inflammatory cells, leading to chemotaxis and the synthesis of different proinflammatory mediators. These factors involve proliferation, differentiation, inflammation, and fibrosis [23]. Additionally, it was described that AngII enhances insulin resistance [40]. In addition, DKD in humans causes kidney RAAS changes, including enhanced local AngII synthesis, proinflammatory marker induction, and tubular cell activation, suggesting AngII is a mediator for initiating renal inflammation that may explain RAAS blockade's benefits [23].

Molecular mechanism of DKD. Hyperfiltration may be caused by circulatory molecules that act mostly within the glomeruli. Multiple mediators increase intraglomerular hydrostatic pressure by affecting efferent and efferent arterioles' tone. High levels of AngII, endothelin (ET) 1, reactive oxygen species (ROS), and thromboxane A2 may increase efferent arteriole vascular tone [35]. Conversely, decreasing nitric oxide, high cyclooxygenase-2 prostanoids, atrial natriuretic peptide, activating the kallikrein-kinin system, increasing insulin levels and sensitivity, and angiotensin 1–7 might reduce afferent arteriole resistance [35].

Another suggestion is that tubular processes drive intraglomerular hydrostatic pressure [41]. At the early stages of DM, glucose transport routes are activated in the PCT, enhancing glucose and salt reabsorption [41]. Moreover, sodium transport to the nephron's late portions diminishes, initiating tubule-glomerular feedback mechanisms that stimulate the afferent dilation and constrict the efferent arteriole [42]. Furthermore, SGLT2 enhances glucose reabsorption in the PCTs, decreasing the macula densa sodium chloride concentration [43], and leading to renin release and RAAS activation. Additionally, reduced tubuloglomerular feedback, dilated afferent arterioles, and elevated AngII in efferent arterioles cause vasoconstriction [44].

It was mentioned that insulin secretion increases in the earlier phases of DKD. Insulin directly reduces afferent arteriole tone. Hence, it was proposed that insulin contributes to hyperfiltration by directly or indirectly altering the intraglomerular hydrostatic pressure [23]. Furthermore, insulin increase alone may boost PCT salt and glucose transport and reabsorption by PCT cells, promoting tubule-glomerular feedback [23].

Gut microbiota and DKD pathogenesis. Growing evidence indicates that gut microbiota plays a sizable role in DKD progression, contributing to insulin resistance, RAAS activation, immune responses, oxidative stress, and inflammation. Therapies targeting gut microbiota encompass dietary fiber, prebiotics, probiotics, fecal microbiota transplantation, and diabetic agents that influence gut microbiota, including metformin, sodium-glucose transporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor antagonists (GLP-1RAs), and dipeptidyl peptidase-4 (DPP-4) inhibitors [25].

The gut microbiota maintains a symbiotic (mutualistic) relationship with the host under healthy conditions [45]. Alterations in the normal microbiota composition, called gut dysbiosis, disrupt the balance and lead to various disease conditions [46], including DKD development and its progression [47].

Inflammation and fibrosis mechanisms in DKD. DKD development involves interrelated pathways, and inflammation is a key factor. DM causes inflammation via oxidative stress, ischemia, obesity, and cellular damage [48]. These mechanisms produce inflammatory molecules. The research found that CCL11 (a chemokine) may negatively impact DKD patients' GFR and interstitial inflammation [49].

A new study found that IL-1α produced by renal tubule cells, drives renal inflammation in DKD [50]. Additionally, IL-1α levels in DM patients' urine and plasma are related to and can be indicators of podocyte and PCT epithelial cell damage [51]. Even without urine albumin, urinary IL-6 may help to diagnose DKD [52]. IL-6 levels in DKD patients are elevated and associated with increased glomerular basement membrane thickness [23]. Additionally, The IL-6 and mRNA expression in the interstitial and glomerular cells in DKD patients was linked to mesangial proliferation and renal damage [23].

Furthermore, TNF-α is a vital transcriptional regulator for inflammation induction [53]. High serum TNF-α levels and its receptor in DKD patients indicate renal deterioration and increased ESKD risk [54]. In-

flammation causes macrophage and polymorphous infiltration, immune complex formation, and lipoprotein oxidation [55]. This chronic inflammation increases amyloid A protein synthesis and deposition, indicating disease progression [55].

