e-ISSN: 2320-4230, p-ISSN: 2961-6085

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 12, Issue 06; 2024, 92-97

Diabetic Nephropathy: Pharmacological and Emerging Approches

Himanshu Peshwani[1], Surbhi Jangir[1*], Divya Singh[2], Rakesh Sharma[3]

[1]Research Scholar, Department of Pharmacology, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

[1*]Associate Professor, Department of Pharmacology, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

[2] Professor, Department of Pharmacology, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

[3]Associate Professor, Department of Pharmacology, Jaipur College of Pharmacy, Jaipur, Rajasthan, India.

Received: 16-10-2024 / Revised: 16-11-2024 / Accepted: 11-12-2024

Corresponding author: Surbhi Jangir

Conflict of interest: No conflict of interest.

Abstract:

Diabetic nephropathy is diagnosed by persistent albuminuria on two or more occasions, separated at least by three months on early morning urine samples. Persistent albuminuria is greater than 300 mg over 24 hours or greater than 200 micrograms per minute. Moderately increased albuminuria is when the urine albumin excretion rate is between 30 to 300 mg over 24 hours and is a marker of early DN. It is critical to exclude a urinary tract infection as the cause of albuminuria by a urinalysis. Proteinuria is the hallmark of diabetic nephropathy. The absence of retinopathy makes diabetic nephropathy less likely in T1DM. The scenario is more difficult in T2DM than with T1DM. The exact time of the onset of T2DM is unclear in most patients. History and physical exam play a crucial role in diagnosing diabetic nephropathy in T2DM. Diabetic nephropathy (DN) is a significant microvascular complication of diabetes mellitus, affecting 30-40% of diabetic patients and serving as the leading cause of end-stage renal disease (ESRD) worldwide. DN is characterized by progressive kidney damage due to chronic hyperglycemia, oxidative stress, and hemodynamic abnormalities, resulting in glomerular hypertrophy, mesangial expansion, podocyte loss, and tubulointerstitial fibrosis. The pathogenesis of DN involves the activation of multiple pathways, including the polyol pathway, advanced glycation end-products (AGEs) formation, protein kinase C (PKC) activation, and renin- angiotensin-aldosterone system (RAAS) overactivity. These mechanisms collectively promote inflammation, oxidative stress, and fibrosis, leading to impaired kidney function and proteinuria. While conventional treatments such as RAAS blockade and glycemic control remain essential, emerging therapies offer new hope for better management. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists have shown promising reno-protective effects. Novel therapies, including endothelin receptor antagonists, Bardoxolone methyl, gene therapy, and stem cell-based interventions, target key molecular pathways to halt or reverse disease progression. This review highlights the pathophysiology, current pharmacological treatments, and emerging approaches, emphasizing the importance of early diagnosis and novel interventions in improving renal outcomes for diabetic patients.

Key words: Diabetic nephropathy, diabetes mellitus, RAAS, SGLT-2 inhibitors, etc..

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia due to defects in insulin secretion, action, or both. It is a major contributor to global morbidity, leading to significant microvascular and macrovascular complications, alongside other comorbidities. Microvascular complications include diabetic retinopathy, nephropathy, and neuropathy. Diabetic retinopathy results from prolonged hyperglycemia, damaging the retinal blood vessels, ultimately impairing vision or leading to blindness if untreated. Diabetic nephropathy, characterized by progressive kidney damage, can advance to chronic kidney disease (CKD) and end-stage renal disease (ESRD), requiring dialysis or transplantation [1-3]. Neuropathy, another common complication, leads to nerve damage, causing pain, numbness, and loss of autonomic function, particularly in the extremities. Diabetic nephropathy (DN) is one of the most significant and devastating microvascular complications of diabetes mellitus, affecting approximately 30-40% of diabetic patients worldwide [4,5]. It is characterized by progressive renal damage due to chronic hyperglycemia and other metabolic and hemodynamic abnormalities associated with diabetes. Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) globally, contributing to increased mortality and morbidity in diabetic patients. Its pathogenesis involves a complex interplay of metabolic, genetic, and hemodynamic factors that initiate kidney injury, culminating in structural changes such as glomerular hypertrophy, mesangial expansion, podocyte injury, and tubulointerstitial fibrosis. Over the last few decades, the prevalence of diabetic nephropathy has risen significantly, paralleling the growing burden of diabetes mellitus worldwide. With the global diabetes population expected to reach 700 million by 2045, the incidence of diabetic nephropathy is predicted to escalate proportionally, particularly in regions with high diabetes prevalence. Early diagnosis and intervention are critical to slowing the progression of diabetic nephropathy and preventing ESRD. Understanding the etiology, pathophysiology, and risk factors for this condition is essential for developing targeted therapies to improve renal outcomes and quality of life for diabetic patients [6,7].

