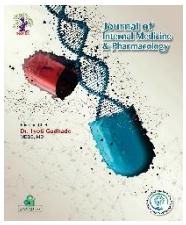
SENNOS

Journal of Internal Medicine & Pharmacology

Journal homepage: https://sennosbiotech.com/JIMP/1



Review Article

Revisiting and Expanding the Understanding of Molecular Mechanisms Underpinning Diabetic Nephropathy: An Updated and Comprehensive Review of Recent Advance

Ganesh R. Pawar[1], Anjali Aldurge[1], Bhushan G. Gudalwar[2], Jagadish V. Manwar[3*]

[1]Department of Pharmacology, Kamalprakash pharmacy College and Research Centre Kherda, Karanja (Lad) Dist. Washim, Maharashtra India- 444107

ARTICLEINFO

ABSTRACT

Diabetic nephropathy (DN) stands as a critical complication of diabetes mellitus, often culminating in end-stage renal disease (ESRD). The intricate molecular mechanisms underlying DN progression necessitate comprehensive exploration for effective therapeutic interventions. This review outlines key molecular insights into DN pathogenesis, including glomerular hypertrophy and hyperfiltration driven by hyperglycaemia-induced renal vasodilation. Renal fibrosis, characterized by ECM protein accumulation, is mediated by TGF-β signalling. Chronic low-grade inflammation, oxidative stress, and activation of the renin-angiotensin-aldosterone system (RAAS) contribute significantly to renal injury. Epigenetic modifications, such as DNA methylation and non-coding RNA regulation, further influence gene expression patterns in response to hyperglycaemia. Dysregulated signalling pathways including PKC, NF-κB, and mTOR play pivotal roles in cellular responses to hyperglycaemia and oxidative stress. Understanding these molecular mechanisms offers potential therapeutic targets, including agents targeting inflammation, oxidative stress, and fibrosis, alongside strategies for glycaemic and blood pressure control. Emerging therapies targeting epigenetic regulators and cellular signalling pathways hold promise for preventing and treating diabetic nephropathy.

Keywords: Diabetic nephropathy, molecular mechanisms, glomerular hypertrophy, hyperfiltration, renal fibrosis, inflammation, oxidative stress

⁎⁎ Corresponding author

Jagadish V. Manwar*

Kamalprakash Pharmacy college and Research Centre, Kherda, Karanja (Lad) Dist. Washim, Maharashtra, India-444107

Email id: jvmanwar@gmail.com

Received date: 01-Jul-2024 Revised date: 25-Jul-2024 Accepted date:15-Aug-2024

DOI: https://doi.org/10.61920/jimp.v1i02.22

1.Introduction

Diabetic nephropathy (DN) is a common and severe consequence of diabetes mellitus that causes gradual harm to the kidneys and eventually leads to kidney failure [1]. The study of the molecular processes of this condition is crucial for optimal management and therapeutic approaches, since it is a significant contributor to illness and death in people with diabetes [2]. In recent decades, there has been substantial advancement in understanding the molecular mechanisms that cause DN. Hyperglycemia, which is the defining characteristic of diabetes, has a pivotal role in triggering a series of molecular processes that ultimately lead to kidney damage [3]. Prolonged exposure to high glucose levels triggers the activation of many signalling pathways, such as those related to advanced glycation end-products (AGEs), protein kinase C (PKC), and the polyol pathway, among others [4]. These pathways have a role in the occurrence of oxidative stress, inflammation, and cellular damage in the kidney. Aside from hyperglycaemia, the dysregulation of the renin-angiotensin-aldosterone system (RAAS) is also a significant molecular aberration involved in the development of DN [5]. Additionally, recent findings indicate that epigenetic alterations, including as DNA methylation, histone acetylation, and microRNA dysregulation, have a role in the formation and advancement of DN. These epigenetic changes can modulate gene expression patterns, alter cellular function, and contribute to the pathophysiological alterations observed in diabetic kidneys [6]. Understanding the molecular mechanisms of DN not only provides insights into its pathogenesis but also identifies potential targets for therapeutic intervention. Several pharmacological agents targeting specific molecular pathways, such as RAAS inhibitors, antioxidant agents, and antiinflammatory drugs, have shown promise in preclinical and clinical studies for the treatment of DN [7]. In this review, we aim to provide a comprehensive overview of the molecular insights into the pathogenesis of DN, focusing on the key signalling pathways, molecular abnormalities, and potential therapeutic targets implicated in this condition. By elucidating the intricate molecular mechanisms underlying DN, we can pave the way for the development of more effective strategies for its prevention and treatment, ultimately improving outcomes for individuals affected by this devastating complication of diabetes mellitus.

