

Toll-like receptor 2 and 4 expression in diabetic nephropathy patients undergoing hemodialysis: implications for innate immune activation and dialysis duration

Abstract

Background: Diabetic nephropathy (DN) is a major global cause of end-stage renal disease and is now recognized as an immuno-metabolic disorder driven by innate immune activation. Toll-like receptors (TLR2 and TLR4) mediate sterile inflammation, yet their expression in DN patients undergoing hemodialysis (HD) remains underexplored.

Objectives: To evaluate TLR2 and TLR4 gene expression in hemodialysis patients with diabetic nephropathy compared with non-diabetic HD patients and healthy controls, and to analyze correlations with clinical and laboratory parameters.

Methods: A cross-sectional study of 90 participants divided equally into three groups: non-diabetic HD patients, diabetic nephropathy HD patients, and healthy controls. Clinical evaluation, laboratory tests, cytokine measurement, and qPCR quantification of TLR2/TLR4 expression ($2^{-\Delta\Delta Ct}$) were performed. Statistical analyses included ANOVA, Kruskal–Wallis, χ^2 tests, and correlation assessment.

Results: TLR2 and TLR4 expression levels were significantly higher in DN patients on HD compared with non-diabetic HD patients and healthy controls ($p < 0.001$). Hemodialysis duration demonstrated strong positive correlations with TLR2 ($r = 0.832$, $p = 0.001$) and TLR4 ($r = 0.712$, $p = 0.001$). No significant associations with HbA1c, creatinine, urea, or age were observed.

Conclusion: DN patients on HD exhibit markedly elevated innate immune activation, reflected by increased TLR2 and TLR4 expression. Dialysis duration is a major determinant of TLR upregulation. TLR markers may serve as biomarkers for inflammatory burden and potential therapeutic targets in diabetic ESRD.

Keywords: diabetic nephropathy, Toll-like receptors, TLR2, TLR4, hemodialysis, innate immunity, inflammation, ESRD

Volume 14 Issue 1 - 2026

Heba E Salama, Feday M Abbas

Department of Nephrology, Ahmed Maher Teaching Hospital, Cairo, Egypt

Correspondence: Feday M. Abbas, Department of Nephrology, Ahmed Maher Teaching Hospital, Military Hosp, Sabhan, Kuwait, Cairo, Egypt

Received: February 13, 2026 | **Published:** April 15, 2026

Introduction

Diabetic nephropathy (DN) remains the principal cause of end-stage renal disease (ESRD) globally, accounting for nearly 40–50% of patients initiating renal replacement therapy in both developed and developing countries. Its prevalence continues to rise in parallel with the escalating global burden of type 2 diabetes mellitus (T2DM), increasing life expectancy, and improved survival of diabetic patients due to advances in cardiovascular and metabolic care. Despite significant strides in therapeutic strategies targeting hyperglycemia, hypertension, and renin–angiotensin–aldosterone system (RAAS) blockade, progression to ESRD remains alarmingly frequent, underscoring the presence of alternative pathogenic mechanisms beyond traditional hemodynamic and metabolic pathways.¹⁻⁴

Historically, DN was identified as a predominantly metabolic and hemodynamic disorder characterized by glomerular hyperfiltration, mesangial expansion, and progressive glomerulosclerosis. However, accumulating evidence over the past two decades has redefined DN as a complex immuno-metabolic disease in which chronic low-grade inflammation and innate immune activation play pivotal roles in its initiation and progression.⁵⁻⁸ This paradigm shift has led to extensive exploration of the molecular and cellular components of innate immunity, particularly the involvement of pattern-recognition receptors such as Toll-like receptors (TLRs) in mediating renal injury in diabetic conditions.

Histopathological observations have demonstrated that tubulointerstitial inflammation correlates more closely with the rate of renal function decline

than glomerular changes alone. Inflammatory infiltrates consisting of macrophages, T lymphocytes, and dendritic cells contribute to the secretion of profibrotic cytokines and chemokines, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), transforming growth factor- β (TGF- β), and monocyte chemoattractant protein-1 (MCP-1), which drive extracellular matrix accumulation, podocyte loss, and interstitial fibrosis.⁹⁻¹² These inflammatory processes are organized through complex signaling networks mediated by both endogenous metabolic products and exogenous stimuli.