Pathophysiology of Diabetic Nephropathy

Diabetic nephropathy (DN) is a chronic microvascular complication of diabetes that gradually leads to kidney damage, primarily driven by prolonged hyperglycemia and metabolic disturbances. The pathophysiological process involves both hemodynamic and metabolic factors, which together trigger structural and functional changes in the kidneys. Persistent hyperglycemia results in the activation of metabolic pathways, including the polyol pathway, hexosamine pathway, and advanced glycation end-products (AGEs) formation. AGEs accumulate in the kidney tissues and induce oxidative stress, inflammation, and extracellular matrix (ECM) deposition, leading to glomerular damage [8,9]. Additionally, the activation of protein kinase C (PKC) plays a significant role by altering renal hemodynamics and promoting inflammation and fibrosis. Hemodynamic changes, characterized by hyperfiltration, occur early in DN. Hyperglycemia induces increased renal blood flow and intraglomerular hypertension, which cause mechanical stress on glomerular capillaries. This stress leads to podocyte injury and the subsequent thickening of the glomerular

basement membrane (GBM). Podocyte loss and foot process effacement impair the filtration barrier, allowing proteinuria, a hallmark of DN progression. The renin-angiotensin-aldosterone system (RAAS) is also activated in diabetic nephropathy. Angiotensin II, a key player in RAAS, causes vasoconstriction, promotes sodium and water retention, and stimulates the production of pro-inflammatory and profibrotic mediators. This accelerates glomerulosclerosis and tubulointerstitial fibrosis. Chronic inflammation is another major contributor to DN pathogenesis. Hyperglycemia-induced oxidative stress activates nuclear factor-kappa B (NF-κB), which promotes the expression of inflammatory cytokines like TNF-α, IL-6, and chemokines. These mediators further exacerbate kidney injury by recruiting inflammatory cells and promoting fibrosis. Structural changes in diabetic nephropathy include mesangial expansion, GBM thickening, and nodular glomerulosclerosis (Kimmelstiel-Wilson nodules). Tubulointerstitial fibrosis, a late-stage characteristic, results from the excessive accumulation of ECM proteins and loss of renal tubular cells [10,11].

Table 1: Pharmacological treatment for Diabetic Nephropathy:

S. No.	Category/Class	Name of Drugs (Examples)	Mechanism of Action
1	ACE Inhibitors	Enalapril, Ramipril, Lisinopril	Inhibit angiotensin-converting enzyme, reducing angiotensin II levels, thereby decreasing intraglomerular pressure and proteinuria.
2	Angiotensin II Receptor Blockers (ARBs)	Losartan,Valsartan, Telmisartan	Block angiotensin II receptors, reducing vasoconstriction, proteinuria, and glomerular damage.
3	SGLT-2 Inhibitors	Dapagliflozin, Empagliflozin, Canagliflozin	Reduce glucose reabsorption in the kidney, leading to glycosuria, decreased hyperfiltration, and renal protection.
4	Mineralocorticoid Receptor Antagonists (MRAs)	Spironolactone, Finerenone	Block aldosterone receptors, reducing inflammation, fibrosis, and albuminuria.
5	Endothelin Receptor Antagonists	Atrasentan, Bosentan	Block endothelin-1 receptors, reducing vasoconstriction, inflammation, and proteinuria.
6	Calcium Channel Blockers	Amlodipine, Nifedipine	Inhibit calcium influx into vascular smooth muscle, lowering blood pressure and improving renal perfusion.
7	Beta Blockers	Metoprolol, Carvedilol	Reduce blood pressure by blocking beta-adrenergic receptors, decreasing renal hyperfiltration.
8	Antioxidants	Vitamin E, Bardoxolone	Reduceoxidative stress and inflammation, protecting renal tissues.
9	Renin Inhibitors	Aliskiren	Inhibit renin, reducing angiotensin II production and protecting kidney function.
10	Non-Steroidal Anti-Inflammatory Agents	Pentoxifylline	Reduceinflammation and cytokine production, mitigating renal injury.

