REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Overview of Key Molecular Processes Behind Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is one of the diabetic chronic microvascular consequences and a leading cause of end-stage renal disease (ESRD). The traditional presentation of DN is defined by hyperfiltration and albuminuria in the early stages, followed by gradual renal function deterioration. The appearance of diabetic kidney disease (DKD) might vary, especially in individuals with type 2 diabetes mellitus, where the concurrent presence of various glomerular/tubular pathologies and severe peripheral vascular disease can become key confounding factors. The fundamental question driving current research is "What is the primary mechanism leading to the molecular development of DN's disease pathology?" This review examines the molecular processes that cause oxidative stress (OS), hypoxia, dysregulated autophagy and apoptosis, and epigenetic alterations cause kidney inflammation and fibrosis.

Keywords: Diabetic kidney disease; Oxidative stress; Inflammation; Apoptosis; Autophagy.

1. Introduction

Diabetic nephropathy (DN) is a common and severe complication of diabetes mellitus (DM), linked to increased morbidity and mortality in diabetic patients. Globally, as diabetes prevalence rises particularly in developing nations, the incidence of DN is also expected to increase unless preventive strategies are improved **(Lim, 2014) (Figure 1)**.

Diabetic nephropathy typically develops after several years in about one-third of diabetic patients. There remains debate on whether to screen for microalbuminuria or predict DN using personalized medicine, which could allow for the allocation of more intensive therapy to high-risk individuals **(Burrows et al., 2017)**. Microalbuminuria, a marker of kidney damage, often appears when significant glomerulopathy has already occurred. However, many patients with microalbuminuria may revert to normoalbuminuria. Diagnosing DN is also complicated by cases that deviate from the typical progression of the disease, including patients without retinopathy or those with nonproteinuric DN, which is more common in type 2 DM patients **(Zhang et al., 2016)**.

The pathogenesis of DN is complex and not fully understood, resulting in limited therapeutic success. Standard treatments, including tight control of blood sugar and blood pressure, have not been able to prevent progression to end-stage renal disease (ESRD) or reduce DN-related mortality **(Xue et al., 2017)**. Research continues to explore the underlying mechanisms of DN, including pathways involving oxidative stress (OS), angiotensin II, and inflammation, all of which are increasingly recognized as significant contributors **(Caramori et al., 2002)**. A better understanding of these mechanisms may help identify new therapeutic targets, particularly in the realm of anti-