Among the most extensively studied mediators of innate immunity are Toll-like receptors, a family of transmembrane pattern-recognition receptors expressed on immune cells such as monocytes, macrophages, and dendritic cells, as well as on renal parenchymal cells including podocytes, mesangial cells, and tubular epithelial cells. TLRs function as critical sensors of both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), enabling the immune system to detect sterile inflammation triggered by metabolic stress in diabetes.¹³⁻¹⁷

TLR2 and TLR4, in particular, have been consistently implicated in the pathogenesis of diabetic kidney disease. These receptors recognize endogenous ligands such as advanced glycation end products (AGEs), oxidized low-density lipoproteins, free fatty acids, heat-shock proteins, and high-mobility group box-1 (HMGB1), all of which are abundantly increased in the diabetic milieu. Engagement of these receptors activates intracellular signaling cascades involving nuclear factor-kappa B (NF- κ B) and mitogen-activated protein kinases (MAPKs), leading to transcription of pro-inflammatory genes and perpetuation of local and systemic inflammation.¹⁸⁻²²

Experimental studies have demonstrated that sustained hyperglycemia induces upregulation of TLR2 and TLR4 expression in renal tubular epithelial cells and circulating monocytes. This enhanced expression promotes the release of cytokines and chemokines that exacerbate oxidative stress, disrupt endothelial function, and accelerate renal fibrogenesis. Animal models of DN have shown that genetic deficiency or pharmacologic inhibition of TLR4 significantly reduces albuminuria, attenuates structural damage, and improves renal function, reinforcing the biological relevance of TLR signaling pathways in diabetic kidney injury.²³⁻²⁷

Clinical investigations have further validated these findings, demonstrating increased TLR2 and TLR4 expression in circulating monocytes of patients with diabetes, particularly in those with microvascular complications and renal impairment. Elevated TLR expression has been associated with increased inflammatory biomarkers, worsened glycemic control, and accelerated decline in estimated glomerular filtration rate (eGFR). Moreover, dialysis-dependent patients exhibit persistent TLR activation, likely attributable to uremic toxins, bioincompatible dialysis membranes, endotoxin exposure, and repetitive oxidative stress during extracorporeal circulation.²⁸⁻³³

In the context of hemodialysis, persistent immune activation constitutes a major contributor to systemic inflammatory syndrome, which has implications for vascular access dysfunction, cardiovascular morbidity, and post-transplant outcomes. This phenomenon is consistent with earlier reports highlighting chronic inflammation as a feature of advanced kidney disease, driven by uremia, oxidative stress, and metabolic dysregulation.^{30,32,33} Recent multicenter analyses similarly revealed that chronic innate immune activation in long-term dialysis patients shapes transplant readiness and post-transplant immunologic behavior.³⁴ Emerging evidence suggests that innate immune activation in dialysis patients may adversely impact graft survival and immune tolerance following renal transplantation, highlighting the relevance of TLR-mediated pathways beyond DN and into the realm of transplant immunology.³⁵⁻³⁹

Recent studies have also emphasized the potential prognostic utility of TLR2 and TLR4 as biomarkers for disease severity and progression in diabetic nephropathy. Their expression patterns may reflect cumulative inflammatory burden and serve as indicators for identifying patients at high risk of rapid progression to ESRD.⁴⁰⁻⁴³ Genetic studies also indicate that Toll-like receptor polymorphisms may influence susceptibility to ESRD progression in diabetic populations, supporting the contribution of innate immune variation to DN severity.⁴⁴ Furthermore, TLR-targeted therapies, including monoclonal antibodies and small-molecule inhibitors, are currently under investigation as novel therapeutic interventions to modulate excessive immune activation in diabetic renal disease.^{40-42,44-48}

Notably, evolving research up to 2025 has further supported the central role of innate immune dysregulation in DN, identifying the integration of metabolic stress and mitochondrial dysfunction with TLR signaling in promoting renal injury. These insights highlight the multidimensional nature of DN pathogenesis and reinforce the need for targeted immunomodulatory strategies.⁴⁹⁻⁵³ Recent 2025 translational data further demonstrate that mitochondrial stress amplifies innate immune signaling in ESRD, reinforcing its relevance as a driver of DN-related inflammation.³⁵

Our current study aims to evaluate the expression of TLR2 and TLR4 in patients with diabetic nephropathy undergoing hemodialysis and to compare these findings with non-diabetic ESRD patients and healthy controls. By delineating the relationship between TLR expression and dialysis duration, this research seeks to provide insight into the immune inflammatory landscape of DN and its implications on patient management, prognosis, and potential therapeutic targeting in the setting of chronic kidney disease and transplantation.