2. Pathophysiology of diabetic nephropathy

Various variables contribute to the pathophysiological processes involved in the development of DN. Hyperglycaemia is the initial cause of glomerular hyperfiltration, as well as hypertrophy of the glomerular and tubular epithelium, and the presence of microalbuminuria [8]. As a result, the basement membrane of the glomerulus thickens, there is a buildup of the mesangial matrix, proteinuria becomes evident, and eventually glomerulosclerosis and end-stage renal disease.

3. Pathological changes

Kimmelstiel and Wilson defined nodular glomerulosclerosis as the defining feature of diabetic neuropathic pain. All renal compartments are harmed by diabetes mellitus, including glomerulosclerosis, vascular disorders, and tubulointerstitial alterations, including tubular atrophy and interstitial fibrosis. The initial morphological alteration of DN is the extension of the mesangial region, which is brought on by an increase in extracellular matrix and mesangial cell hypertrophy. P27Kip1 causes mesangial cell

growth to stop in the G1-phase of the cell cycle as a result of hyperglycaemia [10].

Additionally, P 27Kip 1, the mediator of G1-phase arrest, is enhanced by ANG-II. Increased glucose-mediated mesangial damage occurs when ANG-II is blocked. After type 1 diabetes develops and worsens over the course of a year, glomerular basement membrane (GBM) thickening may begin as early as the next year. DN causes several metabolic changes in the GBM. Collagen type IV deposition is increasing, whereas heparin sulphate expression and sulfation level are decreasing. GBM includes α3, α4, and α5 chains of type IV collagen, while the mesangial matrix mostly expresses α1 and α2. Mesangial cells in DN have an upregulation of α1 (IV) and α2 (IV) chains, whereas the GBM exhibits a rise in α3 (IV) and α4 (IV) expression. Collagen types I and III are deposited in the mesangial region later rather than earlier in the glomerulosclerosis process.

Metabolic pathways

Mesangial cell extracellular formation is significantly influenced by glucose transport activity. Glucose, which enters kidney cells through the glucose transporter-1 (GLUT-1), triggers the formation of mesangial cell matrix, mesangial cell death, structural alterations, and mesangial growth [11]. Even in cases where glucose levels are normal, overexpression of GLUT-1 will cause comparable alterations in renal cells. Mesangial cells express both brain-type (GLUT-1) and insulin-sensitive

extracellular glucose transporters (GLUT4), which facilitate the easy entry of excess glucose into the cell without the need for insulin. The activation of VEGF, TGF-β, interleukin-1 (IL-1), IL-6, IL-18, and tumour necrosis factor alpha (TNF-α) is caused by non-enzymatic glycosylation that results in advanced glycosylation end products (AGE), activation of protein kinase C (PKC), and acceleration of the polyol pathway along with hemodynamic changes.

Oxidative stress

In diabetes, hyperglycaemia causes an increase in oxidative stress and an excess of reactive oxygen species (ROS). These ROS cause renal vasoconstriction, protein oxidation, peroxidation of cell membrane lipids, and damage to deoxyribonucleic acid (DNA)(12). The increased production of ROS also stimulates other metabolic processes, namely PKC pathways, AGE formation, TGF-β, and ANG-II.

Histopathology shows that the nodular lesion and extended mesangial matrix of a diabetic kidney specimen have a buildup of lip oxidation and glycoxidation products.