In addition, complement system activation strongly affects DKD development. Persistent hyperglycemia increases glycan and galactosamine-bound molecules identified, activating complement [56]. New complement inhibitors may assist DKD patients, but they must be carefully monitored for effects on infection and immunological complex disease vulnerability [23].

Deposition of extracellular matrix in the kidney tissues may cause tubulointerstitial fibrosis or glomerulosclerosis [55]. DM causes activated myofibroblast infiltration, which is rare in healthy people. However, myofibroblasts, notably epithelial to mesenchymal transition when tubular epithelial cells become myofibroblasts in DKD, are still debated [23]. In late-stage DKD, renal fibrosis is a major pathological change that increases mortality. Different pathways and mechanisms are involved in fibrosis in DKD patients [23]. These mechanisms or pathways significantly affect extracellular matrix formation, collagen and fibronectin expression, and protein secretion [57].

Genetics and epigenetics of DKD. Histone modifications play a dedicated role in adjusting gene expression patterns associated with DKD progression [58]. It was noted that specific histone modifications, including acetylation and methylation, correlate with gene dysregulation with inflammation, oxidative stress responses, and fibrosis in DKD [23]. The histone modifications establish a molecular environment, facilitating pro-inflammatory and pro-fibrotic pathway activation, resulting in structural and functional alterations in diabetic kidneys. Kidney tissues of DKD patients exhibited decreased H3 lysine 4 mono-methylation levels in podocytes, glomerular, and tubular cells [59]. Additionally, exposure to high plasma glucose levels during early life, especially in fetal development, increases the likelihood of adulthood type 2 DM [59]. Evidence indicates that sustained hyperglycemia induces a "metabolic memory" via epigenetic changes in DKD, affecting gene expression [59]. The genetic and pregenetic role in DKD pathogenesis might have a role; however, further large cohort studies worldwide are required to prove this interplay in DKD pathogenesis.

Endothelin 1 role in DKD pathophysiology. Endothelin system activation produces endothelin (ET) peptides, of which ET-1 acts on ET A and B receptors [60]. Endothelin system activation is tightly linked to different chronic disease pathogenesis, including CKD pathogenesis and progression, irrespective of the primary cause [61]. ET-1 is a strong vasoconstrictor generated by endothelial, vascular smooth muscle, epicardial, mesangial, kidney glomerular epithelial, and medullary collecting duct cells [61]. ET-1 acts in an autocrine or paracrine manner on two types of endothelin receptors: ET-A receptors, which are found on glomerular arterioles, podocytes, arcuate arteries, mesangial cells, and the vasa recta in the kidneys. On the other hand, ET-B receptors are present in the collecting system of the nephrons [61]. ET-A receptor activation induces vasoconstriction of efferent and afferent vessels, matrix deposition, and cell proliferation. Conversely, ET-B receptor activation leads to efferent vasodilation, antifibrotic, and antiproliferative effects [62]. Most forms of CKD enhance endogenous kidney ET-1 synthesis, promoting CKD development largely via ET-A receptor-mediated effects on the renal microenvironment [62]. It was described that plasma ET-1 levels are potentially linked to decreased kidney function, albuminuria in DKD, and higher ET-1 staining in kidney biopsies from IgAN patients with proteinuria [61]. Furthermore, ET-1 activation via the ET-A receptor causes renovasoconstriction and angiotensin II overproduction, which increases kidney ET-1 synthesis [61]. This positive feedback loop promotes hypertension, endothelial damage, and podocyte. In addition, ET-1 synthesis causes ETA receptor-mediated mitochondrial oxidative stress in glomeruli endothelial cells and glycocalyx loss [63], promoting further kidney disease in diabetics and even non-diabetics [61].

Clinical presentation of DKD. DKD has different presentations that depend upon the stage of kidney injuries [64]. The following conditions should always be considered in differential diagnosis of proteinuria: light-chain deposition disease, nephrosclerosis, idiopathic and secondary nephrotic syndrome, multiple myeloma, myeloma kidney, renal vein thrombosis, renal artery stenosis, HTN, especially renovascular HTN, and tubular and interstitial kidney diseases.