Patients and methods

This cross-sectional study included 90 participants recruited from Ahmed Maher Teaching Hospital. Participants were assigned to three equal groups:

Group I—hemodialysis patients without diabetic nephropathy; Group II hemodialysis patients with diabetic nephropathy; and Group III—apparently males healthy controls with matched age. All participants were ≥18 years of age.

Exclusion criteria were acute infection or recent hospitalization for infectious disease, active malignancy, autoimmune disease, or current therapy with statins or immunosuppressive agents. Controls females, proteinuria were excluded as per A/C ratio and fundus examination. Written informed consent was obtained from all participants, and the study adhered to the Declaration of Helsinki.⁵⁵

All participants underwent medical history, physical examination, and measurement of body mass index and blood pressure. Laboratory testing included fasting glucose, lipid profile, blood urea nitrogen, serum creatinine, glycated hemoglobin (HbA1c), and high-sensitivity C-reactive protein (hs-CRP) using standardized enzymatic colorimetric methods; estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation.

Peripheral venous blood (5 mL) was collected into EDTA tubes. Peripheral blood mononuclear cells were isolated by Ficoll density-gradient centrifugation. Total RNA was extracted using a silica-membrane spin-column procedure and reverse transcribed into cDNA. Quantitative real-time PCR (qPCR) was performed to determine TLR2 and TLR4 gene expression using SYBR Green chemistry on an Applied Biosystems platform. β-actin served as the endogenous control, and relative expression was calculated using the 2^{-ΔΔCt} method. All reactions were performed in duplicate with no-template controls in each run. Serum pro-inflammatory cytokines (TNF-α, IL-6) were quantified using commercially available ELISA kits following manufacturer instructions. Statistical analysis was performed using SPSS version 28 (IBM Corp., USA). Data distribution was assessed by the Kolmogorov–Smirnov test. Normally distributed variables are presented as mean ± SD and compared using one-way ANOVA with Tukey’s post-hoc test; non-normal variables were analyzed using the Kruskal–Wallis test with Dunn’s post-hoc comparisons. Categorical variables were compared by χ² or Fisher’s exact test. Correlations were evaluated by Pearson or Spearman coefficients as appropriate. A two-sided p value < 0.05 was considered statistically significant.

Ethical approval was obtained from the Institutional Review Board of Ahmed Maher Teaching Hospital; all procedures complied with institutional and international standards for human research.

Results

Study groups: Ninety participants were analyzed in three equal groups: hemodialysis without diabetic nephropathy (Group 1), hemodialysis with diabetic nephropathy (Group 2), and healthy controls (Group 3). Demographic features are summarized in Table 1; laboratory data are in Table 2. Group 3 comprised 30 male volunteers (35–50 years; mean ± SD 42.1 ± 4.8) with normal renal profile, normal fundus, and normal HbA1c.

Table 1 Demographic data of study groups

Variable	Group 1 (non-DM)	Group 2 (DM)	Control Group
Age (years)	50.8 ± 11.22	56 ± 10.9	42.1 ± 4.8
Sex (M/F)	17 / 13	17 / 13	30 / 0
Duration of hemodialysis (years)	5.4 ± 3.39	1.7 ± 1.6	—
Hypertension	73.30%	80%	0%
Ischemic heart disease	33.30%	20%	0%
Both HTN + IHD	13.30%	30%	0%

Table 2 Laboratory data of study groups

Lab Test	Group 1	Group 2	Control
Creatinine	11.08 ± 2.26	9.8 ± 2.6	1.08 ± 0.28
Urea	180 ± 39.6	168.7 ± 48.9	32.9 ± 5.9
HbA1c	4.6 ± 0.4	7.2 ± 0.7	3.45 ± 0.65
TLR2	0.28 ± 0.16	1.18 ± 0.54	0.15 ± 0.06
TLR4	0.5 ± 0.2	2.13 ± 0.9	0.4 ± 0.14