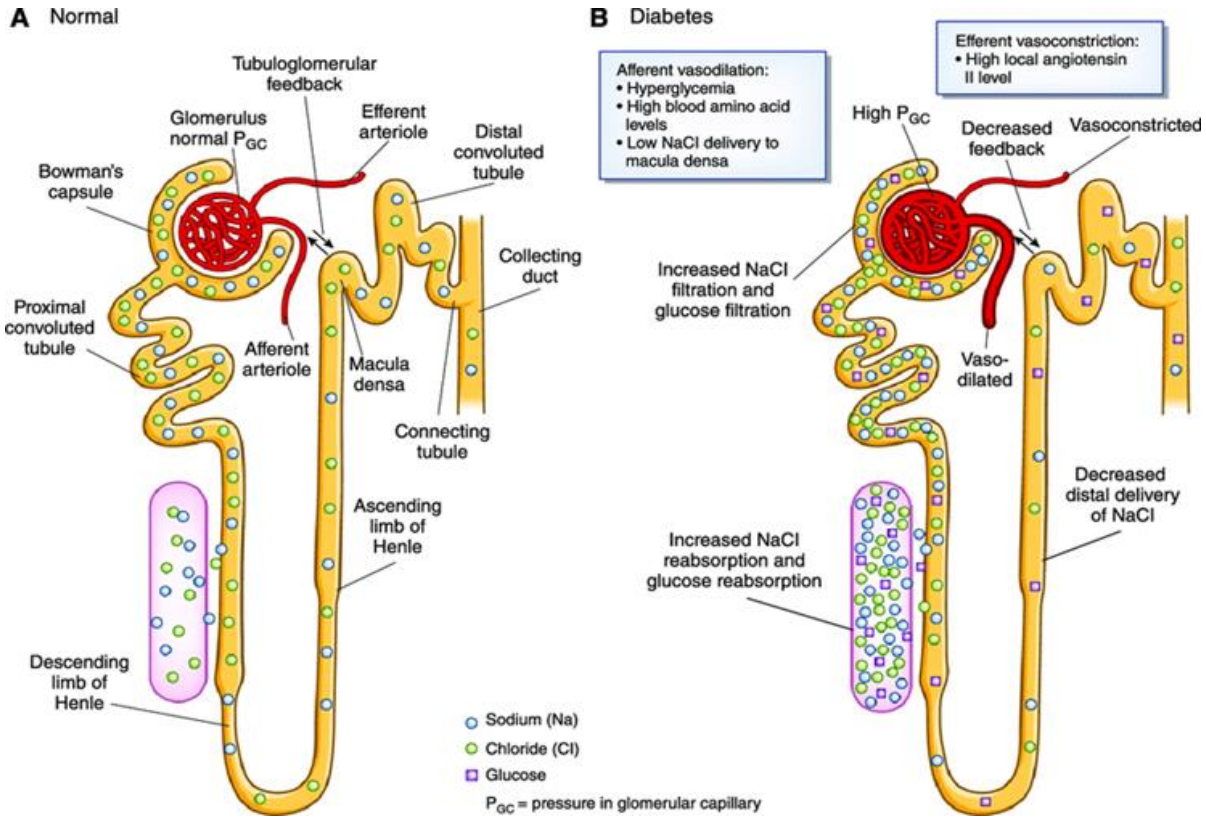

Figure 1. Normal and diabetic nephron with altered renal hemodynamics **(Alicic et al., 2017)**.

inflammatory strategies **(Susztak and Böttinger, 2006)**. This review examines the pathogenesis of DN, focusing on OS, Ang-II, and inflammation, along with current and potential future treatments targeting these processes.

2. Epidemiology

Diabetic kidney disease (DKD) is widespread globally. Studies show that patients with diabetes have an estimated 1.75 times higher risk of developing chronic kidney disease (CKD) (95% CI: 1.62–1.89). In China, a risk assessment program reported a 38.8% CKD prevalence among 15,856 diabetic patients. Additionally, a population-based study found that 2.9% of rural Chinese residents have DKD, while research conducted in India by our group reported a 34.4% prevalence of DKD. A multicentre study from India indicated a composite prevalence of diabetic CKD at around 62.3%. Similarly, a population-based study from the United Arab Emirates found a cumulative CKD incidence of 11.4% after a 9-year follow-up (**Hussain et al., 2021)**.

In the Eastern Mediterranean, the highest prevalence of DM and diabetic CKD was found among the elderly. In Japan, 15.3% of patients with type 2 DM had low estimated glomerular filtration rates (GFR), based on diabetes clinical data. Meanwhile, the United Kingdom's prospective diabetes study of 4,006 T2DM patients revealed that 28% developed renal impairment after a median follow-up of 15 years **(Hussain et al., 2021)**.

The growing number of T2DM patients worldwide, including 7.5 million people in Egypt in 2013, highlights the need to address the prevalence and risk factors of DKD, particularly among newly diagnosed patients who may already present with complications like DKD at diagnosis **(Aboelnasr et al., 2020)**.

3. Risk factors of progressivity of diabetic nephropathy

Hyperglycemia, hypertension, obesity, smoking, race, gender, dyslipidemia, age, and genetic factors are the primary risk factors contributing to the development and progression of DN. The incidence of DN is notably higher among African Americans, Asians, and Native Americans compared to Caucasians **(Murea et al., 2012)**.

The progression of DN is typically classified into five stages. Microalbuminuria is defined as a persistent albumin excretion rate between 30 and 300 mg/day (20-200 mg/min), while an albumin excretion rate exceeding 300 mg/day is referred to as overt nephropathy **(Sarafidis and Bakris, 2006)**. The presence of albuminuria significantly increases the risk of cardiovascular disease and progressive kidney disease. Once DN occurs, patients with type 1 and type 2 DM experience a decline in GFR and the negative effects of hypertension. The GFR decreases linearly at a rate of 2-20 mL/min/year as DN progresses. Without aggressive intervention, DN typically advances to ESRD within an average of 6-7 years **(Pafundi et al., 2021)**.

The rate of renal function decline after the onset of DN varies among individuals and is influenced by factors such as blood pressure and glycemic control. More rapid progression is often seen with higher levels of albuminuria and hypertension. Additionally, the presence of retinopathy serves as a predictor for faster progression of DN **(Xing et al., 2024)**.