Family history, personal history of DM, frothy urine, increased urine frequency, and blurred vision are indicators for DM, and they might be clues for diabetes-kidney complications' appearance. Edema of the face, lower limb, or the whole body with increased body weight can be evidence for proteinuria and increased interstitial fluid content. DKD is typically diagnosed following albumin detection by routine urinalysis in diabetics.

Patients may exhibit physical findings related to chronic DM, including the following: the presence of HTN and its complications, and peripheral vascular occlusive illness that is characterized by diminished peripheral pulses and carotid bruits new occurrence. The presence of the fourth heart sound is noted during cardiac auscultation, due to mainly overload and heart failure. Diabetic neuropathy is evidenced by reduced fine sensations and decreased tendon reflexes. Chronic skin ulcers and osteomyelitis appear in some patients. Type 1 diabetics with DKD exhibit indicators of diabetic microvascular disease, including retinopathy and neuropathy [65]. Retinopathy in these patients, the condition generally occurs before overt nephropathy development [65], and the converse does not hold. In advanced retinopathy, a minority of patients exhibit glomeruli his-

tologic changes and increased proteinuria, typically within the microalbuminuric range. At the same time, the majority show minimal or no renal disease, as determined by renal biopsy. On the contrary, diabetic type 2 patients exhibit significant proteinuria and retinopathy generally present with diabetic nephropathy, whereas individuals lacking retinopathy often demonstrate non-diabetic glomerular disease [66].

Other long-term complications, including diabetic foot disease and cardiovascular (CV) manifestations like atherosclerosis, large and small peripheral blood vessel diseases, and diabetes-induced chronic comorbidities, should be thoroughly assessed. Regular checkups for these complications improve early detection, lifestyle, and survival rates and diminish diabetic complications. Regular urine check-up for albuminuria is a good cheap screen test for DKD. Protein (albumin)/creatinine ratio and 24-hour total urine protein are evident measures of the total protein loss. There are different approaches for early detection and diagnosis of DKD. We found different flow charts in different literature. After careful consideration, the best of all most probably is the one suggested by McGrath K & Edi R, 2019 review [67]; however, others have almost some recommendations with some minor differences.

Management of DKD. The prevention of DKD should be the objective for all diabetic patients [68]. While attaining this objective is challenging and may be unfeasible for many diabetics, effective management of the contributing variables would undoubtedly reduce the onset of early DKD. Regular follow-up and multidisciplinary team collaboration are always required to manage DM. Most experts and recommendations advocate maintaining glycosylated hemoglobin (HbA1C) ≤ 7.0%. Sustaining euglycemia diminishes microalbuminuria but may not impede disease advancement once DKD is established [64]. Normalization of lipid profiles is essential for all diabetics to avert CV events, fatty liver, and stroke risk [69]. Table 1 summarizes the DKD therapy outlines.

Table 1

Summary of therapeutic options for DKD prevention and therapies

Intervention	Description
Diet and lifestyle	A high-fiber diet, low carbohydrates, low salt intake, and regular exercise.
Glycemia control	Tight glycemic control using oral hypoglycemic agents (e.g., GLP-1 receptor agonists, SGLT-2 inhibitors), insulin, and diet, along with regular exercise.
Blood pressure control	Aggressive BP control aiming for BP < 130/80 mmHg. ACE inhibitors and ARBs are first-line therapies. Calcium channel blockers are second-line options.
Erythropoiesis-stimulating agents	Reduce the risk of fluid overload and heart failure. Evidence suggests that erythropoiesis-stimulating agents may reduce the progression of CKD in both diabetic and non-diabetic patients. Further studies are required due to limited data.
Non-steroidal mineralocorticoid receptor antagonists	Lower the rate of eGFR decline and progression to CKD and ESKD. Can be used with a maximum dose of RAAS inhibitors.
Microbiota	Intermittent fasting, dietary composition control, high-fiber diet, and healthy fecal microbiota transplantation.
Kidney transplantation	Indicated in patients with ESKD who have well-controlled blood pressure and glycemia. Can be performed along with pancreas transplantation.

