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REVIEW OPEN ACCESS

From pathophysiology to personalized care: A comprehensive review of diabetic kidney disease

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Abstract

Diabetic kidney disease (DKD) stands as a prevalent and significant complication in individuals with type 2 diabetes, impacting nearly half of this population. It holds the primary position as the cause of chronic kidney disease and end-stage kidney disease globally, associated with heightened cardiovascular morbidity and mortality. Despite the array of available interventions to prevent and manage DKD, such as regulating blood sugar levels, controlling blood pressure, and inhibiting the renin-angiotensin system, numerous patients continue to grapple with the ongoing decline in kidney function and unfavorable outcomes. This comprehensive review offers an updated exploration of the pathophysiology, diagnosis, prevention, and treatment of DKD. Special attention is devoted to emerging treatment modalities displaying promising outcomes in clinical trials, notably sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, non-steroidal mineralocorticoid receptor antagonists, and innovative agents addressing inflammation and fibrosis. The discourse also delves into the complexities and opportunities associated with integrating these therapies into clinical practice, emphasizing the necessity for personalized and all-encompassing care for DKD patients. The conclusion outlines future directions, urging further research and providing recommendations to advance both understanding and practical approaches in this domain.

Keywords: pathophysiology; personalized care; diabetic kidney disease

Introduction

Diabetic kidney disease (DKD), a chronic and progressive complication linked to diabetes, profoundly impacts kidney structure and function. Hallmarks of this condition include albuminuria, diminished glomerular filtration rate (GFR), and an elevated risk of progressing to end-stage renal disease (ESRD) [1]. It stands as a prevalent and significant concern, affecting roughly 40% of individuals with type 2 diabetes (T2D) and 20% of those with type 1 diabetes (T1D). Globally, diabetic nephropathy is the foremost contributor to ESRD, accounting for over 50% of cases in developed nations [2].

Beyond its renal implications, diabetic nephropathy substantially heightens cardiovascular morbidity and mortality while diminishing patients' health-related quality of life [3]. The International Diabetes Federation's latest figures suggest a staggering rise in global diabetes cases, projecting a surge from 537 million adults (20–79 years old) in 2021 to over 780 million by 2045 [4], with 90–95% of cases attributed to T2D [5].

The pathophysiology of diabetic nephropathy is intricate and multifaceted, involving hyperglycemia, associated metabolic disruptions, glomerular hemodynamic shifts, and proinflammatory/profibrotic factors. These pathways often culminate in glomerular hyperfiltration and hypertrophy, with hypertension exacerbating the progression to sclerosis. Diagnosis hinges on detecting albuminuria and/or reduced GFR in diabetic patients, necessitating the exclusion of alternative kidney disease etiologies [6].

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Efforts to prevent and manage diabetic nephropathy center on mitigating kidney function decline, and cardiovascular events, and enhancing patients' quality of life. Although traditional strategies like glycemic control and blood pressure management offer modest benefits, renin-angiotensin system (RAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), play pivotal roles in pharmacological therapy. Despite their efficacy in reducing albuminuria, slowing GFR decline, and delaying ESRD, residual renal and cardiovascular risks persist [7].

This underscores the urgent need for novel therapeutic approaches that augment existing RAS inhibition benefits. Recent advancements have yielded promising new treatment modalities such as sodium-glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP-1 RA), non-steroidal mineralocorticoid receptor antagonists (MRA), and innovative agents targeting inflammation and fibrosis. These therapies exhibit encouraging outcomes in mitigating albuminuria, preserving GFR, forestalling ESRD, and enhancing cardiovascular health in diabetic nephropathy patients [8, 9].

However, integrating these treatments into clinical practice poses challenges concerning cost, availability, safety, adherence, and the lack of evidence for specific patient subgroups, necessitating more comprehensive long-term data. Further research is warranted to delineate the optimal combination, sequencing, and potential synergies or interactions with RAS inhibitors and other drugs. Hence, personalized, and holistic care tailored to individual patient characteristics, preferences, and goals, as well as local resources and guidelines, is paramount.