	(Investigational)		
11	Anti-VEGF Agents	Bevacizumab	Inhibit vascular endothelial growth factor, reducing glomerular injury and proteinuria.
12	Diuretics	Furosemide, Torsemide	Promote diuresis, reducing fluid overload and hypertension.
13	GLP-1 Receptor Agonists	Liraglutide, Semaglutide	Improve glucose control, reduce inflammation, and provide renal protection.

Emerging Approaches for the Treatment of Diabetic Nephropathy

Diabetic nephropathy (DN) is a major complication of diabetes and a leading cause of end-stage renal disease. While conventional treatments like renin-angiotensin-aldosterone system (RAAS) inhibitors and glycemic control remain mainstays, emerging therapeutic approaches are addressing novel molecular pathways and mechanisms involved in DN progression [12].

Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors have emerged as key players beyond their glucose-lowering effects. Agents like *dapagliflozin* and *empagliflozin* reduce glomerular hyperfiltration by lowering intraglomerular pressure and improving renal outcomes. These drugs also provide cardiovascular protection, making them highly beneficial for patients with diabetes and kidney disease [13].

Nonsteroidal Mineralocorticoid Receptor Antagonists (MRAs) such as *finerenone* have shown promise in reducing inflammation and fibrosis with a reduced risk of hyperkalemia compared to traditional MRAs. Finerenone has been shown to slow DN progression by modulating mineralocorticoid receptor overactivation, which plays a role in renal injury [14].

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) like *liraglutide* and *semaglutide* are another emerging class of drugs that not only enhance glucose control but also exhibit renal-protective effects. These agents reduce albuminuria and improve overall cardiovascular outcomes, which are closely linked to diabetic kidney disease [15].

Endothelin Receptor Antagonists (ERAs), such as *atrasentan*, target endothelin-1, a potent vasoconstrictor involved in inflammation and glomerular damage. By blocking this pathway, ERAs effectively reduce proteinuria and slow DN progression when combined with standard RAAS inhibitors [16].

Bardoxolone Methyl, an Nrf2 activator, offers a novel approach by reducing oxidative stress and inflammation, both of which are critical contributors to DN. It enhances renal function and reduces kidney damage by activating pathways involved in cellular protection [17].

Gene and RNA-Based Therapies, including small interfering RNA (siRNA) and antisense oligonucleotides, target specific molecules like *TGF-β* and *VEGF* that contribute to fibrosis and angiogenesis. These therapies aim to prevent structural damage to the kidney and halt disease progression [18].

Stem Cell Therapy is also being explored for its regenerative potential. Mesenchymal stem cells (MSCs) have shown promise in reducing renal inflammation, promoting tissue repair, and improving kidney function through their immunomodulatory effects [19].

SUMMARY

Diabetic nephropathy remains a major global health challenge due to its significant contribution to morbidity, mortality, and healthcare burden. Its pathogenesis is multifactorial, involving complex interactions between metabolic,

hemodynamic, inflammatory, and oxidative stress pathways. Conventional therapies, including renin-angiotensin-aldosterone system inhibitors and strict glycemic control, are effective in delaying disease progression but are often insufficient to prevent end-stage renal disease. The emergence of novel therapies has revolutionized the management of DN, addressing specific molecular targets and offering additional renal protection. SGLT-2 inhibitors, GLP-1 receptor agonists, and nonsteroidal MRAs have demonstrated significant benefits in reducing hyperfiltration, proteinuria, and inflammation. Furthermore, innovative approaches such as endothelin receptor antagonists, Nrf2 activators like Bardoxolone methyl, and gene-based therapies are promising tools to counteract oxidative stress, fibrosis, and kidney injury. Stem cell-based therapies, though still under investigation, hold potential for kidney regeneration and repair. The integration of these emerging therapies with existing treatment strategies presents an opportunity to improve renal outcomes and quality of life for diabetic patients. Future research must focus on understanding the long-term safety and efficacy of these therapies, as well as exploring combination approaches to maximize clinical benefits. Early diagnosis and a personalized treatment strategy will be essential to combat the growing burden of diabetic nephropathy.

