

Review Article

Novel approaches and therapeutic targets for diabetic nephropathy: Advances and promising strategies

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Sent for review: 29 July 2023

Revised accepted: 25 November 2023

Abstract

Diabetic nephropathy is a progressive condition characterized by kidney damage and functional decline, primarily attributed to hyperglycemia. Special keywords and probes related to diabetic nephropathy were utilized by Google search engine to obtain relevant information from Google, Google Scholar, PubMed, Science Alert, and Google Scholar databases. This review explores the interconnected mechanisms underlying its pathogenesis. Hyperglycemia initiates glomerular hypertrophy and increased glomerular filtration rate as compensatory responses, but persistent hyperglycemia leads to renal inflammation, oxidative stress, abnormal extracellular matrix (ECM) accumulation, and increased albuminuria. These processes contribute to structural changes, declining glomerular filtration rate, and potential end-stage renal disease (ESRD) progression. Advanced glycation end products (AGEs) and the renin-angiotensin system (RAS) play key roles in hyperglycemic-induced glomerular hypertrophy. Glomerular hyperfiltration, mediated by the renin-angiotensin-aldosterone system (RAAS), impaired tubuloglomerular feedback, and increased capillary filtration coefficient, further contributes to increased glomerular filtration rate. Inflammation and oxidative stress, triggered by hyperglycemia and AGEs, promote kidney damage. Abnormal ECM accumulation, driven by hyperglycemia and the transforming growth factor-beta pathway, leads to structural changes. Hyperglycemia-induced microalbuminuria and proteinuria reflect early signs of kidney damage. Managing diabetic nephropathy poses challenges, but ongoing research offers potential solutions. Novel therapeutic targets, combination therapies, personalized medicine approaches, regenerative medicine, and gene therapy are being explored. Advancements in diagnostics, including targeted therapies and non-invasive tools, show promise in preventing or mitigating the progression of diabetic nephropathy. Understanding these mechanisms is crucial for early detection, glycemic control, blood pressure management, and targeted therapies to slow disease progression. Collaboration among healthcare stakeholders is essential in finding effective solutions for this complex condition. This review therefore highlights the importance of a comprehensive approach to managing diabetic nephropathy and improving patient outcomes.

Keywords: Diabetic nephropathy, Hyperglycemia, Glomerular hypertrophy, Glomerular filtration rate, Renin-angiotensin, Inflammation, Oxidative stress, Extracellular matrix accumulation

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INTRODUCTION

Diabetic nephropathy, recognized as diabetic kidney disease, is a progressive complication caused by damage to the kidneys' blood vessels and structures, leading to impaired kidney function over time [1,2]. Diabetic nephropathy, or diabetic kidney disease, is a leading cause of chronic kidney disease (CKD) globally, roughly one-third of people with diabetes develop diabetic nephropathy, which accounts for 20 – 40 % of all cases of end-stage renal disease (ESRD) worldwide [3,4]. In Nigeria, the prevalence of diabetic nephropathy is limitedly documented. A study published in 2017 reported a prevalence of 72.6 % among diabetic patients in Nigeria, while another study in Nigeria in 2019 found a prevalence of 42.9 % among type 2 diabetes patients [5,6]. Nigeria, being the most populous country in Africa, faces a significant burden of diabetes and its complications, including diabetic nephropathy. The prevalence of diabetes in Nigeria has been increasing, attributed to factors such as urbanization, lifestyle changes, and a genetic predisposition [1]. Diabetic nephropathy contributes to the overall burden of chronic kidney disease (CKD) in the country. Several studies have highlighted the rising prevalence of diabetic nephropathy in Nigeria and other West African countries [2].

