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Editorial

Need for Early Diagnosis of Diabetic Nephropathy: From Silent Beginnings to Therapeutic Opportunity

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Diabetes mellitus has emerged as one of the most formidable global health challenges of the 21st century, affecting over 500 million adults worldwide, with projections suggesting that this number may exceed 850 million by 2050 [1]. Diabetes imposes a significant metabolic burden and serves as a precursor to a wide spectrum of chronic complications affecting nearly every organ system, including retinopathy, neuropathy, cardiovascular disease, and nephropathy [2]. Among these, diabetic kidney disease (DKD), also known as diabetic nephropathy (DN), stands out as the most serious and life-limiting complication, accounting for up to 40% of people living with diabetes being affected by chronic kidney disease (CKD) globally [1,2]. DKD is poised to become an even greater contributor to the global CKD burden as the prevalence of diabetes continues to rise, challenging both developed and developing healthcare systems in the coming decades [1].

Diabetic nephropathy remains the prototypical microvascular complication of diabetes and one of the foremost causes of CKD and end-stage renal disease (ESRD) globally [2]. The first descriptions of renal changes in diabetes date back to the mid-20th century, when clinicians correlated proteinuria in long-standing diabetic patients with progressive renal failure. Landmark work by Mogensen and colleagues subsequently identified microalbuminuria as an early harbinger of overt nephropathy, revolutionizing the paradigm of DN monitoring and prevention [3]. In classical teaching, DN is conceptualized as a progressive sequence from glomerular hyperfiltration to microalbuminuria, overt proteinuria, declining glomerular filtration, and ultimately ESRD [3,4]. However, growing evidence indicates that structural and molecular injury may precede measurable albuminuria, and that some patients progress without the canonical microalbuminuric stage [4,5]. Despite decades of research, DN continues to impose a heavy toll on patients and health systems, largely because it is often detected only after irreversible nephron loss has occurred [2,5].

In the earliest or "silent" phase, glomeruli undergo adaptive changes in response to chronic hyperglycemia, hypertension, and metabolic stress, including glomerular basement membrane thickening, mesangial expansion, and podocyte stress or detachment [5]. Tubular epithelial cells also sustain subclinical injury due to glucose toxicity, oxidative stress, and local inflammation [5]. These changes, though initially compensatory, can evolve into irreversible injury if the metabolic and hemodynamic insults persist. Histologic studies have shown that even normoalbuminuric diabetic kidneys may harbour early mesangial expansion and nodular lesions [5]. Over time, the compensatory reserve is overwhelmed, and microalbuminuria develops as glomerular.

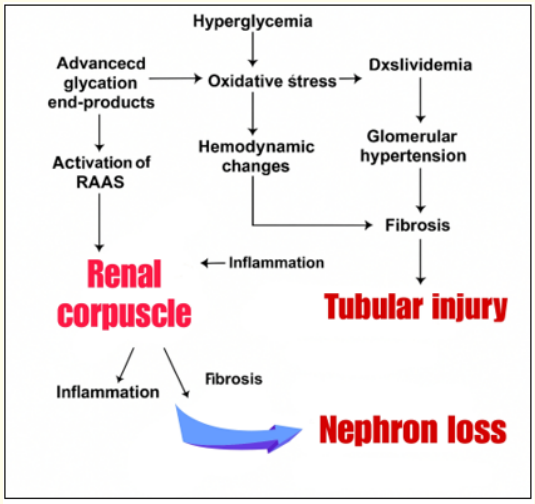

Figure 1: Schematic representation of the pathophysiology of diabetic nephropathy, emphasizing hyperglycemia-induced oxidative stress, RAAS activation, inflammation, and progressive nephron loss. (Figure generated with illustration tool BioRender: Scientific Image and Illustration Software for conceptual representation).

permeability increases, with urinary albumin excretion rising to 30–300 mg/day [3]. This stage marks the first detectable clinical indicator of DN, though structural injury is already well established [3,5]. Some patients remain stable or revert with proper control, while others progress toward overt proteinuria, GFR decline, and worsening hypertension. Without timely diagnosis, progression continues silently until late stages, when symptoms such as fatigue, edema, electrolyte imbalance, and uremic manifestations emerge, marking the "point of no return" where damage becomes largely irreversible [5]. Notably, recent work has demonstrated that excreted albumin of diabetic microalbuminuria cases exhibits pseudo-esterase activity, suggesting an early structural/functional change not captured by conventional immunoassays [6].

The current diagnostic standards—albuminuria testing, serum creatinine, and eGFR—have been invaluable but possess important limitations [7]. Spot urine albumin-to-creatinine ratio remains the most widely used test, yet conventional immunoassays detect only immunoreactive albumin, overlooking modified or immunounreactive albumin species that may indicate early renal leakage [7]. Similarly, eGFR based on serum creatinine lacks sensitivity in early DN since creatinine only rises after significant nephron loss, and initial hyperfiltration can mask underlying damage [8]. Even microalbuminuria, though useful, is a functional marker rather than a truly preclinical one [3,7]. Urinary albumin excretion is variable, influenced by posture, infection, or exercise, and non-albuminuric DN phenotypes—characterized by GFR decline without albuminuria—further challenge reliance on a single marker [9,10].