References

1. Zakir, M., Ahuja, N., Surksha, M. A., Sachdev, R., Kalariya, Y., Nasir, M., ... & Mohamad, T. (2023). Cardiovascular complications of diabetes: from microvascular to macrovascular pathways. Cureus, 15(9).
2. Lu, Y., Wang, W., Liu, J., Xie, M., Liu, Q., & Li, S. (2023). Vascular complications of diabetes: A narrative review. Medicine, 102(40), e35285.
3. Yang, T., Qi, F., Guo, F., Shao, M., Song, Y., Ren, G., ... & Zhao, Y. (2024). An update on chronic complications of diabetes mellitus: from molecular mechanisms to therapeutic strategies with a focus on metabolic memory. Molecular Medicine, 30(1), 71.
4. Galiero, R., Caturano, A., Vetrano, E., Beccia, D., Brin, C., Alfano, M., ... & Sasso, F. C. (2023). Peripheral neuropathy in diabetes mellitus: pathogenetic mechanisms and diagnostic options. International Journal of Molecular Sciences, 24(4), 3554.
5. Lu, Y., Wang, W., Liu, J., Xie, M., Liu, Q., & Li, S. (2023). Vascular complications of diabetes: A narrative review. Medicine, 102(40), e35285.
6. Samsu, N. (2021). Diabetic nephropathy: challenges in pathogenesis, diagnosis, and treatment. BioMed research international, 2021(1), 1497449.
7. Lim, A. K. (2014). Diabetic nephropathy–complications and treatment. International journal of nephrology and renovascular disease, 361-381.
8. Wu, T., Ding, L., Andoh, V., Zhang, J., & Chen, L. (2023). The mechanism of hyperglycemia-induced renal cell injury in diabetic nephropathy disease: an update. Life, 13(2), 539.
9. Lin, Y. C., Chang, Y. H., Yang, S. Y., Wu, K. D., & Chu, T. S. (2018). Update of pathophysiology and management of diabetic kidney disease. Journal of the formosan Medical Association, 117(8), 662-675.
10. Pan, D., Xu, L., & Guo, M. (2022). The role of protein kinase C in diabetic microvascular complications. Frontiers in Endocrinology, 13, 973058.
11. Samsu, N. (2021). Diabetic nephropathy: challenges in pathogenesis, diagnosis, and treatment. BioMed research international, 2021(1), 1497449.

12. Elendu, C., Okah, M. J., Fiemotongha, K. D., Adeyemo, B. I., Bassey, B. N., Omeludike,
13. E. K., & Obidigbo, B. (2023). Comprehensive advancements in the prevention and treatment of diabetic nephropathy: A narrative review. Medicine, 102(40), e35397.
14. Khakhar, Z., Manji, S., Patel, R. K., & Ali, S. K. (2024). Sodium-Glucose Transport Protein 2 (SGLT2) inhibitors and the risk of pancreatitis: A case report. Cureus, 16(6), e62957.
15. Shah, M., Awad, A. S., & Abdel-Rahman, E. M. (2023). Nonsteroidal Mineralocorticoid Receptor Antagonist (Finerenone) in Cardiorenal Disease. Journal of Clinical Medicine, 12(19), 6285.
16. Michos, E. D., Bakris, G. L., Rodbard, H. W., & Tuttle, K. R. (2023). Glucagon-like peptide-1 receptor agonists in diabetic kidney disease: A review of their kidney and heart protection. American Journal of Preventive Cardiology, 14, 100502.
17. Martínez-Díaz, I., Martos, N., Llorens-Cebrià, C., Álvarez, F. J., Bedard, P. W., Vergara, A., & Soler, M. J. (2023). Endothelin receptor antagonists in kidney disease. International Journal of Molecular Sciences, 24(4), 3427.
18. Reisman, S. A., Chertow, G. M., Hebbar, S., Vaziri, N. D., Ward, K. W., & Meyer, C. J. (2012). Bardoxolone methyl decreases megalin and activates nrf2 in the kidney. Journal of the American Society of Nephrology, 23(10), 1663-1673.
19. Zhang, Y., Zhang, Y., Song, J., Cheng, X., Zhou, C., Huang, S., ... & Yang, L. (2024). Targeting the “tumor microenvironment”: RNA-binding proteins in the spotlight in colorectal cancer therapy. International Immunopharmacology, 131, 111876.
20. Rota, C., Morigi, M., & Imberti, B. (2019). Stem cell therapies in kidney diseases: progress and challenges. International journa*l of molecular sciences*, *20*(11), 2790.