Polyol pathways

The polyol pathway involves aldose reductase converting glucose to sorbitol and sorbitol dehydrogenase converting fructose. More glucose enters the polyol route as a result of higher glucose absorption into the cell [13]. The reduction of glucose to sorbitol necessitates the depletion of NADPH in cells, which is a crucial substrate for glutathione regeneration and exacerbates intracellular oxidative stress. An intermediate called three-deoxyglucone is a precursor to AGEs.

Protein kinase C pathways

The processes of diabetic nephropathy (DN) have also been linked to an elevation in TGF-β levels and an augmented influx of glucose via the hexosamine pathway. This pathway transforms fructose-6-phosphate, which is generated during glycolysis, into glucosamine-6-phosphate [14]. The transcription of TGF-β is enhanced by the addition of N-acetylglucosamine to a transcription factor, such as Sp1, by glycosylation. Moreover, an

increase in flow via the hexosamine pathway enhances the generation of upstream activating factors (USFs), which activate the promoter of TGF-β1 [15].

Advanced glycation end products Long-term hyperglycaemia is caused by an excess of glucose combining with tissue proteins or free amino acids. The development of DN is caused by this glycosylation. This process first produces early glycosylation products that are reversible, and then it produces irreversible AGE. Because of the rise in AGEs, the glomerular epithelial cells collect matrix proteins, which also create a fault in the tight connection between the cells and a reduction in collagenase activity.

Cytokines and growth factors

Numerous cytokines, chemokines, growth factors, and vasoactive substances have been linked to DN structural alterations. The precise function of insulin-like growth factors (IGFs), one of the most extensively and historically researched growth factors in DN, is still unknown [16]. Several animal models of diabetes show an early and transient rise in renal IGF-I protein after the beginning of the disease, which is brought on by hyperglycaemia. In several animals, interference with the IGF-I axis partially attenuates DN.

Transforming growth factor-b references changes

The profibrotic growth factor transforming growth factor-β is responsible for renal hypertrophy and mesangial matrix enlargement in DN. Measurements of TGFB levels in the glomeruli of streptozotocindiabetic rats have shown elevated levels. It was found that in type 2 db/db mice, neutralising TGF-β antibodies inhibited the development of renal failure, mesangial matrix growth, and diabetic renal atrophy. Patients with diabetes have fibrogenic effects on their kidneys due to the heat shock proteins and connective tissue growth factor, which are encoded by TGF-

β. Nonetheless, the reduced expression of renal bone morphogenic protein 7 offsets the profibrogenic effects of TGF-β1. Mechanical strain stimulates TGF-β1 gene and protein expression [17]. ***Synthesis of endothelial***

Overexpression of VEGF, TGF-β1, ANGII, and hyperglycaemia all stimulate nitric oxide, which results in vasodilatation and hyperfiltration. Increased collagen chain formation due to overexpression of VEGF contributes to the thickening of GBM DN. Some research disputes the idea that elevated VEGF levels cause DN. Conversely, the data suggest that low amounts are detrimental. VEGF messenger ribonucleic acid (RNA) concentrations were found to be lower in the glomeruli of individuals with diabetic nephropathy (DN), and this was shown to relate to a decrease in podocyte count and the advancement of renal disease [18].

4. Intracellular signal pathways

Nuclear factor-kB

The suppression of nuclear factor-κB results in apoptosis, which plays a significant role in cell survival. Diabetes patients with nephropathy had higher monocyte NF-κB activity compared to diabetics without nephropathy. Stretch, AGEs, AGN II, and high glucose all potently activate NF-κB, mostly via the production of ROS and PKC activation, according to in vitro research. These findings shed light on the cellular pathways that activate NF-B in the diabetic kidney [19].

Peroxisome proliferator-activated receptor-g

Nuclear transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ) is the pharmacologic target of thiazolidinediones (TZDs),

an insulin sensitizer class of drugs. According to preliminary research, TZDs may help type 2 diabetes individuals who have microalbuminuria excrete less albumin in their urine. Furthermore, TZDs in rats with streptozotocin-induced diabetes have antiproteinuric actions apart from their insulin-sensitising effect [20].

Hypoxia and diabetic nephropathy Anaemia speeds up the pathophysiological process in diabetic nephropathy patients. Erythropoietin therapy administered early on reduces the course of renal disease.