4. Mechanisms of diabetic kidney disease

4.1. Oxidation-antioxidant balance

Hyperglycemia leads to glucose metabolism disorders, which are the primary cause of excessive superoxide production and increased OS in the kidneys. To mitigate OS damage to cells, the body activates antioxidant defense systems to scavenge free radicals **(González et al., 2023)**. NADPH oxidase 4 is the predominant isoform in most cell types. Excessive activation of NOX4 has been linked to complications in the diabetic retina, endothelial vasculature, and kidneys, as well as the development of insulin resistance in peripheral tissues. Notably, in the kidneys, AMP-activated protein kinase (AMPK) inactivation triggers NOX4 stimulation, leading to a superoxide burst that damages glomerular cells, thereby contributing to DN **(Yaribeygi et al., 2018)**.

4.2. Mitochondrial quality control is unsustainable

Mitochondria is the primary target of oxidative damage. It plays a vital role in repair, regeneration, and autophagic degradation to ensure mitochondrial quality control. In DKD, renal autophagy activity is suppressed, leading to the accumulation of damaged mitochondria. This accumulation intensifies intracellular OS and disrupts renal structure and function. Peroxisome proliferator-activated receptor gamma coactivator 1α, a crucial regulatory molecule that enhances autophagy, expression in the kidneys is significantly reduced. This downregulation decreases mitochondrial production and impairs the synthesis of essential proteins, such as ATPase, in damaged mitochondria. As a result, ATP supply becomes insufficient, leading to impaired energy provision, which significantly contributes to structural alterations and functional decline in the kidneys **(Hou et al., 2024)**.

4.3. Activation of protein kinase C signaling

The activation of protein kinase C (PKC) and increased OS can regulate the expression of multiple pathogenic genes associated with DKD. This includes the downregulation of nitric oxide synthase (NOS), responsible for producing the vascular endothelial relaxing factor, and the upregulation of endothelin-1, a vascular endothelial contractile factor. These alterations lead to reduced renal blood flow and disturbances in renal hemodynamics **(Noh and King, 2007)**.

Furthermore, PKC activation promotes the expression of collagen fibers and pro-inflammatory factors, accelerating renal fibrosis. This process occurs through pathways involving transcription factor β, plasminogen activator inhibitor 1 (PAI-1), and nuclear transcription factor-κB (NF-κB) amplifying inflammation and apoptosis **(Wang and Zhang, 2024)**.

4.4. Hyperactivation of the hexosamine pathway

Hyperactivation of the hexosamine pathway results in the production of uridine diphosphate (UDP) and N-acetylglucosamine (GlcNAc). The buildup of GlcNAc interferes with the phosphorylation of Akt/eNOS and HSP72 through kinase-like mechanisms involving serine/threonine phosphorylation. This inhibition increases the expression of transforming growth factor-β and PAI-1, thereby promoting OS and fibrosis in DKD **(Paneque et al., 2023)**.

4.5. Inflammation

Increasing evidence from clinical and experimental studies highlights the critical role of inflammation in the onset and progression of DKD. Central elements of this inflammatory response include macrophages, inflammatory cytokines, and signaling pathways such as NF-κB and Janus kinase/signal transducer and activator of transcription (JAK/STAT) **(Matoba et al., 2019)**.

In DM, activation of the mononuclear phagocyte system triggers the release of cytokines and the recruitment of immune cells, contributing to inflammation-induced structural changes in the kidneys. Moreover, mast cells may infiltrate the tubulointerstitium, releasing inflammatory mediators and proteolytic enzymes, which can potentially lead to a reduction in the eGFR **(Pichler et al., 2017)**.

Cytokines, including interleukins (IL-1, IL-6, IL-18) and tumor necrosis factor-alpha (TNF-α), are signaling polypeptides produced by kidney cells and are closely involved in the progression of DKD. In diabetes models, increased renal IL-1 levels are linked to higher chemotactic factor expression and greater vascular endothelial cell permeability **(Donate-Correa et al., 2021)**.