The epidemiology of diabetic nephropathy in Africa is influenced by various factors, including the diversity of healthcare infrastructure, socio-economic conditions, and genetic predispositions. Limited access to healthcare and resources in some regions may impact the ability to diagnose and manage diabetic nephropathy effectively [3]. In Africa, there is a growing awareness of the need for comprehensive diabetes care, including strategies to prevent and manage complications such as diabetic nephropathy. Globally, the prevalence of diabetic nephropathy is expected to rise due to the increasing incidence of diabetes [5]. According to the Global Burden of Disease Study, diabetes-related kidney disease was the 12th leading cause of global deaths in 2019 [5]. Early detection, optimal glycemic control, blood pressure management, and lifestyle interventions are crucial in reducing the burden of diabetic nephropathy on a global scale. However, these rates vary depending on factors such as the population studied, diagnostic criteria, and other considerations [5].

METHODS

This review titled "Novel Approaches and Therapeutic Targets for Diabetic Nephropathy:

Advancements and Promising Strategies" was conducted through a comprehensive literature review of over fifty academic journal publications. The search was performed using Google, Google Scholar, PubMed, Science Alert, and Google Scholar databases. Special keywords and probes related to diabetic nephropathy were utilized to obtain relevant information. The selection criteria included peer-reviewed journal articles focusing on the pathogenesis, treatment, or novel therapeutic targets for diabetic nephropathy, while non-journal publications were excluded. The gathered information was extracted, organized thematically, and synthesized to form a coherent narrative. Data analysis involves comparing, synthesizing, and critically evaluating the findings to identify advancements, trends, and promising strategies in the field. The review discussed the implications of the research, highlighted identified advancements and promising strategies, and proposed future research directions. Multiple revisions were made to ensure clarity, accuracy, and coherence, incorporating feedback from experts, and leading to the preparation of the final version for publication or dissemination.

Pathogenesis of diabetic nephropathy

Hyperglycemia plays a central role in the pathogenesis of diabetic nephropathy, leading to various interconnected mechanisms that contribute to kidney damage and decline in function. It initiates glomerular hypertrophy and increased glomerular filtration rate (GFR) as a compensatory response [7]. However, persistent hyperglycemia causes renal inflammation, oxidative stress, and abnormal accumulation of extracellular matrix (ECM) components, resulting in structural changes in the kidneys and increased albuminuria. Over time, the kidneys further deteriorate, leading to declining glomerular filtration rate, nephron damage, and the potential progression to end-stage renal disease (ESRD) [7,8].

Mechanism of hyperglycemic-induced glomerular hypertrophy

Hyperglycemic-induced glomerular hypertrophy is driven by increased formation of advanced glycation end products (AGEs) and activation of the intrarenal renin-angiotensin system (RAS). AGEs trigger inflammatory and oxidative stress pathways, leading to inflammation, oxidative damage, and fibrosis in the glomeruli [9-11]. Hyperglycemia stimulates the production and release of angiotensin II, causing vasoconstriction, inflammation, and fibrosis in the

glomeruli, contributing to glomerular hypertrophy [9-11].

Mechanism of hyperglycemic-induced glomerular hyperfiltration

Glomerular hyperfiltration, another consequence of hyperglycemia, occurs as a compensatory response to elevated blood glucose levels. It involves the activation of the renin-angiotensin-aldosterone system (RAAS), impaired tubuloglomerular feedback (TGF) mechanism, and increased capillary filtration coefficient (Kf) [7]. These mechanisms contribute to increased glomerular filtration rate by altering arteriolar resistance, blood flow, and glomerular permeability [7,8,12-14].

Mechanism of hyperglycemic-induced inflammation and oxidative stress

Hyperglycemia-induced inflammation and oxidative stress play significant roles in the development and progression of diabetic nephropathy. Hyperglycemia activates pro-inflammatory pathways and increases reactive oxygen species (ROS) production, leading to inflammation, oxidative damage, and fibrosis in the kidneys [9,15-18]. Advanced glycation end products (AGEs) further contribute to inflammation and fibrosis through interactions with their receptors [9-11]. The accumulation of extracellular matrix (ECM) components, such as collagen, is a characteristic feature of diabetic nephropathy [19,20]. Hyperglycemia disrupts the balance between ECM synthesis and degradation, resulting in excessive ECM deposition and impaired ECM turnover [21, 22]. Activation of the transforming growth factor-beta (TGF- β) pathway and protein glycation contribute to ECM accumulation, leading to structural changes and tissue damage in the kidneys [23-25].