This review provides an updated exploration of diabetic nephropathy's pathophysiology, diagnosis, prevention, and treatment, with a spotlight on emerging therapeutic avenues exhibiting promise in clinical trials. It also addresses the challenges and opportunities inherent in implementing these therapies in clinical settings, advocating for personalized and comprehensive care for diabetic nephropathy patients. The conclusion outlines future research directions and offers recommendations for advancing both understanding and practice in this domain.

Pathophysiology and insights into molecular mechanisms

DKD is a significant complication of diabetes that impacts the kidneys, potentially leading to end-stage kidney failure. It arises from prolonged exposure to elevated glucose levels, triggering various molecular pathways that harm kidney cells and structures.

The polyol pathway transforms excess glucose into sorbitol and fructose and induces osmotic and oxidative stress within kidney cells.

The hexosamine pathway, which escalates the production of O-linked N-acetylglucosamine (O-GlcNAc), alters the functionality of proteins involved in inflammation, fibrosis, and apoptosis [10].

The protein kinase C (PKC) pathway, activates different PKC isoforms, thereby enhancing the expression of pro-inflammatory and pro-fibrotic factors like transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), and endothelin-1.

The advanced glycation end products (AGEs) pathway, forms irreversible links between glucose and various biomolecules, accumulating in the extracellular matrix and triggering oxidative stress, inflammation, and fibrosis [10, 11].

These pathways detrimentally affect various kidney cell types such as podocytes, endothelial cells, mesangial cells, and tubular cells, leading to structural alterations in glomeruli and tubules. These changes, including glomerular basement membrane thickening, mesangial expansion, podocyte loss, tubular atrophy, and interstitial fibrosis, impair the kidney's filtration and regulatory functions, resulting in proteinuria, hypertension, and progressive kidney function loss [12].

Therapeutic strategies for DKD focus on modulating these molecular pathways to prevent or slow kidney damage. Established treatments include glucose and blood pressure control, as well as inhibition of the renin-angiotensin-aldosterone system (RAAS). Emerging treatments such as sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown promise in reducing blood glucose, blood pressure, and the risk of kidney failure and cardiovascular events in DKD patients. Other potential therapies undergoing investigation in preclinical and clinical studies include inhibitors targeting PKC, AGEs, RAGEs, TGF-β, VEGF, and O-GlcNAc [13, 14].

Epidemiology and burden of DKD worldwide

The global impact and prevalence of DKD pose a significant threat to public health, with far-reaching consequences including chronic kidney disease (CKD), end-stage kidney disease (ESKD), cardiovascular complications, and mortality. Recent data from the Global Burden of Disease 2019 Study [15] revealed the

following alarming statistics attributed to DKD: 2.62 million new instances of CKD, 134.58 million prevalent cases of CKD, 405.99 thousand deaths, 13.09 million disability-adjusted life-years (DALYs). Comparing these figures to those of 1990 underscores a troubling trend: 1.25 million new, KD cases, 55.95 million prevalent CKD cases, 184.81 thousand deaths, and 6.28 million DALYs.

Addressing DKD necessitates robust prevention, diagnosis, and treatment approaches. Key risk factors include inadequate glycemic control, hypertension, obesity, smoking, and genetic predisposition. Timely detection and management of DKD can mitigate the progression to ESKD and enhance the quality of life for individuals with diabetes [16, 17].

Clinical manifestations and diagnosis

Diabetic nephropathy or DKD affects around 40% of people worldwide with uncontrolled diabetes. It is known by the malfunction of kidney filters (glomeruli), leading to the leakage of proteins (albuminuria) and a decrease in kidney function (glomerular filtration rate, GFR). The clinical manifestations of DKD vary depending on the stage and severity, some of the common clinical manifestations are.

Albuminuria: The initial indication of DKD presents as an albumin-to-creatinine ratio (ACR) exceeding 30 mg/g in urine. This highlights damage to the glomeruli and heightens the susceptibility to kidney and cardiovascular complications. Proteinuria can be categorized as either microalbuminuria (ACR 30-300 mg/g) or macroalbuminuria (ACR > 300 mg/g), discerned through routine urine screenings among individuals with diabetes [18].