Anaemia-induced renal hypoxia exacerbates interstitial fibrosis by stimulating factors such as VEGF and TGF-β. 84 A significant part of this is also played by ANG-II and hypoxia-inducing factor-1 (HIF-1) [21].

Inflammation and diabetic nephropathy Hyperglycaemia causes mesangial cells to express more MCP-1, RANTES, and MCP1 in the tubule. Elevated hyperglycaemia causes ROS production and boosts the formation of AGEs. Proteinuria is induced by local ANG-II formation that is stimulated by reactive oxygen species; however, tubular ANG-II synthesis is further enhanced by proteinuria. In addition to increasing the development of AGEs, angiotensin-II plays a crucial role in the activation of many cytokines and growth factors [22].

5. Renin-Angiotensin-Aldosterone System (RAAS)

The renin-angiotensin-aldosterone system (RAAS) plays a central role in the pathogenesis and progression of diabetic nephropathy. This system is a complex hormonal cascade involved in regulating blood pressure, fluid balance, and electrolyte levels [23]. In the context of diabetic nephropathy, the RAAS becomes dysregulated, contributing to kidney damage through various mechanisms:

Vasoconstriction

Angiotensin II, a key component of the RAAS, causes vasoconstriction of both afferent and efferent arterioles in the kidneys. This leads to increased intraglomerular pressure, resulting in glomerular hypertension, hyperfiltration, and ultimately, glomerular damage.

Increased intraglomerular pressure Hyperglycemia and other factors associated with diabetes mellitus lead to increased production of angiotensin II within the kidneys. Angiotensin II causes preferential constriction of the efferent arterioles, which increases the intraglomerular pressure. This hyperfiltration contributes to glomerular injury over time.

Proteinuria

Angiotensin II promotes the development and progression of proteinuria (excessive protein in the urine) by inducing glomerular injury and increasing the permeability of the glomerular filtration barrier. Proteinuria is both a marker and a mediator of kidney damage in diabetic nephropathy.

Inflammation and fibrosis Angiotensin II stimulates the release of proinflammatory cytokines and growth factors within the kidneys, leading to inflammation, oxidative stress, and fibrosis.

Podocyte injury

Podocytes are specialized cells that play a crucial role in maintaining the integrity of the glomerular filtration barrier. Angiotensin II contributes to podocyte injury and loss, further impairing glomerular function and promoting the development of proteinuria and glomerulosclerosis [28]. ***Renal hypertrophy and remodelling*** Chronic activation of the RAAS in diabetic nephropathy

leads to renal hypertrophy (enlargement) and maladaptive remodelling of the renal vasculature and tubulointerstitial, exacerbating kidney damage and dysfunction.

Given its central role in the pathogenesis of diabetic nephropathy, the RAAS has become a primary target for therapeutic intervention. Drugs that inhibit the RAAS, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), have been shown to slow the progression of diabetic nephropathy by reducing intraglomerular pressure, proteinuria, inflammation, and fibrosis. These medications are commonly used as part of the management strategy for diabetic nephropathy to help preserve kidney function and reduce the risk of endstage renal disease.

Acknowledgment

The authors are grateful to the Kamalprakash Pharmacy College and Research Centre Kherda, Karanja (Lad.) Dist. Washim, for giving facilities to carry out this review work.

Declaration of Competing Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Refrences:

1. Tuttle KR, Agarwal R, Alpers CE, Bakris GL, Brosius FC, Kolkhof P, Uribarri J. Molecular mechanisms and therapeutic targets for diabetic kidney disease. Kidney international. 2022 Aug 1;102(2):248-60.
2. Whitehead M, Wickremasinghe S, Osborne A, Van Wijngaarden P, Martin KR. Diabetic retinopathy: a complex pathophysiology requiring novel therapeutic strategies. Expert opinion on biological therapy. 2018 Dec 2;18(12):1257-70.
3. Patel N, Yaqoob MM, Aksentijevic D. Cardiac metabolic remodelling in chronic kidney disease. Nature Reviews Nephrology. 2022 Aug;18(8):524-37.
4. Ameer OZ. Hypertension in chronic kidney disease: What lies behind the scene. Frontiers in pharmacology. 2022 Oct 11;13:949260.
5. Ameer OZ. Hypertension in chronic kidney disease: What lies behind the scene. Frontiers in pharmacology. 2022 Oct 11;13:949260.
6. Saini T, Mazumder PM. Current advancement in the preclinical models used for the assessment of diabetic neuropathy. Naunyn-Schmiedeberg's Archives of Pharmacology. 2024 May;397(5):2727-45.
7. Charlton A, Garzarella J, Jandeleit-Dahm KA, Jha JC. Oxidative stress and inflammation in renal and cardiovascular complications of diabetes. Biology. 2020 Dec 30;10(1):18.
8. Mukherjee N, Lin L, Contreras CJ, Templin AT. β-Cell death in diabetes: past discoveries, present understanding, and potential future advances. Metabolites. 2021 Nov 22;11(11):796.
9. Lemaire M. Novel Fanconi renotubular syndromes provide insights in proximal tubule pathophysiology. American Journal of Physiology-Renal Physiology. 2021 Feb 1;320(2):F145-60.
10. Alicic RZ, Cox EJ, Neumiller JJ, Tuttle KR. Incretin drugs in diabetic kidney disease: biological mechanisms and clinical evidence. Nature Reviews Nephrology. 2021 Apr;17(4):227-44.

11. Vermot A, Petit-Härtlein I, Smith SM, Fieschi F. NADPH oxidases (NOX): an overview from discovery, molecular mechanisms to physiology and pathology. Antioxidants. 2021 Jun 1;10(6):890.
12. Kumar D, editor. Clinical molecular medicine: principles and practice. Academic Press; 2019 Nov 30.
13. Mapiye DS. Computational genomics approaches for kidney diseases in Africa.
14. Keefe D, Bowen J, Gibson R, Tan T, Okera M, Stringer A. Noncardiac vascular toxicities of vascular endothelial growth factor inhibitors in advanced cancer: a review. The oncologist. 2011 Apr 1;16(4):432-44.
15. Sharma D, Bhattacharya P, Kalia K, Tiwari V. Diabetic nephropathy: new insights into established therapeutic paradigms and novel molecular targets. Diabetes Res Clin Pract. 2017;128:91–108.
16. Wu T, Ding L, Andoh V, Zhang J, Chen L. The mechanism of hyperglycemia-induced renal cell injury in diabetic nephropathy disease: An update. Life. 2023;13(2):539
17. Gonçalves NP, Vægter CB, Andersen H, Østergaard L, Calcutt NA, Jensen TS. Schwann cell interactions with axons and microvessels in diabetic neuropathy. Nature Reviews Neurology. 2017 Mar;13(3):135-47.
18. Hutcheson JD, Goettsch C, Rogers MA, Aikawa E. Revisiting cardiovascular calcification: A multifaceted disease requiring a multidisciplinary approach. InSeminars in Cell & Developmental Biology 2015 Oct 1 (Vol. 46, pp. 68-77). Academic Press.
19. Stepto NK, Moreno-Asso A, McIlvenna LC, Walters KA, Rodgers RJ. Molecular mechanisms of insulin resistance in polycystic ovary syndrome: unraveling the conundrum in skeletal muscle?. The Journal of Clinical Endocrinology & Metabolism. 2019 Nov;104(11):5372-81.
20. Ptinopoulou AG, Pikilidou MI, Lasaridis AN. The effect of antihypertensive drugs on chronic kidney disease: a comprehensive review. Hypertension Research. 2013 Feb;36(2):91-101.
21. Waikar SS, McMahon GM. Expanding the role for kidney biopsies in acute kidney injury. InSeminars in nephrology 2018 Jan 1 (Vol. 38, No. 1, pp. 12-20). WB Saunders.
22. Tangestani Fard M, Stough C. A review and hypothesized model of the mechanisms that underpin the relationship between inflammation and cognition in the elderly. Frontiers in aging neuroscience. 2019 Mar 13;11:56
23. .