Demographics: Group 1 (non-DM HD) had mean age 50.8 ± 11.22 years; 17/13 male/female; hemodialysis duration 5.4 ± 3.39 years. Hypertension was present in 73.3%, ischemic heart disease (IHD) in 33.3%, and both in 13.3%. Group 2 (DN on HD) had mean age 56 ± 10.9 years; 17/13 male/female; hemodialysis duration 1.7 ± 1.6 years; hypertension in 80%, IHD in 20%, and both in 30%.

Laboratory findings: Mean creatinine/urea were highest in dialysis groups versus controls. HbA1c was ~4.6% in Group 1, ~7.2% in Group 2, and ~3.45% in controls. TLR2 and TLR4 expression were higher in Group 2 than Group 1 and controls; Group 1 exceeded controls for TLRs as well.

Group comparisons: Reported figures (Figures 1 & 2) indicate significantly higher TLR2 and TLR4 levels in end-stage diabetic nephropathy compared with non-diabetic HD and controls.

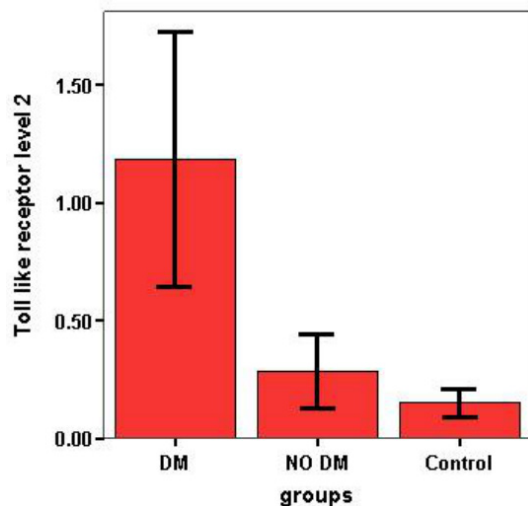


Figure 1 TLR-2 expression among study groups.

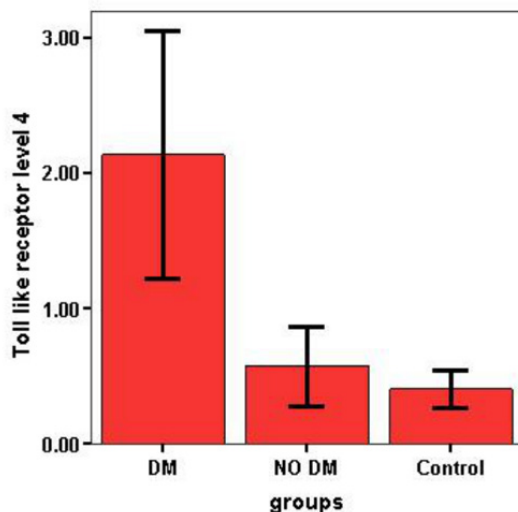


Figure 2 TLR-4 expression among study groups.

Correlations in Group 1 (non-DM HD): Hemodialysis duration correlated positively with TLR2 ($r = 0.661, p = 0.001$) and TLR4 ($r = 0.523, p = 0.003$), while other correlations (age, creatinine, urea, HbA1c) were not significant (Table 3).

Table 3 Correlations in group 1 (Non-DM)

Clinical/laboratory data	TLR2		TLR4	
	r	p	r	p
Age	-0.106	0.579	0.091	0.632
Duration of hemodialysis (years)	0.661	0.001	0.523	0.003
Cr	-0.335	0.071	-0.154	0.416
Urea	0.27	0.149	0.324	0.08
HbA1c	0.169	0.372	0.231	0.219

Correlations in Group 2 (DN on HD): Hemodialysis duration showed strong positive correlations with TLR2 ($r = 0.832, p = 0.001$) and TLR4 ($r = 0.712, p = 0.001$). Other correlations, including age, duration of diabetes, creatinine, urea, and HbA1c, were not statistically significant (Table 4).