Mechanism of hyperglycemic-induced microalbuminuria and proteinuria

Hyperglycemic-induced microalbuminuria and proteinuria are early signs of kidney damage in diabetic nephropathy. Hyperglycemia leads to dysfunction of the glomerular filtration barrier, increased glomerular pressure, and direct injury to podocytes [25-30]. These processes disrupt the selective permeability of the filtration barrier, allowing the passage of albumin and other proteins into the urine [7,8,31-33]. Understanding these mechanisms is crucial for the effective management and development of targeted therapies for diabetic nephropathy. Early detection, glycemic control, blood pressure

management, and targeted therapies are essential for slowing disease progression and preserving kidney function [34,35]. Additionally, interventions targeting pro-inflammatory pathways, oxidative stress, and ECM accumulation may hold promise in preventing or mitigating the progression of diabetic nephropathy [34,35].

Targeted therapies for the management of diabetic nephropathy

In diabetic patients, several pathways are targeted with therapies to manage complications and promote better health outcomes. The Renin-Angiotensin-Aldosterone System (RAAS) pathway, involved in blood pressure regulation, is targeted with medications like Angiotensin-Converting Enzyme (ACE) inhibitors (e.g., Enalapril, Lisinopril, Ramipril) and Angiotensin Receptor Blockers (ARBs) (e.g., Losartan, Valsartan, Irbesartan) are commonly employed. ACE inhibitors block the conversion of angiotensin I to angiotensin II, reducing vasoconstriction, aldosterone release, and sodium retention. This aids in lowering blood pressure and slowing the progression of kidney damage, especially in conditions like diabetic nephropathy and chronic kidney disease. ARBs, on the other hand, block angiotensin II at its receptor sites, leading to vasodilation and decreased aldosterone secretion. ARBs are often preferred for patients intolerant to ACE inhibitors. Both classes of medications play a crucial role in managing kidney damage by modulating the RAAS pathway [36]. Chronic inflammation and immune system dysfunction play a significant role in diabetic complications, and therapies aimed at reducing inflammation, such as non-steroidal anti-inflammatory drugs (NSAIDs) or immune-modulating agents, may be beneficial. The utilization of non-steroidal anti-inflammatory drugs (NSAIDs) in managing diabetic nephropathy is a subject of ongoing research, and specific medications for this purpose may vary. While NSAIDs are generally recognized for their anti-inflammatory properties, their use in diabetic nephropathy is controversial due to concerns about potential adverse effects on renal function, particularly in patients with pre-existing kidney disease. One NSAID that has been studied in this context is ibuprofen, a non-selective NSAID that inhibits cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), enzymes involved in prostaglandin synthesis. However, the use of ibuprofen and other NSAIDs in diabetic nephropathy necessitates careful consideration of potential risks, as these medications may have adverse effects on kidney function. Additionally, the exploration of immune-

modulating agents in the context of diabetic complications and inflammation is ongoing, with specific examples and their usage in diabetic nephropathy subject to variation and active research [37,38]. Increased oxidative stress is characteristic of diabetes, and antioxidant therapies through diet or supplementation may help reduce tissue damage [39]. Glycemic control is achieved through medications like insulin or oral hypoglycemic agents, like biguanides (e.g., metformin), sulfonylureas (e.g., glipizide, glyburide, glimepiride), dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, saxagliptin, linagliptin), sodium-glucose co-transporter-2 (SGLT-2) inhibitors (e.g., canagliflozin, dapagliflozin, empagliflozin), and thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone is essential in preventing complications [40]. These medications act through various mechanisms to regulate blood glucose levels, and their selection is based on factors like diabetes type, individual health, and treatment response. Careful monitoring and adjustment of these medications contribute significantly to effective glycemic control, thereby mitigating the risk of diabetes-related complications. Insulin, available in short-acting forms like Regular insulin, intermediate-acting forms such as NPH insulin, and long-acting forms including insulin glargine, detemir, and degludec, facilitates glucose uptake by cells. Oral hypoglycemic agents encompass diverse classes like biguanides (e.g., metformin), sulfonylureas (e.g., glipizide, glyburide, glimepiride), dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, saxagliptin, linagliptin), sodium-glucose co-transporter-2 (SGLT-2) inhibitors (e.g., canagliflozin, dapagliflozin, empagliflozin), and thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone. These medications act through various mechanisms to regulate blood glucose levels, and their selection is based on factors like diabetes type, individual health, and treatment response. Careful monitoring and adjustment of these medications contribute significantly to effective glycemic control, thereby mitigating the risk of diabetes-related complications [40].