Abbreviations: GLP-1, Glucagon-like peptide-1; SGLT-2, sodium-glucose co-transporter 2; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; NS-MRA, non-steroidal mineralocorticoid receptor antagonists; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; ESKD, end-stage kidney disease.

Diet and lifestyle modification. Diet modification is an important intervention in DKD prevention and progression reduction [47]. Restricting dietary protein has varied outcomes. The American Diabetes Association advises those with diabetes and evident DKD to limit protein intake to 0.8 - 1.2 grams/kilogram of body weight/day; however, extensive protein restriction is inadvisable. Supplementation of vitamin D3 (partially activated vitamin D), and sodium bicarbonate, administered to sustain a blood bicarbonate content above 22 mmol/L, may decelerate DKD and CKD development. Therapeutic interventions for edema include the following: salt restriction (e.g., < 2 g/day), fluid intake restriction, and use of loop diuretics, when necessary, with wise titration to prevent hypovolemia. Regular exercise is always advisable for DM and hypertension.

Diet is the key external factor affecting gut microbiota composition [70]. High-fat and high-fructose diets enhance uremic toxins, gut Lipopolysaccharides microbiota, and insulin resistance [71]. Conversely, high-fiber diets reduce systemic inflammation, lower blood uremic toxins, and proinflammatory cytokines, and reverse renal damage in CKD [79]. Recent research showed that dietary fiber promotes short-chain fatty acids-producing bacteria (hallii and Odoribacter), reduces inflammatory and oxidative stress, ameliorates diabetes-related dysbiosis, and prevents DKD.

Intermittent fasting or time-restricted food has also been proven to prevent DKD by improving gut microbiota [71, 72]. β-hydroxybutyrate (β-HB), a key ketone body produced by time-restricted eating (either by fasting or eating fatty food), may reduce oxidative stress and podocyte senescence in diabetic mice [72].

Fecal microbiota transplantation from healthy donors restores microbiome dysbiosis [73]. Fecal microbiota transplantation from lean donors may enhance insulin sensitivity and gut microbiota composition in obese metabolic syndrome patients [74]. Current data suggests Fecal microbiota transplantation may be safe and successful for inflammatory and immunological illnesses linked to gut microbiota changes [75], although, in DKD treatment, the available data is very limited [25].

Blood sugar control. Strict blood sugar control is an essential strategy to decrease risk and prevent the progression of DKD [68]. Intensive glycemic control delays albuminuria and eGFR decrease in type 1 and type 2 diabetes [68]. In early DKD stages, glycemic control is fundamental to delay DKD development. Based on the CKD stage, life expectancy, comorbidity load, and hypoglycemia risk, KDIGO guidelines suggest a customized HbA1C goal of <6.5% to <8.0% for DKD patients not on dialysis [76]. DKD glucose-lowering medications are chosen and dosed based on kidney function assessment by eGFR, and agents having renal and CV benefits [77]. Different agents can achieve glycemic results. We will restrict our discussion to SGLT2 inhibitors and GLP1 agonists only.

SGLT2 inhibitors and GLP-1Ras. SGLT2 inhibitors are indicated for type 2 diabetics but not for those with type 1 DM or an eGFR of less than 20 mL/minl1.73 m^2. Inhibition of the sodium-glucose transporter has shown a decline along with kidney disease progression, even post-kidney transplantation [78–80]. For most type 2 diabetics with DKD, SGLT2 inhibitors with renal benefits are advised for eGFR ≥20 mL/min/1.73 m^2, regardless of HbA1C or glucose reduction needs [81]. Strong evidence intimates that SGLT2 inhibitors and RAAS inhibitors reduce DKD development, heart failure, and atherosclerotic CV disease risk in DKD patients due to type 2 DM [80].

DKD is a CV disease risk factor. Kidney GLP-1R distribution is contentious. GLP-1Rs are described in the kidney cortex and PCT; however, others did find GLP-1R in the nephron tubules [82]. Another report revealed that the renal tubules lack GLP-1R, while the renal vasculature does [83]. Monoclonal antibodies against GLP-1R showed that it is mostly in renal vasculature [84]. Interestingly, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibition via averting renal oxidative stress by GLP-1RAs reduces further DKD progression [82].