It was revealed that IL-6 facilitates neutrophil infiltration into the tubulointerstitium, disrupting extracellular matrix balance and contributing to renal hypertrophy and thickening of the glomerular basement membrane, conditions associated with albuminuria (Jha et al., 2024). TNF-α drives inflammatory cell differentiation, causes cytotoxicity in kidney cells, induces apoptosis, and impairs glomerular hemodynamics. These effects exacerbate vascular endothelial permeability and OS. Notably, TNF-α mRNA levels are elevated in glomerular and tubular cells during early diabetes stages **(Chaudhari et al., 2020)**.

A key transcription factor, NF-κB, activated by cytokines and oxygen radicals during renal inflammation in diabetes, is also triggered via JAK/STAT pathways. This activation contributes to structural damage and functional impairments in DKD. In renal cells, NF-κB responds quickly to stimuli such as hyperglycemia and advanced glycation end products (AGEs), further exacerbating disease progression **(Sinha and Nicholas, 2023)**.

The kidneys are especially susceptible to damage from AGEs, being the first organ affected by diabetes and also responsible for clearing AGEs. Hyperglycemia and OS lead to increased production of AGEs and their receptor, RAGE, which further intensifies OS and NF-κB activation in endothelial cells (Wang and Zhang, 2024). This not only promotes the expression of adhesion molecules but also causes glomerular epithelial cells to transform into interstitial cells, decreases NOS activity, and worsens renal vasoconstriction and vascular sclerosis. Moreover, AGEs are believed to diffuse out of cells, damaging circulating albumin and triggering the transcription and secretion of systemic inflammatory mediators **(Ratliff et al., 2016)**.

Although clinical trials have not demonstrated significant benefits of anti-AGE treatments for DKD patients, first-line drugs like metformin have shown promise in reducing tubulointerstitial injury. This is achieved through the activation of AMPK, inhibition of the AGE-RAGE axis, and reduction of reactive oxygen species and matrix metalloproteinase 2 production **(Kawanami et al., 2020)**.

4.6. Key regulators of mitochondrial function and autophagic activity

The interaction between mTOR (mammalian target of rapamycin), AMPK, and silent information regulator 1 (SIRT1) plays a key role in regulating mitochondrial function and autophagic activity, particularly in the context of DN **(Wang et al., 2019)**.

The mTOR is a serine/threonine protein kinase that belongs to the PI3K-related protein kinase family and functions through two complexes: mTORC1 and mTORC2. mTORC1 is particularly responsible for regulating cell growth by promoting translation and ribosome biogenesis while inhibiting autophagic activity **(Powell and Delgoffe, 2010)**. This regulation is driven by various upstream signaling pathways that influence gene expression and protein modification. When it comes to diet and hyperglycemia, high-fat diets can lead to overactivation of mTORC1, which inhibits the phosphorylation of insulin receptor substrate 1 (IRS-1) **(Koundouros and Blenis, 2022)**.

This inhibition contributes to increased insulin resistance, impairing glucose uptake and glycogen synthesis. Studies have shown that hyperglycemia-

induced activation of mTOR is linked to tubular cell proliferation and apoptosis in DKD, and knocking down the mTOR gene can help alleviate tubular injury. Furthermore, the mTOR inhibitor rapamycin has been shown to improve blood glucose uptake, enhance insulin sensitivity, and improve renal health by reducing glomerular injury, promoting autophagic activity, and decreasing proteinuria **(Selim et al., 2025)**.

The SIRT1 is a member of the sirtuin family of NAD-dependent deacetylases and plays a critical role in cellular repair, OS response, and autophagic regulation. SIRT1 exerts its effects by deacetylating various substrate proteins, which enhances autophagic activity. It activates proteins like Atg5 and promotes the synthesis of autophagosomes and lysosomes through the PINK1/parkin pathway **(Lee et al., 2008)**.

In diabetes, the expression of SIRT1 is significantly reduced, likely due to lower NAD+ levels in diabetic tissues. Resveratrol, a SIRT1 agonist, has been shown to upregulate SIRT1 expression, thereby improving glucose homeostasis, reducing mesangial cell proliferation, enhancing renal autophagy, and alleviating OS and inflammation. In addition, SIRT1 plays a key role in energy regulation by interacting with essential proteins to maintain energy balance, promoting gluconeogenesis, and enhancing fatty acid oxidation to stabilize blood glucose levels **(Qi et al., 2022)**.