Reduced GFR: Serving as a comprehensive gauge of renal function, GFR is evaluated via creatinine levels in the bloodstream. A GFR surpassing 90 mL/min/1.73 m^2 is deemed within the normal range, whereas a GFR dipping below 60 mL/min/1.73 m^2 indicates the onset of CKD, spanning stages 1 through 5, with the latter marking end-stage kidney disease (ESKD). Symptoms associated with dwindling GFR include weariness, queasiness, emesis, appetite loss, weight reduction, and itching, accompanied by complications like anemia, osteopathy, acidosis, and electrolyte imbalances [19].

Hypertension: emerges as a prominent DKD risk factor, exacerbating renal injury by instigating pressure and inflammation in the glomeruli. Elevated blood pressure also escalates the likelihood of cardiovascular ailments. Diagnosis entails blood pressure measurements, with hypertension delineated by readings at or beyond 130/80 mmHg. Intervention encompasses pharmaceuticals, lifestyle alterations, and sodium restriction [19].

Electrolyte abnormalities: are common and serious complications of DKD, which affect the balance of minerals and fluids in the body. Some of the electrolyte disorders that can occur in DKD are hyperkalemia (high potassium level), hyponatremia (low sodium level), hypocalcemia (low calcium level), hyperphosphatemia (high phosphate level), and hypomagnesemia (low magnesium level). These abnormalities can cause various symptoms and signs, such as muscle weakness, arrhythmias, confusion, seizures, and bone disease. Electrolyte abnormalities in DKD are mainly caused by impaired kidney function, but can also be influenced by other factors, such as diet, medications, acid-base status, and hormonal changes [19].

Edema: Fluid buildup stemming from impaired renal function surfaces as swelling, primarily in the lower extremities. Edema assessment involves applying pressure to the swollen area to ascertain the persistence of an indentation (pitting edema). It may also manifest in the respiratory system, triggering dyspnea and respiratory distress. Management entails diuretics to bolster urine output and curtail fluid overload [20].

Other indications: Additional DKD signs may include frothy or sanguineous urine, frequent or imperative urination, muscular spasms, and cognitive impairment, signaling advanced renal impairment or infection.

DKD diagnosis necessitates detecting proteinuria and/or diminished GFR in diabetic individuals while ruling out alternative primary etiologies of kidney impairment. Validation entails repetitive assessments over an extended duration. Supplementary appraisals, such as urine microscopy, culture, blood urea nitrogen (BUN), electrolyte levels, hemoglobin A1c (HbA1c), lipid profile, uric acid, and renal ultrasound, may be conducted to eliminate alternative diagnoses or gauge complications.

Prevention and management of DKD are paramount for augmenting the well-being and longevity of individuals with diabetes. Vital approaches encompass regulating hyperglycemia, hypertension, hyperlipidemia, smoking cessation, and embracing a healthful lifestyle. Pharmacological interventions may encompass angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, statins, and diuretics. Advanced scenarios may necessitate kidney biopsy, dialysis, or transplantation.

Management and current guidelines and emerging therapies

The management of DKD constitutes a nuanced and evolving domain, necessitating a personalized and holistic strategy to optimize outcomes for individuals grappling with diabetes and CKD. The existing guidelines for DKD management draw insights from recent clinical trials and consensus statements provided by expert entities like the American Diabetes Association (ADA), Kidney Disease: Improving Global Outcomes (KDIGO), and the National Kidney Foundation (NKF). The primary objectives of this management approach are to decelerate the progression of renal damage, forestall or postpone the onset of end-stage kidney disease (ESKD), and mitigate the risks associated with cardiovascular complications. The core strategies encompass.

Screening and diagnosis: DKD diagnosis involves assessing the albumin-to-creatinine ratio (ACR) and glomerular filtration rate (GFR) in individuals with diabetes while eliminating other potential causes of kidney impairment. Annual screening is recommended, particularly for those with prolonged diabetes duration, inadequate glycemic control, hypertension, a family history of kidney issues, or other coexisting conditions [21, 22].

Glycemia monitoring: Effective glycemic control is pivotal in DKD prevention and management, with the target and monitoring methodology contingent on the CKD stage, hypoglycemia risk, and patient preferences. Generally, the recommended HbA1c target is 7% or lower, but individualization based on patient characteristics may warrant higher or lower thresholds. In advanced CKD, alternative monitoring methods like self-monitoring of blood glucose or continuous glucose monitoring may be preferred [23].