A Comparative Effectiveness (GRADE) Study found no differences in kidney outcomes for type 2 diabetics receiving sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, or insulin glargine with metformin [85]. A meta-analysis showed that SGLT2 inhibitors and GLP-1RAs improve cardiorenal outcomes in type 2 DM [86].

GLP-1RAs are frequently utilized to treat type 2 DM. Clinical and experimental research showed that GLP-1RAs benefit DKD via natriuresis, anti-inflammatory, and anti-oxidative stress, regardless of their glucose-lowering ability. Furthermore, GLP-1RAs inhibit kidney fibrosis. In T2D patients at elevated risk for CVD, GLP-1RAs improve kidney outcomes in recent clinical studies. These data imply that GLP-1RAs may reduce DKD development and progression. GLP-1RAs lower albuminuria but their impact on ESKD development is unknown [82], and this issue is worth investigating.

In major CV outcome studies [68, 87], GLP-1 receptor agonists improved secondary kidney outcomes (albuminuria progression), but primary renal outcome data is unavailable. As an add-on to first-line glucose-lowering treatment (SGLT2 inhibitor plus metformin), GLP-1 receptor agonists are preferred in type 2 DM and DKD patients who do not reach glucose objectives or have persistent albuminuria [68, 81]. Although SGLT2 inhibitors' glucose-lowering effects decrease with eGFR, their cardiorenal advantages remain.

GLP-1RAs increase glucose-dependent insulin secretion and decrease glucagon release to enhance glucose metabolism, and SGLT2is acts mainly by impairing the filtered glucose and sodium by the PCT cells. The SGLT2i and LP-1Ras are recommended over sulfonylureas, which have a higher risk of hypoglycemia adverse effects, especially in CKD.

In summary, despite the conflicting reported data about the effectiveness of GLP-1Ras, they benefit DKD prevention and progression. Hence, further projects are required to explore these issues in large studies.

Blood pressure control. Aggressive management of HTN, commencing with RAAS inhibition, is strongly advised for all diabetic patients, with a target of blood pressure ≤ 120/80 mmHg. Blood pressure below 130/80 mm Hg was recommended by some authors, while several experts now advocate for a threshold of < 140/90 mmHg. Others advocate for a blood pressure range of 110 - 120/65 - 80 mm Hg, especially in individuals with protein excretion over 1 gm/day. Interestingly, others assert that blood pressure levels below 120/85 mmHg correlate with heightened CV mortality and heart failure [88].

RAAS inhibition. RAAS system activation is a main player in DKD pathogenesis because it causes systemic and intraglomerular hypertension. Consequently, ACEis or ARBs are the preferred antihypertensives because they lower blood pressure and proteinuria while decelerating the advancement of DKD. ACEis are often more cost-effective; however, ARBs may be utilized as an alternative if ACEis induce intolerable adverse effects. Treatment should begin at the detection of microalbuminuria, irrespective of the presence of HTN; several specialists advocate the use of these drugs even before the manifestation of kidney involvement by DKD. Most individuals require diuretics with angiotensin inhibition to achieve the targeted blood pressure levels. The dosage should be reduced if orthostatic hypotension symptoms or serum creatinine persistently rises above > 30% of the baseline levels.

Calcium channel blockers. Non-dihydropyridine calcium channel blockers, like verapamil and diltiazem, possess antiproteinuric and renoprotective properties and may be utilized if proteinuria does not significantly diminish upon achieving target blood pressure or as alternatives for patients who have contraindications to ACE inhibitors or ARBs, like hyperkalemia or chronic non-productive cough. On the contrary, the dihydropyridine calcium channel blockers (e.g., amlodipine, nifedipine, and felodipine) do not diminish proteinuria; nevertheless, they serve as beneficial adjuncts for blood pressure management and provide cardioprotection when used with ACEis. Nondihydropyridine calcium channel blockers and ACEis have augmented antiproteinuric and renoprotective effects when administered together, with their antiproteinuric efficacy further augmented by sodium restriction, leading to leg edema. Nondihydropyridine calcium channel blockers must be used cautiously in individuals on beta-blockers due to the risk of exacerbating bradycardia.