The AMPK is a serine/threonine protein kinase that acts as a key energy sensor in cells. In diabetic models, AMPK expression is often reduced, which impairs energy homeostasis and contributes to insulin resistance **(Hardie, 2011)**. Increasing AMPK activity has been shown to improve renal filtration barrier function, enhance autophagic activity, and reduce renal fibrosis. AMPK detects changes in cellular energy levels, and when ATP levels are low, it inhibits mTOR activity to help maintain energy balance. An increase in AMP activates AMPK, leading to inhibition of mTORC1 and promoting autophagy **(Zaha and Young, 2012) (Figure 2)**.

5. Conclusion

Diabetic nephropathy is a multifactorial disease driven by hyperglycemia, OS, and inflammation, leading to renal dysfunction. Key molecular pathways, including mTOR, JAK/STAT, and NF-κB, contribute to kidney damage by promoting fibrosis, inflammation, and OS. AGEs accumulate in the kidneys, exacerbating damage and impairing AGE clearance. Mitochondrial dysfunction and impaired autophagy further worsen renal injury. Inflammatory cytokines like TNF-α, IL-1, and IL-6 accelerate kidney damage. Dysregulation of SIRT1 and AMPK disrupts energy metabolism and cellular functions, leading to fibrosis and glomerulosclerosis. Despite ongoing research, clinical trials targeting these pathways have shown mixed results, highlighting the need for better treatments. Understanding these molecular mechanisms is crucial for developing more effective therapies for DN.

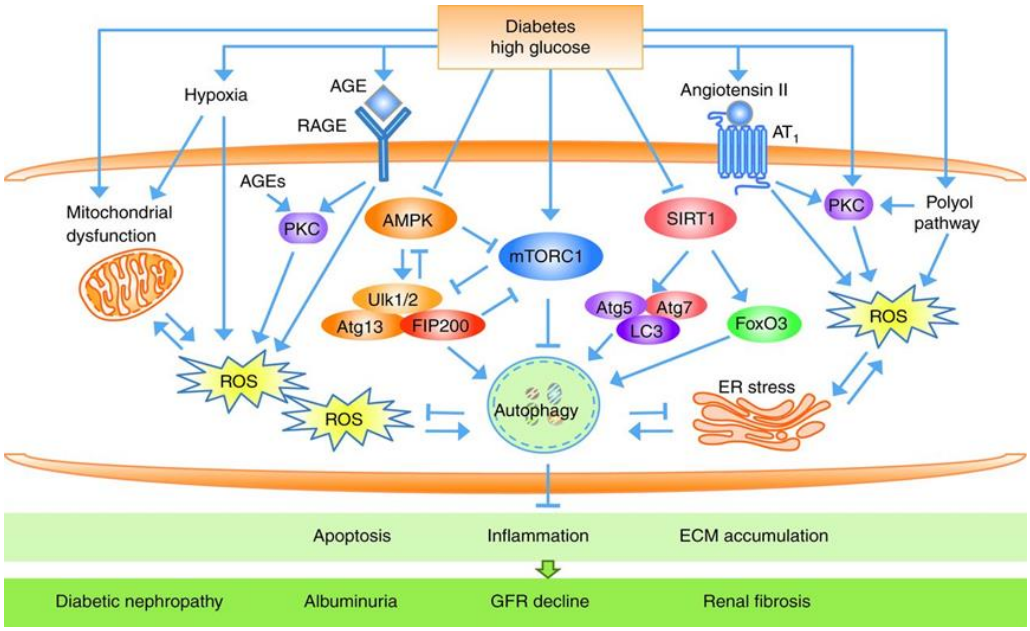

Figure 2. Autophagy in diabetic nephropathy **(Ding and Choi, 2015)**

References

Aboelnasr M, Shaltout A, AlSheikh M, Abdelhameed A, Elrefaey W, 2020. Diabetic kidney disease in patients newly diagnosed with type-2 diabetes mellitus: Incidence and associations. Saudi Journal of Kidney Diseases and Transplantation 31, 191. https://doi.org/10.4103/1319-2442.279940

Alicic RZ, Rooney MT, Tuttle KR, 2017. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clinical Journal of the American Society of Nephrology 12, 2032–2045. https://doi.org/10.2215/CJN.11491116

Burrows NR, Hora I, Geiss LS, Gregg EW, Albright A, 2017. Incidence of End-Stage Renal Disease Attributed to Diabetes Among Persons with Diagnosed Diabetes — United States and Puerto Rico, 2000–2014. Morbidity and Mortality Weekly Report 66, 1165–1170. https://doi.org/10.15585/mmwr.mm6643a2

