Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2026.66.010370

# Immunological and Molecular Mechanisms in Diabetic Nephropathy: A Mini Review

**Athanasiadou V*, Panokostas D and E Grapsa**

*Department of Nephrology, School of Medicine, Aretaieion University Hospital, National and Kapodistrian University of Athens, Greece*

***Corresponding author:** Virginia Athanasiadou, Department of Nephrology, School of Medicine, Aretaieion University Hospital, National and Kapodistrian University of Athens, Greece

**ARTICLE INFO**

**Received:** August 27, 2026

**Published:** September 02, 2026

**Citation:** Athanasiadou V, Panokostas D and E Grapsa. Immunological and Molecular Mechanisms in Diabetic Nephropathy: A Mini Review. Biomed J Sci & Tech Res 66(4)-2026. BJSTR. MS.ID.010370.

**ABSTRACT**

Diabetic nephropathy (DN) is a leading cause of end-stage renal disease and a major complication of diabetes mellitus. Although traditionally attributed to metabolic and hemodynamic disturbances, recent evidence highlights the central role of immune-mediated inflammation in disease progression. Hyperglycemia-induced oxidative stress and advanced glycation end-products activate innate and adaptive immune pathways, leading to chronic renal inflammation, fibrosis, and functional decline. Key signaling cascades, including NF-κB, Toll-like receptors (TLRs), and the NLRP3 inflammasome, orchestrate cytokine production and immune cell recruitment. Furthermore, epigenetic modifications sustain inflammatory responses through metabolic memory. Emerging therapies targeting these immunological mechanisms offer promising renoprotective effects. This mini review summarizes the current understanding of immune involvement in DN and highlights modern therapeutic strategies.

**Keywords:** Diabetic Nephropathy; Immune Response; Inflammation; NF-κB; Nlrp3 Inflammasome; Fibrosis; Metabolic Memory; Jak/Stat; Sglt2 Inhibitors

**Abbreviations:** DN: Diabetic Nephropathy; TLRs: Toll-Like Receptors; DKD: Diabetic Kidney Disease; ESRD: End-Stage Renal Disease; AGEs: Advanced Glycation End-Products; ROS: Reactive Oxygen Species; DAMP: Damage-Associated Molecular Pattern; PRRs: Pattern Recognition Receptors; NETosis: Neutrophil Extracellular Trap Formation; EMT: Epithelial-To-Mesenchymal Transition; T2D: Type 2 Diabetes

## Introduction and Pathophysiology

Diabetic nephropathy, also widely referred to as diabetic kidney disease (DKD), represents the primary cause of end-stage renal disease (ESRD) and a major global driver of cardiovascular morbidity [1,2]. Although classical paradigms attributed disease development to intraglomerular hyperfiltration, hemodynamic stress, and metabolic toxicity driven by hyperglycemia, accumulating evidence establishes that chronic, sterile, low-grade inflammation and immune system dysregulation serve as central pathophysiological engines [3-6]. Persistent hyperglycemia accelerates the non-enzymatic glycation of long-lived proteins to form advanced glycation end-products (AGEs), enhances the generation of reactive oxygen species (ROS) via mitochondrial and NADPH oxidase pathways, increases polyol pathway flux, and promotes local angiotensin II synthesis [3,4,6,7]. These cumulative stressors induce cellular injury across glomerular endothelial cells, mesangial cells, podocytes, and tubular epithelial cells, triggering damage-associated molecular pattern (DAMP) release [4,6,7]. DAMPs engage pattern recognition receptors (PRRs), initiating leukocyte recruitment, pro-inflammatory cytokine release, microvascular rarefaction, podocyte detachment, and tubulointerstitial fibrosis [3-6,8].

## Innate and Adaptive Immune Mechanisms

In innate immunity, neutrophils in diabetic patients exhibit defective chemotaxis, impaired phagocytosis, and delayed apoptosis, paired with a heightened propensity to undergo neutrophil extracellular trap formation (NETosis) [3-6]. Unregulated NETosis releases cytotoxic histones, myeloperoxidase, and proteolytic enzymes, exacerbating glomerular endothelial damage and amplifying localized necrosis [4,5,6]. Monocytes and macrophages represent the predominant infiltrating immune cell types; their absolute density within glomeruli and tubulointerstitium correlates directly with proteinuria

and the rate of eGFR decline [4,6,7]. Driven by local chemokines—specifically MCP-1/CCL2 and CSF-1—and endothelial adhesion molecules (ICAM-1, VCAM-1), monocytes infiltrate the renal tissue and mature into pro-inflammatory M1 macrophages [3-8]. M1 macrophages produce abundant TNF-α, IL-1β, and IL-6, whereas the transition to an anti-inflammatory M2 phenotype is suppressed [3-8]. Dendritic cells act as primary biosensors processing DAMPs to connect innate metabolic stress to adaptive immune activation, while natural killer (NK) cells execute direct perforin- and granzyme-dependent cytotoxicity against stressed tubular cells [4-6]. In adaptive immunity, helper T cell polarization is markedly disrupted [3,4,6,9].