Table 4 Correlations in group 2 (DM)

Clinical / laboratory data	TLR2		TLR4	
	r	p	r	p
Age	0.278	0.137	-0.299	0.108
Duration of DM	0.147	0.437	0.111	0.559
Duration of hemodialysis (years)	0.832	0.001	0.712	0.001
Cr	0.11	0.564	0.92	0.63
Urea	-0.062	0.746	0.022	0.906
HbA1c	0.326	0.078	0.261	0.163

Additional correlations: In Group 1, hemodialysis duration correlated weakly and non-significantly with age ($r = -0.152, p = 0.424$), creatinine ($r = 0.222, p = 0.238$), urea ($r = 0.215, p = 0.254$), and HbA1c ($r = 0.002, p = 0.991$).

Graphical correlations: TLR2 and TLR4 levels increased with longer hemodialysis duration, more pronounced in the diabetic nephropathy cohort compared with non-diabetic HD (Figures 3 & 4).

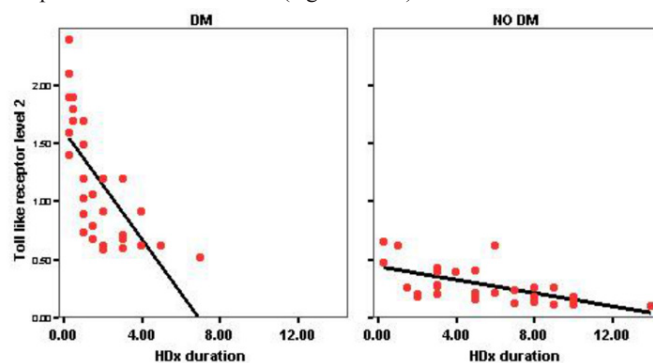


Figure 3 Correlation between TLR-2 levels and hemodialysis duration.

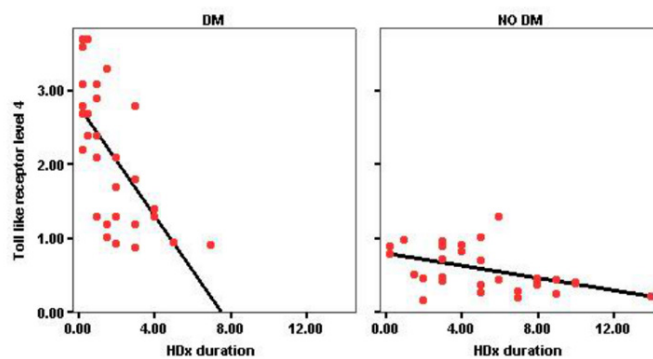


Figure 4 Correlation between TLR-4 levels and hemodialysis duration.

Discussion

The present study demonstrates markedly elevated TLR2 and TLR4 gene expression in hemodialysis patients with diabetic nephropathy compared with both non-diabetic hemodialysis patients and healthy controls. This gradient of expression reflects the increasing inflammatory burden associated with diabetes, renal injury, and dialysis exposure. The significantly higher expression in the diabetic nephropathy group parallels prior work showing that diabetic renal disease induces stronger innate immune activation than non-diabetic ESRD.

Aly et al.⁵⁶ similarly reported that diabetic patients with renal impairment exhibit significantly higher monocyte TLR2 and TLR4 expression compared with non-diabetic subjects, supporting our observation that diabetic nephropathy amplifies TLR-mediated inflammatory signaling. Their findings also highlighted the link between TLR activation and systemic inflammatory markers, in agreement with the elevated inflammatory status expected in our DN on HD group.

Badr et al.⁵⁷ demonstrated that TLR2 expression increases in type 2 diabetes and correlates with microvascular complications. This aligns with our results, where the DN group showed the highest expression of TLR2 and TLR4, consistent with more advanced microvascular and renal injury in diabetic nephropathy patients.

Our finding that non-diabetic hemodialysis patients also showed elevated TLR2 and TLR4—though lower than diabetic nephropathy—agrees with several studies indicating that the dialysis procedure itself contributes to chronic immune activation. Contact of blood with dialysis membranes, oxidative stress, endotoxin contamination, and the uremic milieu all activate TLR pathways even in the absence of diabetes. This explains why Group 1 (non-diabetic HD) demonstrated intermediate levels between DN patients and healthy controls.