For diagnosing abnormalities in diabetic patients, various approaches are used. Regular blood tests such as fasting blood glucose, oral glucose tolerance tests, Hemoglobin A1c, and HbA1c measurements, provide valuable information about glycemic control. Urine tests, including Albumin-to-Creatinine Ratio, and ACR, detect early signs of kidney damage and monitor diabetic nephropathy. Kidney function tests like serum creatinine, Blood Urea Nitrogen, BUN, and estimated Glomerular Filtration Rate, eGFR help assess kidney function and identify renal

abnormalities. Imaging procedures like ultrasound, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) are used to determine kidney structure and function, detecting anatomical abnormalities or signs of damage [41]. To provide a definitive diagnosis and assess the extent of kidney damage in suspected nephropathy, a kidney biopsy may be performed.

Advancements in the management and diagnosis of diabetic nephropathy

Advancements in diagnosing and managing diabetic nephropathy have significantly improved patient outcomes. Several therapies targeting the Renin-Angiotensin-Aldosterone System (RAAS) pathway, such as ACE inhibitors and ARBs, have shown effectiveness in slowing the progression of nephropathy by controlling blood pressure and reducing proteinuria [42]. Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors, developed for glycemic control, have also demonstrated renal-protective effects and cardiovascular benefits [43].

Research is focused on developing novel therapies for targeting specific pathways involved in diabetic nephropathy, including inflammation, oxidative stress, fibrosis, and apoptosis. Personalized treatment approaches based on genetic profiling and biomarker analysis help identify individuals at higher risk and predict their response to specific treatments, enabling tailored therapy and optimizing outcomes.

In terms of diagnosis, early detection biomarkers have been a significant advancement. Urinary proteins, inflammatory markers, and fibrosis-related markers are used to detect signs of nephropathy before clinical symptoms appear, allowing for timely intervention and management. Advanced imaging techniques, such as MRI, provide detailed information about kidney structure and function, aiding in assessing the extent of renal damage and guiding treatment decisions [44,45].

Artificial intelligence (AI) and machine learning algorithms have shown promise in analyzing large datasets to identify patterns related to diabetic nephropathy [46,47]. These technologies assist in risk prediction, early diagnosis, and assessing treatment response, potentially improving patient outcomes. Non-invasive diagnostic tools, such as point-of-care tests and wearable devices, are being developed to monitor kidney function in real-time, offering convenience, reducing patient burden, and facilitating early intervention [48].

The advancements in managing and diagnosing diabetic nephropathy aim to achieve early detection, individualized treatment and improved patient well-being. Ongoing research and clinical trials will likely bring more innovative approaches to the forefront, further enhancing patient care and reducing the burden of diabetic nephropathy.