Expanded Th1 and Th17 cells secrete IFN-γ, TNF-α, and IL-17, activating intrarenal NF-κB signaling and recruiting additional leukocytes [4,6,9]. Conversely, CD4+CD25+FoxP3+ regulatory T cells (Tregs) suffer numerical depletion and functional impairment, failing to release adequate IL-10 to suppress tissue injury [3,4,6,9]. Cytotoxic CD8+ T cells directly induce tubular cell apoptosis via Fas/Fas ligand interactions [3,4,6,9]. As renal function deteriorates and uremic toxins accumulate, patients exhibit a dual immunological state: severe localized intrarenal sterile inflammation combined with systemic uremic immunosuppression (marked by elevated PD-1 and CTLA-4 checkpoint exhaustion), impairing overall host defense [2,4,6,9].

## Intracellular Signaling Pathways and Cell-Specific Lesions

Intracellular nuclear transduction of metabolic stress involves several key signaling networks [4,6,10]. The NF-κB p50/p65 pathway serves as the master transcription factor; hyperglycemia, ROS, AGEs, and angiotensin II activate IκB kinase (IKK), leading to IκB degradation and nuclear translocation of NF-κB to transcribe TNF-α, IL-1β, IL-6, MCP-1, and ICAM-1 [4,6,7]. Toll-like receptors (TLR2 and TLR4) bind endogenous DAMPs (HMGB1, heat shock proteins), triggering MyD88/TRAF6 downstream cascades [4,5,6]. The NLRP3 inflammasome assembles in response to ROS and mitochondrial stress, activating caspase-1 to process pro-IL-1β and pro-IL-18 into mature forms while cleaving gasdermin D to induce pyroptotic cell death [4,6,10]. The JAK/STAT pathway (via STAT1/STAT3) is activated by IL-6, IFN-γ, and angiotensin II, upregulating profibrotic gene networks (TGF-β1, CTGF) that promote epithelial-to-mesenchymal transition (EMT) and cellular senescence [4,6,7]. Complement activation yields C3a/C5a anaphylatoxins and sublytic C5b-9 complexes that disrupt podocyte F-actin cytoskeletons [4-6]. Pathologically, glomerular endothelial cells suffer glycocalyx loss, reduced eNOS activity, and microvascular rarefaction, leading to focal glomerular ischemia [4,6].

Podocytes experience loss of slit diaphragm proteins (nephrin, podocin) and foot process effacement, causing podocyte detachment and heavy albuminuria [3,4,6]. In the mesangium, TGF-β1/Smad2/3 hyperactivation drives excessive collagen type IV and fibronectin deposition, forming pathognomonic nodular glomerulosclerosis (Kimmelstiel-Wilson lesions) [4,6]. Proximal tubular epithelial cells undergo EMT, transforming into active myofibroblasts driving interstitial fibrosis [4,6].

## Epigenetic Regulation and Metabolic Memory

The persistence of intrarenal inflammation despite long-term glycemic normalization is driven by epigenetic chromatin modifications [4,6,9]. Prior high-glucose exposure induces permissive histone methylation marks, such as H3K4me3, at the promoter regions of p65 (NF-κB) and TGF-β1, keeping chromatin open for continuous pro-inflammatory transcription [4,6]. Protective marks like H3K9me3 are simultaneously reduced at antioxidant promoters [4,6]. DNA promoter hypermethylation silences protective anti-fibrotic genes, while pro-fibrotic microRNAs (such as miR-21) are upregulated to enhance Smad3-dependent fibrogenesis over the suppressed anti-fibrotic miR-29 family [4,6].

## Integrated Therapeutic Frontiers

Modern clinical strategies employ a multi-target paradigm addressing metabolic, hemodynamic, and inflammatory axes [4,11-16]:

- **SGLT2 Inhibitors (*dapagliflozin*, *canagliflozin*, *empagliflozin*)**: Beyond restoring tubuloglomerular feedback, they directly suppress intrarenal NLRP3 inflammasome assembly, downregulate MCP-1 and cytokine expression, attenuate oxidative stress, and alleviate renal hypoxia [4,11-13]. Major outcomes trials (DAPA-CKD, CREDENCE) confirm significant reductions in eGFR decline, ESRD, and cardiovascular death [11,12].
- **Non-Steroidal MRAs (*finerenone*)**: Selectively block mineralocorticoid receptors to inhibit aldosterone-driven genomic and non-genomic pro-inflammatory signaling, suppressing macrophage infiltration and TGF-β1 production [4,14,15]. Phase III trials (FIDELIO-DKD, FIGARO-DKD) demonstrate sustained reductions in albuminuria and slowed disease progression [14,15].
- **GLP-1 Receptor Agonists (*semaglutide*)**: As validated in the FLOW trial, long-term administration lowers major renal outcomes, cardiovascular events, and mortality in Type 2 diabetes (T2D) with CKD [13,16,17].
- **Novel Targeted Immunomodulators:** Selective JAK/STAT inhibitors (baricitinib), complement C3a/C5a receptor blockers, and chemokine antagonists (MCP-1/CCR2 inhibitors) represent promising targeted therapies [2,4,13].