Caramori ML, Kim Y, Huang C, Fish AJ, Rich SS, Miller ME, Russell G, Mauer M, 2002. Cellular Basis of Diabetic Nephropathy. Diabetes 51, 506–513. https://doi.org/10.2337/diabetes.51.2.506

Chaudhari S, Yazdizadeh Shotorbani P, Tao Y, Davis ME, Mallet RT, Ma R, 2020. Inhibition of interleukin-6 on matrix protein production by glomerular mesangial cells and the pathway involved. American Journal of Physiology-Renal Physiology 318, F1478–F1488. https://doi.org/10.1152/ajprenal.00043.2020

Ding Y, Choi ME, 2015. Autophagy in diabetic nephropathy. Journal of Endocrinology 224, R15–R30. https://doi.org/10.1530/JOE-14-0437

Donate-Correa J, Ferri CM, Sánchez-Quintana F, Pérez-Castro A, González-Luis A, Martín-Núñez E, Mora-Fernández C, Navarro-González JF, 2021. Inflammatory Cytokines in Diabetic Kidney Disease: Pathophysiologic and Therapeutic Implications. Frontiers in Medicine 7, 628289. https://doi.org/10.3389/fmed.2020.628289

González P, Lozano P, Ros G, Solano F, 2023. Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections. International Journal of Molecular Sciences 24, 9352. https://doi.org/10.3390/ijms24119352

Hardie DG, 2011. AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function. Genes & Development 25, 1895–1908. https://doi.org/10.1101/gad.17420111

Hou Y, Tan E, Shi H, Ren X, Wan X, Wu W, Chen Y, Niu H, Zhu G, Li J, Li Y, Wang L, 2024. Mitochondrial oxidative damage reprograms lipid metabolism of renal tubular epithelial cells in the diabetic kidney. Cellular and Molecular Life Sciences 81, 23. https://doi.org/10.1007/s00018-023-05078-y

Hussain S, Chand Jamali M, Habib A, Hussain MS, Akhtar M, Najmi AK, 2021. Diabetic kidney disease: An overview of prevalence, risk factors, and biomarkers. Clinical Epidemiology and Global Health 9, 2–6. https://doi.org/10.1016/j.cegh.2020.05.016

Jha R, Lopez-Trevino S, Kankanamalage HR, Jha JC, 2024. Diabetes and Renal Complications: An Overview on Pathophysiology, Biomarkers and Therapeutic Interventions. Biomedicines 12, 1098. https://doi.org/10.3390/biomedicines12051098

Kawanami D, Takashi Y, Tanabe M, 2020. Significance of Metformin Use in Diabetic Kidney Disease. International Journal of Molecular Sciences 21, 4239. https://doi.org/10.3390/ijms21124239

Koundouros N, Blenis J, 2022. Targeting mTOR in the Context of Diet and Whole-body Metabolism. Endocrinology 163, bqac041. https://doi.org/10.1210/endocr/bqac041

Lee IH, Cao L, Mostoslavsky R, Lombard DB, Liu J, Bruns NE, Tsokos M, Alt FW, Finkel T, 2008. A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. Proceedings of the National Academy of Sciences of the United States of America 105, 3374–3379. https://doi.org/10.1073/pnas.0712145105

Lim AK, 2014. Diabetic nephropathy - complications and treatment. International Journal of Nephrology and Renovascular Disease 7, 361–381. https://doi.org/10.2147/IJNRD.S40172

Matoba K, Takeda Y, Nagai Y, Kawanami D, Utsunomiya K, Nishimura R, 2019. Unraveling the Role of Inflammation in the Pathogenesis of Diabetic Kidney Disease. International Journal of Molecular Sciences 20, 3393.

https://doi.org/10.3390/ijms20143393

Murea M, Ma L, Freedman BI, 2012. Genetic and environmental factors associated with type 2 diabetes and diabetic vascular complications. Reviews in Diabetes Studies 9, 6–22. https://doi.org/10.1900/RDS.2012.9.6

Noh H, King GL, 2007. The role of protein kinase C activation in diabetic nephropathy. Kidney International 72, S49–S53. https://doi.org/10.1038/sj.ki.5002386