Plant-derived natural product for the treatment of diabetic nephropathy

The use of natural products derived from medicinal plants for the treatment of diabetic nephropathy has gained attention. Several studies have investigated their potential benefits in managing various aspects of diabetic nephropathy, including glycemic control, oxidative stress, inflammation, and renal damage. Some popular natural products include curcumin, resveratrol, *Astragalus membranaceus*, silymarin, berberine, and cinnamon [49,50]. Curcumin, found in turmeric, exhibits anti-inflammatory and antioxidant properties, while resveratrol, found in grapes and red wine, has shown potential renal protective effects [49-52]. *Astragalus membranaceus* (Fabaceae) a traditional Chinese herb, has demonstrated antioxidant and anti-inflammatory effects [53]. Silymarin, derived from milk thistle, exhibits antioxidant, anti-inflammatory, and antifibrotic activities [54]. Berberine, found in various medicinal plants, has been investigated for its antidiabetic and renoprotective effects [55]. Cinnamon, a commonly used spice, has shown benefits in glycemic control and may indirectly contribute to renal protection [46]. However, further research, including well-designed clinical trials, is needed to establish their efficacy, optimal dosages, and potential interactions with conventional treatments. Consultation with healthcare professionals is crucial before incorporating natural products into the treatment plan for diabetic nephropathy.

Prospect of natural products as a solution for diabetic nephropathy

The prospect of finding a potent cure for diabetic nephropathy using natural products is ongoing research. Natural products derived from medicinal plants have shown promising effect in managing certain aspects of diabetic nephropathy, such as inflammation, oxidative stress, and renal damage. These products contain bioactive compounds with diverse properties that influence disease progression.

Research studies have demonstrated the potential of natural products in improving kidney

function, reducing proteinuria, and delaying the progression of diabetic nephropathy. However, more evidence is needed to establish their efficacy and safety.

Diabetic nephropathy is a complex condition involving multiple pathways and factors, making it challenging to develop a single cure. A holistic approach that includes lifestyle modifications, pharmacological interventions, and personalized treatments is probably more effective in managing and preventing disease progression.

While natural products offer hope, rigorous scientific investigation, including well-designed clinical trials is necessary to understand their mechanisms of action and optimize their use. Collaboration among researchers, healthcare professionals, and pharmaceutical companies is essential in advancing natural product-based therapies for diabetic nephropathy.

Overall, investigating natural products as a potential cure for diabetic nephropathy is promising but requires realistic expectations. Comprehensive research, evidence-based approaches, and individualized treatment strategies are crucial to effectively manage and ultimately find a cure for this complex condition.

Challenges in managing diabetic nephropathy

The management of diabetic nephropathy with current therapeutic agents faces challenges including limited efficacy, potential adverse effects, treatment resistance, and issues related to cost and accessibility. However, there is hope for improvement in patient outcomes. Ongoing research is identifying novel therapeutic targets, such as anti-inflammatory agents and antioxidants, which offer the potential for more effective treatments. Combination therapies that combine different agents with complementary mechanisms of action are being investigated to enhance treatment efficacy and overcome resistance. Personalized medicine approaches hold promise in tailoring treatments based on individual characteristics, and optimizing treatment outcomes. Additionally, regenerative medicine and gene therapy breakthroughs offer potential breakthroughs in repairing damaged kidney tissue. Patient education and self-management play a crucial role in empowering individuals to adopt lifestyle modifications and adhere to treatment regimens, leading to better control of blood glucose levels and blood pressure, thus slowing the progression of diabetic nephropathy.

CONCLUDING REMARKS

While challenges exist, ongoing research, combination therapies, personalized medicine, regenerative medicine, and patient education provide hope for improved management of diabetic nephropathy. With further advancements and a multidisciplinary approach, there is potential for better treatment options and outcomes for individuals with this condition.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Abraham Ehinomhen Ubhenin: Participated in the literature search, including keyword selection and database selection. He approved the final version for publication or dissemination. Joshua Onyeka Ikebuiro and Ramatu Iya Idris participated in the literature search. Fatima assisted in the data extraction and organization. Osayemwenre Erharuyi contributed to the synthesis and analysis of the collected data.

The authors declare that all the information presented in this review is based on a thorough literature review and solely for academic purposes. The review should not replace professional medical advice or treatment recommendations. The authors acknowledge

that they are responsible and accountable for the contents of the review.

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