Endothelin receptor antagonists (EtRA). EtRAs represent a potential therapeutic option due to their effects on the pathophysiological processes involved in diabetes mellitus (DM)-associated kidney injuries. Endothelin-1 (ET-1) is primarily generated by the endothelium of small blood vessels, vascular smooth muscle, epicardium, mesangial layers, kidney glomerular epithelial cells, and medullary collecting duct cells [**61**]. It exerts its effects autocrinely or paracrinely on two types of endothelin receptors: ETA and ETB receptors, as described in the pathogenesis section.

There is good evidence about the benefit impacts of ETRAs in heart failure with excessive fluid retention [61]; in contrast, there is not much data in CKD about the ETRAs, and the study period was short (on average 16 weeks). All seven previously reported studies showed consistent albuminuria effects but not eGFR effects. Only the SONAR and ENABLE studies give long-term renal endpoint data, and the ENABLE study uses severe adverse event reporting for kidney failure data. The DUPLEX, PROTECT, and ALIGN studies will give long-term proteinuria reduction and eGFR decrease data to understand ERA kidney protection better [**61**]. New therapies that slow CKD progression are intriguing. Strong clinical evidence shows that ERAs, particularly selective ERAs, added to standard-of-care may reduce albuminuria and preserve the kidneys over time, making them an appealing therapy for non-diabetic and diabetes-associated CKD. Therefore, further studies are required to investigate the long-term impact of ETRAs on CKD and DKD development and progression.

Non-steroidal mineralocorticoid receptor antagonists (NS-MRA) therapy.

Type 2 diabetics with DKD may reduce renal and CV risk using the NS-MRA agent, such as finerenone. Finerenone lowers the risk of sustained eGFR decline, progression to ESKD, nonfatal myocardial infarction, CV death, and heart failure hospitalization for type 2 diabetics who have CKD [**68**]. Finerenone can be used in type 2 diabetics with eGFR ≥25 mL/min/1.73 m^2, normal serum potassium, and albuminuria (UACR ≥30 mg/g) even with maximally tolerated RAAS inhibitors [**68**].

Kidney transplantation. Kidney transplantation, without or with concurrent or later pancreas transplantation, is a viable alternative for individuals with ESKD. Studies reported variable results. The five-year survival rate for type 2 diabetics after kidney transplantation is around 77%, in contrast to 88% for patients without diabetes. At five years, kidney graft survival rates are more than 97% for life and 77% for dead donor transplant recipients [**89–91**]Swanson KJ, Aziz F, Garg N, et al. Outcomes after simultaneous kidney-pancreas versus pancreas after kidney transplantation in the current era. Clin Transplant. 2019;33(12.

Outcomes. Proteinuria predicts morbidity and death risk. Microalbuminuria and macroalbuminuria are 30–35% common in the two main types of DM. In DM, microalbuminuria and macroalbuminuria raise the death rate from any cause and independently predict CV morbidity. In the non-diabetic population, microalbuminuria increases coronary disease and CV mortality risk. The low relative death rate is in patients without proteinuria, whereas those with proteinuria have a 40-fold higher risk [**92**]. Type 1 DM patients with proteinuria had a bell-shaped connection between DM duration/age and death, peaking at 34–38 years. ESKD kills 59-66% of type 1 DM and nephropathy patients. The 5-year survival rate in Germany reported research was fewer than 10% for elderly type 2 diabetics and 40% for younger type 1 patients. Type 1 diabetics with proteinuria had a 50% cumulative rate of ESKD 10 years from proteinuria start, compared to 3-11% in European type 2 DM patients [**93**].