Dialysis duration showed a strong positive correlation with TLR2 and TLR4 expression in both dialysis groups. This reinforces experimental evidence from Chen et al.³¹ and Pushpakumar et al.,⁵⁰ who reported that persistent exposure to inflammatory stimuli and oxidative stress drives progressive TLR upregulation. Our findings extend these observations to human dialysis populations, highlighting dialysis duration as an important determinant of innate immune activation.

Importantly, TLR2 and TLR4 levels did not correlate significantly with HbA1c, creatinine, urea, or diabetes duration in either dialysis group. This indicates that TLR expression reflects inflammatory burden rather than glycemic control or renal clearance parameters. Similar observations were noted in prior studies,^{10,23,31,40} suggesting that TLR activation is driven by tissue stress and sterile inflammation rather than metabolic indices alone.

Overall, our results reinforce the concept that diabetic nephropathy confers an amplified innate immune inflammatory phenotype, which persists even after progression to end-stage renal disease and is further intensified by chronic dialysis exposure. These findings correspond closely with multiple clinical studies^{50,56-59} highlighting the central role of TLR-mediated inflammation in the pathogenesis and progression of diabetic renal injury. The elevated TLR2 and TLR4 expression observed in our DN on HD cohort may therefore serve as a potential biomarker of heightened inflammatory status and could represent a future therapeutic target in diabetic ESRD. To note, it was observed that women generally exhibit high level of expression of Toll like receptors due to stronger innate immunity, as reported by Klein et al.⁵⁴ We preferred not to include female healthy control group to avoid the false high results of Toll like receptors expression.

Conclusion

This study demonstrates significantly elevated TLR2 and TLR4 gene expression in hemodialysis patients with diabetic nephropathy compared with both non-diabetic hemodialysis patients and healthy controls, highlighting the

amplified innate immune activation associated with diabetic renal disease. The strong positive correlation between dialysis duration and TLR expression in both dialysis groups reinforces the contribution of chronic dialysis-related inflammation to immune dysregulation. These findings support the role of TLR-mediated pathways in the progression of diabetic nephropathy and suggest their potential utility as biomarkers of inflammatory burden and future therapeutic targets in advanced kidney disease.

Acknowledgements

None

Conflicts of interest

The authors of this article confirmed the absence conflict of interests, financial or any other support which should be reported.

Funding

None.

References

1. Zhang H, Wang K, Zhao H, et al. Diabetic kidney disease: from pathogenesis to multimodal therapy—current evidence and future directions. *Front Med (Lausanne)*. 2025;12:1631053.
2. Wajchenberg BL, Sabbaga E, Fonseca JA. The natural history of diabetic nephropathy in type I diabetes and the role of metabolic control in its prevention, reversibility and clinical course. *Acta Diabetol Lat*. 1983;20(1):1–18.
3. Zhao L, Yuan J, Yang Q, et al. Diabetes and its complications: molecular mechanisms, prevention and treatment. *Signal Transduct Target Ther*. 2026;11:22.
4. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. *JAMA*. 2016;316(6):602–610.
5. Xue R, Gui D, Zheng L, et al. Mechanistic insight and management of diabetic nephropathy: recent progress and future perspective. *J Diabetes Res*. 2017;2017:1839809.
6. Lin M, Yiu WH, Wu HJ, et al. Toll-like receptor 4 promotes tubular inflammation in diabetic nephropathy. *J Am Soc Nephrol*. 2012;23(1):86–102.
7. Tesch GH. Diabetic nephropathy—is this an immune disorder? *Clin Sci (Lond)*. 2017;131(16):2183–2199.
8. Lim AK. Diabetic nephropathy—complications and treatment. *Int J Nephrol Renovasc Dis*. 2014;7:361–381.
9. Kanwar YS, Sun L, Xie P, et al. A glimpse of various pathogenetic mechanisms of diabetic nephropathy. *Annu Rev Pathol*. 2011;6:395–423.
10. Tang SCW, Yiu WH. Innate immunity in diabetic kidney disease. *Nat Rev Nephrol*. 2020;16(4):206–222.
11. Donate-Correa J, Ferri CM, Sánchez-Quintana F, et al. Inflammatory cytokines in diabetic kidney disease: pathophysiologic and therapeutic implications. *Front Med (Lausanne)*. 2021;7:628289.
12. Low S, Lim SC, Wang J, et al. Long-term outcomes of patients with type 2 diabetes attending a multidisciplinary diabetes kidney disease clinic. *J Diabetes*. 2018;10(7):572–580.
13. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol*. 2010;11(5):373–384.
14. Akira S, Takeda K. Toll-like receptor signalling. *Nat Rev Immunol*. 2004;4(7):499–511.

15. Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008;454(7203):428–435.
16. Ma L, Liu D, Yu Y, Li Z, Wang Q. Immune-mediated renal injury in diabetic kidney disease: from mechanisms to therapy. *Front Immunol*. 2025;16:1587806.
17. Mudaliar H, Pollock C, Komala MG, et al. The role of Toll-like receptor proteins 2 and 4 in mediating inflammation in proximal tubules. *Am J Physiol Renal Physiol*. 2013;305(2):F143–F154.
18. Dasu MR, Devaraj S, Zhao L, et al. High glucose induces toll-like receptor expression in human monocytes: mechanism of activation. *Diabetes*. 2008;57(11):3090–3098.
19. Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. *Cardiovasc Ther*. 2012;30(1):49–59.
20. Gluba A, Banach M, Hannam S, et al. The role of Toll-like receptors in renal diseases. *Nat Rev Nephrol*. 2010;6(4):224–235. doi:10.1038/nrneph.2010.16
21. McKenzie AI, Reidy PT, Nelson DS, et al. Pharmacological inhibition of TLR4 ameliorates muscle and liver ceramide content after disuse in previously physically active mice. *Am J Physiol Regul Integr Comp Physiol*. 2020;318(3):R503–R511.
22. Sattarinezhad A, Roozbeh J, Shirazi Yeganeh B, et al. Resveratrol reduces albuminuria in diabetic nephropathy: a randomized double-blind placebo-controlled clinical trial. *Diabetes Metab*. 2019;45(1):53–59.
23. Habib R. Multifaceted roles of Toll-like receptors in acute kidney injury. *Heliyon*. 2021;7(3):e06441.
24. Jialal I, Major AM, Devaraj S. Global toll-like receptor 4 knockout results in decreased renal inflammation, fibrosis and podocytopathy. *J Diabetes Complications*. 2014;28(6):755–761.
25. Cohen G. Immune dysfunction in uremia 2020. *Toxins (Basel)*. 2020;12(7):439.
26. Zimmermann J, Herrlinger S, Pruy A, et al. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int*. 1999;55(2):648–658.
27. Stenvinkel P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. *J Intern Med*. 2010;268(5):456–467.
28. Ramírez-Sánchez S, Soriano-Munuera MJ, Gras-Colomer E, et al. Activation and disease control of patients on chronic hemodialysis: an observational study. *Nefrologia*. 2024;44(3):423–430.
29. Nowak KL, Chonchol M. Does inflammation affect outcomes in dialysis patients? *Semin Dial*. 2018;31(4):388–397.
30. Sela S, Shurtz-Swirski R, Shapiro G, et al. Oxidative stress during hemodialysis: effect of heparin. *Kidney Int Suppl*. 2001;78:S159–S163.
31. Niu D, Chen R, Pang X. Immune landscape in kidney transplantation. *J Inflamm Res*. 2025;18:15237–15256.
32. Chen J, Zhou Q, Su L, et al. Mitochondrial dysfunction: the hidden catalyst in chronic kidney disease progression. *Ren Fail*. 2025;47(1):2506812.
33. do Sameiro Faria M, Ribeiro S, Rocha-Pereira P, et al. Vascular access versus the effect of statins on inflammation and fibrinolysis in renal dialysis patients. *J Vasc Access*. 2013;14(4):335–341.
34. Braza F, Brouard S, Chadban S, et al. Role of TLRs and DAMPs in allograft inflammation and transplant outcomes. *Nat Rev Nephrol*. 2016;12(5):281–290.
35. Deng JF, Geng L, Qian YG, et al. The role of toll-like receptors 2 and 4 in acute allograft rejection after liver transplantation. *Transplant Proc*. 2007;39(10):3222–3224.