Pafundi PC, Garofalo C, Galiero R, Borrelli S, Caturano A, Rinaldi L, Provenzano M, Salvatore T, De Nicola L, Minutolo R, Sasso FC, 2021. Role of Albuminuria in Detecting Cardio-Renal Risk and Outcome in Diabetic Subjects. Diagnostics 11, 290. https://doi.org/10.3390/diagnostics11020290

Paneque A, Fortus H, Zheng J, Werlen G, Jacinto E, 2023. The Hexosamine Biosynthesis Pathway: Regulation and Function. Genes 14, 933. https://doi.org/10.3390/genes14040933

Pichler R, Afkarian M, Dieter BP, Tuttle KR, 2017. Immunity and inflammation in diabetic kidney disease: translating mechanisms to biomarkers and treatment targets. American Journal of Physiology-Renal Physiology 312, F716–F731. https://doi.org/10.1152/ajprenal.00314.2016

Powell JD, Delgoffe GM, 2010. The mammalian target of rapamycin: linking T cell differentiation, function, and metabolism. Immunity 33, 301–311. https://doi.org/10.1016/j.immuni.2010.09.002

Qi W, Hu C, Zhao D, Li X, 2022. SIRT1-SIRT7 in Diabetic Kidney Disease: Biological Functions and Molecular Mechanisms. Frontiers in Endocrinology 13, 801303. https://doi.org/10.3389/fendo.2022.801303

Ratliff BB, Abdulmahdi W, Pawar R, Wolin MS, 2016. Oxidant Mechanisms in Renal Injury and Disease. Antioxidants & Redox Signaling 25, 119–146. https://doi.org/10.1089/ars.2016.6665

Sarafidis PA, Bakris GL, 2006. Microalbuminuria and chronic kidney disease as risk factors for cardiovascular disease. Nephrology Dialysis Transplantation 21, 2366–2374. https://doi.org/10.1093/ndt/gfl309

Selim SM, El Fayoumi HM, El-Sayed NM, Mehanna ET, Hazem RM, 2025. Alogliptin attenuates STZ-induced diabetic nephropathy in rats through the modulation of autophagy, apoptosis, and inflammation pathways: Targeting NF-κB and AMPK/mTOR pathway. Life Sciences 361, 123307. https://doi.org/10.1016/j.lfs.2024.123307

Sinha SK, Nicholas SB, 2023. Pathomechanisms of Diabetic Kidney Disease. Journal of Clinical Medicine 12, 7349. https://doi.org/10.3390/jcm12237349

Susztak K, Böttinger EP, 2006. Diabetic Nephropathy: A Frontier for Personalized Medicine. Journal of the American Society of Nephrology 17, 361–367. https://doi.org/10.1681/ASN.2005101109

Wang N, Zhang C, 2024. Oxidative Stress: A Culprit in the Progression of Diabetic Kidney Disease. Antioxidants 13, 455. https://doi.org/10.3390/antiox13040455

Wang W, Sun W, Cheng Y, Xu Z, Cai L, 2019. Role of sirtuin-1 in diabetic nephropathy. Journal of Molecular Medicine 97, 291–309. https://doi.org/10.1007/s00109-019-01743-7

Xing J, Huang L, Ren W, Mei X, 2024. Risk factors for rapid kidney function decline in diabetes patients. Renal Failure 46, 2398188. https://doi.org/10.1080/0886022X.2024.2398188

Xue R, Gui D, Zheng L, Zhai R, Wang F, Wang N, 2017. Mechanistic Insight and Management of Diabetic Nephropathy: Recent Progress and Future Perspective. Journal of Diabetes Research 2017, 1839809. https://doi.org/10.1155/2017/1839809

Yaribeygi H, Farrokhi FR, Rezaee R, Sahebkar A, 2018. Oxidative stress induces renal failure: A review of possible molecular pathways. Journal of Cellular Biochemistry 119, 2990–2998. https://doi.org/10.1002/jcb.26450

Zaha VG, Young LH, 2012. AMP-activated protein kinase regulation and biological actions in the heart. Circulation Research 111, 800–814. https://doi.org/10.1161/CIRCRESAHA.111.255505

Zhang L, Long J, Jiang W, Shi Y, He X, Zhou Z, Li Y, Yeung RO, Wang J, Matsushita K, Coresh J, Zhao M-H, Wang H, 2016. Trends in Chronic Kidney Disease in China. The New England Journal of Medicine 375, 905–906. https://doi.org/10.1056/NEJMc1602469