Lifestyle therapies: Implementing lifestyle adjustments, encompassing a wholesome diet, physical activity, smoking cessation, and weight control, assumes a pivotal role in DKD management and cardiovascular risk reduction. Dietary modifications may involve tailoring sodium, protein, phosphorus, and potassium intake according to CKD stage and patient preferences. Physical activity holds promise in enhancing glycemic control, blood pressure, lipid profiles, and overall quality of life. Smoking cessation contributes to diminished risks of kidney and cardiovascular complications, while weight management influences improved glycemic control, blood pressure, and lipid profiles [24].

Pharmacologic management: Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and mineralocorticoid receptor antagonists showed efficacy in improving kidney and cardiovascular outcomes for individuals with DKD, supplementing glycemic, blood pressure, and lipid control efforts. The selection and dosage of these agents depend on CKD stage, albuminuria presence, risk of adverse effects, and patient preferences [25].

Emerging therapies: Ongoing research explores novel therapies for DKD treatment, encompassing innovative SGLT2 inhibitors, GLP-1 receptor agonists, dual SGLT1/2 inhibitors, endothelin receptor antagonists, G protein-coupled receptor 119 agonists, and stem cell therapy. These potential therapies hold promise for additional benefits in kidney and cardiovascular outcomes; however, further research is indispensable to ascertain their efficacy and safety [25, 26].

Role of glycemic control in preventing and managing

Glycemic regulation serves as a potent shield against the onset and progression of DKD, mitigating the harm inflicted upon kidney filtration units, or glomeruli, while curbing the inflammatory responses and fibrotic changes within renal tissues. This concerted effort not only safeguards kidney health but also steers towards enhanced cardiovascular and overall outcomes, accomplished through the reduction of blood pressure, lipid levels, and oxidative stress [27, 28].

Various pharmacological interventions, encompassing agents like metformin, insulin, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, and dipeptidyl-peptidase-4 inhibitors, alongside lifestyle modifications such as adhering to a balanced diet, engaging in physical activity, and diligently monitoring blood glucose levels, contribute to achieving and sustaining glycemic equilibrium [29, 30].

Tailoring glycemic targets and monitoring methodologies remains imperative, factoring in the DKD stage, severity, hypoglycemic risks, and individual patient preferences. While a HbA1c target of 7% or lower generally stands as the norm, adjustments may be warranted based on patient-specific characteristics. Considering the limitations of HbA1c accuracy in advanced DKD, alternative monitoring approaches like self-monitoring of blood glucose or continuous glucose monitoring might be preferred.

Glycemic management necessitates a delicate balance, mindful of patient safety and quality of life, with

adaptations made in response to fluctuations in kidney function and medication regimens. While glycemic control remains a cornerstone in DKD management, it should be complemented by a multifaceted approach. This encompasses blood pressure regulation, lipid modulation, smoking cessation, and the integration of pharmacological agents proven to ameliorate kidney and cardiovascular outcomes. A comprehensive and personalized care blueprint emerges as the gold standard for individuals navigating the complex interplay of diabetes and DKD [31].

Hypertension management and strategies and challenges

Managing hypertension in individuals with DKD is a critical and multifaceted endeavor that demands a tailored and holistic strategy to enhance patient outcomes. Hypertension, a prevalent and significant risk factor for DKD, exacerbates kidney damage by escalating pressure and inflammation within the kidney's glomeruli. Moreover, hypertension amplifies the susceptibility to cardiovascular ailments, stroke, and heart failure among those with DKD. Hence, effective hypertension management is imperative not only for mitigating DKD but also for curbing the likelihood of cardiovascular complications [32, 33].

Contemporary approaches to hypertension management in DKD are grounded in the latest evidence gleaned from clinical trials and consensus guidelines furnished by expert bodies like the American Diabetes Association (ADA), kidney disease: Improving Global Outcomes (KDIGO), and the National Kidney Foundation (NKF) [34-36]. The overarching objectives of hypertension management encompass attaining a target blood pressure range, ameliorating albuminuria, and enhancing renal and cardiovascular outcomes. Further research is warranted to elucidate their safety and efficacy profiles in DKD populations [36, 37].