A study found in type 2 diabetics that diabetic retinopathy is a strong predictor for ESKD progression [**94**]. Jiang et al. found that type 2 DM patients with more comorbidities had a greater risk of DKD progression. After dividing the study's patients into four groups-low comorbidity/low treatment, low/high treatment, moderate/high insulin use, and high/moderate treat-

ment. The researchers found 5-year DK progression rates of 11.8%, 18%, 16.5%, and 27.7%, respectively [95]. Another study found that type 1 diabetics with macroalbuminuria are at increased risk for ESKD despite transplantation and dialysis [96]. Although both types 1 and 2 DM cause ESKD, most individuals have type 2. The percentage of type 1 DM patients who suffer renal failure has decreased in recent decades. However, 20-40% still have the ESKD risk. On the other hand, 10-20% of type 2 diabetics develop uremia. In contrast, 15–25% of DKD and type 1 DM patients die from CV disease despite the early age of type 1 development. Another newer study reported the cumulative ESKD risk was 2.2% and 7% after 20 and 30 years respectively from the DM diagnosis [97]. The last study concluded that ESKD cumulative risk has diminished noticeably during the last 50 years, emphasizing the critical role of advancements in DM and DKD therapy.

Gaps and prospects in DKD. DKD is poorly understood and needs more studying. Although important determinants and biomarkers have been identified, understanding molecular processes, and developing tailored therapeutics is still challenging. The intricate relationship between genetic predisposition and environmental variables in DKD development and progression is interesting. Future DKD management requires a comprehensive strategy. This involves adapting therapies to genetic, molecular, and clinical traits.

In DKD, precision glucose management and novel inflammatory and fibrosis treatments are essential. RAAS pathway regulation is crucial. Further research has shown significant promises for SGLT2is and GLPRAs receptor agonists, despite the different gaps discussed earlier.

Studying combo therapy, such as ETRAs and SGLT2is, may improve results in DKD patients. The clinical feasibility of novel medicines depends on rigorous efficacy and safety needs for further research projects.

A ntOPN (a glycoprotein) increases kidney tissue injuries. The ntOPN can be used as an early biomarker and possible therapeutic target to reduce DKD fibrosis and inflammation. Pharmacological interventions must be accompanied by patient education and collaborative care. Diversity in clinical trials must be fostered. These comprehensive strategies that combine medication, customized medicine, and modern technology to enhance DKD outcomes and quality of life require further research.

In summary, delayed diabetes diagnosis, late DKD discovery, inefficient glycemic and blood pressure control, insufficient kidney protection, and inadequate care for severe CKD increase ESKD risk. Although novel treatment models and procedures have been built to overcome these issues, they are not routinely and efficiently used. To improve patients' care, we recommend focusing on DKD awareness, access to timely evidence-based care, inclusive patient-centered care, and complex disease management evidence. Patients and their families must be central to these activities. New interventions are available, but due to DKD pathogenesis gaps and scanty research data in DKD, further investigatory projects for pathogenesis and new therapies are highly recommended.

Limitations. Composing one review on a prevalent condition is arduous. The incidence of this condition is escalating in correlation with the growing frequency of DM. A good volume of literature has been published about DKD. It is exceptionally hard to include the published studies on epidemiology, etiology, prevention, and therapy options in a single complete review. While certain aspects were overlooked, we tried to focus on the facts, gaps, and foundations of DKD pathophysiology, prevention, and essential therapies to the greatest extent feasible.

Conclusions. Diabetes is a global affliction that continues to increase annually. The prevalence of diabetic kidney injury in diabetics continues to rise. Diabetic kidney disease physiologically arises from alterations and imbalances in metabolic and hemodynamic variables, yet other factors may also contribute. The interplay of several elements in DKD is the most widely accepted view, rather than attributing it to one cause. Preventing DKD is the optimal strategy; nevertheless, it is often not feasible. Therefore, controlling blood sugar, managing blood pressure, and controlling other parameters are optimal strategies to postpone the most severe impacts of diabetes. New biomolecular-based research projects are necessary to assess the pathogenesis, treatment, and outcome of DKD.

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Author contributions.

Elmukhtar Habas: Principal author, conceptualization, project manager, original draft preparation;

Amnna Rayani: Conceptualization, review and editing;

Aml Habas: Literature analysis;

Kalifa Farfar: Literature analysis;

Eshrak Habas: Literature analysis, figure preparation;

Khaled Alarbi: Literature analysis;

Ala Habas: Literature analysis, table preparation;

Elmehdi Errayes: Review and editing;

Gamal Alfitori: Review and editing.

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