## Conclusion

Diabetic nephropathy is an immunometabolic disorder driven by complex, interdependent networks of metabolic toxicity, hemodynamic stress, and persistent sterile inflammation [3,4,6]. Hyperglycemia and cellular stress trigger DAMP release and PRR activation, driving innate and adaptive immune cell infiltration into the renal architecture [3-6]. Signal transduction via NF-κB, TLRs, NLRP3, and JAK/STAT cascades promotes cytokine release, podocyte effacement, Kimmelstiel-Wilson lesions, and interstitial fibrosis [4,6,7,10]. Epigenetic modifications sustain these responses through metabolic memory [4,6,9]. Combining baseline RAAS inhibition with SGLT2 inhibitors, non-steroidal MRAs, GLP-1 receptor agonists, and novel immunomodulatory agents offers an effective multi-target approach to suppress inflammation and preserve kidney function [4,11-16].

## References

1. Rayego Mateos S, Morgado Pascual JL, Opazo Ríos L, Guerrero Hue M, García Caballero C, et al. (2020) Pathogenic pathways and therapeutic targets in diabetic nephropathy. Int J Mol Sci 21(18): 6798.
2. Biglari S, Harald Mischak, Joachim Beige, Agnieszka Latosinska, Justyna Siwy, et al. (2025) The future of chronic kidney disease treatment: combination therapy (polypill) or biomarker-guided personalized intervention?. Int J Mol Sci 15(6): 809.
3. Chen J, Zhang X, Maimaitiyi A, Wang R, Y, Zhang C, et al. (2022) Immune responses in diabetic nephropathy: Pathogenic mechanisms and therapeutic target. Front Immunol 13: 958790.
4. Ma L, Liu D, Yu Y, Li Z, Wang Q, et al. (2025) Immune-mediated renal injury in diabetic kidney disease: from mechanisms to therapy. Front Immunol 16: 1587806.
5. Tang SCW, Yiu WH (2020) Innate immunity in diabetic kidney disease. Nat Rev Nephrol 16(4): 206-222.
6. Hou G, Dong Y, Jiang Y, Zhao W, Zhou L, et al. (2025) Immune inflammation and metabolic interactions in the pathogenesis of diabetic nephropathy. Front Endocrinol (Lausanne) 16: 1602594.
7. Wada J (2021) The role of inflammation in diabetic nephropathy. Clin Exp Nephrol 25(8): 821-833.
8. Niewczas MA, Pavkov ME, Skupien J, Smiles A, Md Dom ZI, et al. (2019) A signature of circulating inflammatory proteins predicts end-stage renal disease in diabetes. Nat Med 25(5): 805-813.
9. Wang Y, Harris DCH (2019) T cell imbalance in diabetic kidney disease. Kidney Int 96(1): 33-41.
10. Fusco R, Siracusa R, Genovese T, Cuzzocrea S, Di Paola R, et al. (2020) Focus on the role of NLRP3 inflammasome in diseases. Int J Mol Sci 21(12): 4223.
11. Heerspink HJL, Stefánsson BV, Correa Rotter R, Chertow GM, Greene T, et al. (2020) Dapagliflozin in patients with chronic kidney disease. N Engl J Med 383(15): 1436-1446.
12. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, et al. (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 380(24): 2295-2306.
13. Dong H (2025) Mechanism-guided pharmacotherapy for cardiometabolic multimorbidity: from pathophysiology to phenotype-prioritized treatment. Front Pharmacol 16: 12702714.
14. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, et al. (2020) Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 383(23): 2219-2229.
15. Ruilope LM, Pitt B, Anker SD, Rossing P, Kovesdy CP, et al. (2022) Kidney outcomes with finerenone: an analysis from the FIGARO-DKD study. Nephrol Dial Transplant 38(2): 372-383.
16. Mahaffey KW, Tuttle KR, Arici M, Baeres FMM, Bakris G, et al. (2024) Cardiovascular outcomes with semaglutide by severity of chronic kidney disease in type 2 diabetes: the FLOW trial. Eur Heart J 45(38): 3921-3932.
17. Rossing P, Baeres FMM, Bakris G, Bosch-Traberg H, Gislum M, et al. (2023) The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. Nephrol Dial Transplant 38(9): 2041-2051.

**ISSN: 2574-1241**

DOI: 10.26717/BJSTR.2026.66.010370

**Virginia Athanasiadou** . Biomed J Sci & Tech Res



**Submission Link**: https://biomedres.us/submit-manuscript.php