Novel biomarkers for early detection and prognostication

Timely detection and prognostication of DKD play pivotal roles in forestalling or slowing down the advancement of renal impairment and mitigating the risk of cardiovascular complications. Nevertheless, traditional biomarkers commonly utilized in DKD diagnosis and prognosis, such as albuminuria and estimated glomerular filtration rate (eGFR), present inherent shortcomings in sensitivity, specificity, and prognostic accuracy. Consequently, there arises a pressing demand for the identification and validation of novel biomarkers capable of capturing the multifaceted pathogenesis of DKD and furnishing more precise and timely insights into renal function and patient prognosis.

Emerging biomarkers for DKD can be broadly categorized into distinct classes, encompassing functional, structural, inflammatory, metabolic, and genetic biomarkers. Functional biomarkers serve to assess renal function and performance, encompassing parameters like serum creatinine, cystatin C, beta-trace protein, and beta-2 microglobulin. Structural biomarkers, on the other hand, offer insights into kidney damage and injury, encompassing markers such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-beta-D-glycosaminidase (NAG), and liver-type fatty acid-binding protein (L-FABP).

Inflammatory biomarkers shed light on the inflammatory milieu and immune response within the kidney, including tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and C-reactive protein (CRP). Metabolic biomarkers, meanwhile, delineate metabolic perturbations and oxidative stress within the renal microenvironment, encompassing entities such as asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), advanced glycation end products (AGEs), and 8-hydroxy-2'-deoxyguanosine (8-OHdG). Lastly, genetic biomarkers elucidate genetic variants and epigenetic modifications associated with DKD susceptibility and progression, including single nucleotide polymorphisms (SNPs), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and DNA methylation.

Novel biomarkers for DKD hold promise in revolutionizing the landscape of disease diagnosis, staging, monitoring, and prognosis, while also facilitating the tailoring of therapeutic interventions and the advent of personalized medicine for individuals with diabetes. Nonetheless, robust validation studies are imperative to ascertain the clinical utility and cost-effectiveness of these biomarkers and to establish optimal cut-off values and reference ranges tailored to diverse patient populations and healthcare settings.

Patient education, empowerment and management

Education and empowerment initiatives for patients with DKD can significantly enhance outcomes and quality of life by augmenting patient knowledge, skills, confidence, and satisfaction, while concurrently alleviating care burdens, stress, and costs. Moreover, these initiatives can benefit healthcare providers and

systems by improving communication, collaboration, and care coordination, while simultaneously reducing staff workload, burnout, and turnover [39-41].

Translational research and future directions

Delving into the efficacy of emerging Reno protective agents like sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists, which exhibit potential in mitigating the incidence of renal and cardiovascular complications in DN patients. Unraveling the intricate molecular and cellular pathways dictating the onset and progression of DN, including inflammation, oxidative stress, epigenetic modifications, and tubular malfunction. Insight into these mechanisms could unveil novel targets for intervention and preventive strategies. Pioneering the development and validation of biomarkers for early detection, diagnosis, prognosis, and treatment response in DN. These biomarkers, encompassing urinary and serum proteins, metabolites, and microRNAs, could enable risk stratification and facilitate tailored therapeutic interventions.

Spearheading clinical trials to assess the safety and efficacy of both novel and existing therapeutic modalities in DN management. Promising avenues such as immunotherapy, stem cell therapy, gene therapy, and nanomedicine warrant thorough investigation to furnish evidence-based guidelines for optimal DN treatment. Enhancing the translation of preclinical findings into human studies through the adoption of more pertinent animal models, human kidney organoids, and bioengineered tissues. These innovative approaches hold the potential to bolster the reliability and reproducibility of translational DN research [42, 43].

Conclusion

The future directions, urging further research and providing recommendations to advance both understanding and practical approaches in this domain are outlined. Translational investigation involves the application of scientific breakthroughs from fundamental research to practical clinical settings, with the primary objective of enhancing health outcomes and enhancing the quality of life for individuals. Diabetic nephropathy (DN), a prevalent complication of diabetes affecting millions globally, stands as a significant contributor to elevated rates of illness and death. Consequently, advancing translational exploration in DN is imperative to unearth innovative biomarkers, mechanisms, and therapies for this condition.

Conflicts of interest

Authors declare no conflicts of interest.

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