36. Alegre ML, Chong A. Toll-like receptors in transplantation. *Front Biosci (Elite Ed)*. 2009;1(1):36–43.
37. Hojs R, Ekart R, Bevc S, et al. Biomarkers of renal disease and progression in patients with diabetes. *J Clin Med*. 2015;4(5):1010–1024.
38. Root-Bernstein R. Innate receptor activation patterns involving TLR and NLR synergisms in COVID-19, ALI/ARDS and sepsis cytokine storms. *Int J Mol Sci*. 2021;22(4):2108.
39. Zou LX, Hou ZL, Qian CH, et al. Performance of novel biomarkers for prediction of diabetic kidney disease in patients with diabetes mellitus. *Ann Med*. 2025;57(1):2562996.
40. Yang HY, Huang SM, Lu KC, et al. A functional polymorphism in the promoter region of TLR3 is associated with susceptibility to end-stage renal disease. *Am J Nephrol*. 2014;40(2):131–139.
41. Musumeci D, Roviello GN, Montesarchio D. An overview on HMGB1 inhibitors as potential therapeutic agents. *Pharmacol Ther*. 2014;141(3):347–357.
42. Donate-Correa J, Luis-Rodríguez D, Martín-Núñez E, et al. Inflammatory targets in diabetic nephropathy. *J Clin Med*. 2020;9(2):458.
43. Zhang C, Yang Y. Targeting toll-like receptor 4 and the NLRP3 inflammasome. *Biomol Biomed*. 2023;24(4):688–697.
44. Hou G, Dong Y, Jiang Y, et al. Immune inflammation and metabolic interactions in diabetic nephropathy. *Front Endocrinol (Lausanne)*. 2025;16:1602594.
45. Huang G, Zhang Y, Zhang Y, et al. Chronic kidney disease and NLRP3 inflammasome. *Biochem Biophys Rep*. 2022;33:101417.
46. Ward GA, Dalton RP 3rd, Meyer BS, et al. Oxidized mitochondrial DNA engages TLR9 to activate the NLRP3 inflammasome. *Int J Mol Sci*. 2023;24(4):3896.
47. Elbehiry A, Marzouk E, Alhumaydhi FA, et al. Diabetes mellitus as an integrated microbiome, immune, and metabolic disorder. *J Clin Med*. 2026;15(5):1788.
48. Lee TH, Chen JJ, Wu CY, et al. Immunosenescence, gut dysbiosis, and chronic kidney disease. *Biomed J*. 2024;47(2):100638.
49. Pethő ÁG, Fülöp T, Orosz P, et al. Increased cardiovascular mortality in hemodialysis. *Toxins (Basel)*. 2025;17(7):345.
50. Pushpakumar S, Ren L, Kundu S, et al. Toll-like receptor 4 deficiency reduces oxidative stress and macrophage mediated inflammation in hypertensive kidney. *Sci Rep*. 2017;7:6349.
51. Pichler R, Afkarian M, Dieter BP, et al. Immunity and inflammation in diabetic kidney disease. *Am J Physiol Renal Physiol*. 2017;312(4):F716–F731.
52. Yang M, Zhang C. The role of innate immunity in diabetic nephropathy. *J Pharm Anal*. 2024;14(1):39–51.
53. Garibotto G, Carta A, Picciotto D, et al. Toll-like receptor-4 signaling mediates inflammation. *J Nephrol*. 2017;30(6):719–727.
54. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16(10):626–638.
55. World Medical Association. World Medical Association Declaration of Helsinki. *JAMA*. 2013;310(20):2191–2194.
56. Aly RH, Ahmed AE, Hozayen WG, et al. Patterns of toll-like receptor expressions. *Front Physiol*. 2020;11:609223.
57. Badr RE, Salama MI, Abd-Elmaogood AK, et al. Toll-like receptor 2 expression. *Diabetes Metab Syndr*. 2019;13(2):1299–1302.
58. Peng R, Zuo S, Li X, et al. HMGB1 as a potential biomarker for early diabetic nephropathy. *iScience*. 2024;27(2):108834.
59. Root-Bernstein R. Innate receptor activation patterns. *Int J Mol Sci*. 2021;22(4):2108.