To overcome these diagnostic gaps, research has expanded toward novel biomarkers reflecting glomerular, tubular, inflammatory, and oxidative pathways [5,7]. Tubular injury markers such as NGAL, NAG, cystatin C, L-FABP, and KIM-1 often rise earlier than albuminuria, indicating subclinical tubular stress [5]. Glomerular and podocyte-derived proteins including type IV collagen, nephrin, podocin, podocalyxin, transferrin, and ceruloplasmin serve as early indicators of structural injury [5]. Novel molecules like SMAD1, netrin-1, osteopontin, complement factors, and cytokines are also emerging as sensitive indicators of early DN [5,7]. Inflammatory and oxidative markers such as TNF-α, MCP-1, IL-6, and advanced glycation end-products, as well as metabolomic and microRNA signatures, are under investigation for predictive use [7]. Because no single biomarker is sufficient, composite multi-marker panels combining glomerular, tubular, and inflammatory markers are being explored [7]. Multi-omics and machine-learning models integrating proteomic, transcriptomic, and metabolomic data show promise, achieving high predictive accuracy in preliminary studies [7]. Complementing this, early reviews have emphasised the need for innovation in microalbuminuria detection at point-of-care, particularly given the limitations of current immunochemical and dye-binding assays [11]. However, translation to routine practice remains constrained by the need for standardisation, cost-effective platforms, and large-scale validation [7].

The rationale for early diagnosis extends beyond academic interest—it defines a therapeutic window when interventions can still alter the course of disease [2,7]. Studies have shown that early initiation of renoprotective therapies such as RAAS blockade and SGLT-2 inhibitors can reduce albuminuria, improve renal hemodynamics, and delay progression [7,8]. SGLT-2 inhibitors, in particular, confer renal benefits beyond glycaemic control, including reduced intraglomerular pressure, improved tubuloglomerular feedback, and attenuation of oxidative stress and inflammation [7,8]. Meta-analyses of major outcome trials demonstrate that SGLT-2 inhibitors significantly lower risks of kidney disease progression

and cardiovascular events, with benefits even in non-albuminuric individuals [7,8]. Mechanistic studies further reveal their potential to enhance podocyte autophagy and reduce apoptosis [8]. These findings underscore that when initiated during early or even pre-microalbuminuric stages, such interventions can stabilise or reverse renal injury [8].

Figure 2: Schematic representation of the pathophysiology of diabetic nephropathy, emphasizing Therapeutic Strategies, figure provides a conceptual overview of the key drivers and treatment options for diabetic Kidney disease (DKD).

The clinical, economic, and public health implications of early DN detection are profound [1,2,7]. Timely diagnosis can delay ESRD onset, reduce dialysis and transplant burden, mitigate cardiovascular risk, and improve quality of life [2,7]. From a health economics perspective, identifying high-risk individuals allows targeted interventions and more efficient use of healthcare resources [2,7]. Yet several challenges persist—standardisation and availability of biomarker assays, validation in diverse populations, and development of affordable, point-of-care platforms [7]. Translating promising molecular findings into practical diagnostics requires coordinated efforts between clinicians, researchers, and industry [7].

Future directions should prioritize large-scale prospective cohorts with biomarker sampling from normoalbuminuric diabetics, standardisation of emerging assays, and clinical trials testing early interventions in biomarker-positive but albuminuria-negative patients [5,7]. Development of cost-effective multiplex diagnostic tools and integration of biomarker data into predictive AI-based risk models are equally essential [7]. Importantly, understanding and detecting immunounreactive albumin remains an under-explored but crucial area, potentially bridging the gap between structural injury and current detection limits [7].

Diabetic nephropathy remains a silent yet relentless adversary [2]. In the absence of early diagnosis, patients transition from invisible renal injury to overt, irreversible disease, often presenting only when therapeutic options are limited [2,5,7]. Microalbuminuria, while invaluable historically, is no longer sufficient as a standalone sentinel marker—especially in the context of immunoreactive albumin and non-albuminuric phenotypes [9,10]. The advent of molecular biomarkers and multi-omics tools now offers a genuine opportunity to detect DKD at its inception [5,7]. Early diagnosis is therefore not merely desirable; it is imperative [7,8]. Detecting DKD at its earliest molecular stage enables timely, potentially reversible interventions that can change the disease trajectory [8]. The nephrology, diabetology, and biomarker research communities must now move collectively toward proactive renal preservation—through prospective validation, assay standardisation, point-of-care innovation, and integration of predictive models [7,8]. The future of DKD care depends on our capacity to detect the disease before it becomes irreversible; early diagnosis must be embraced as the next frontier in diabetic kidney disease management [7,8].

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Bibliography

1. International Diabetes Federation. "IDF Diabetes Atlas". 11th ed. Brussels: International Diabetes Federation; (2025).

2. Thomas MC., *et al*. "Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease". *Nature Reviews Nephrology* 12.2 (2016): 73-81.

3. Mogensen CE. "Management of early nephropathy in diabetic patients". *Annual Review of Medicine* 46 (1995): 79-93.

4. Looker HC., *et al*. "Changes in Albuminuria But Not GFR are Associated with Early Changes in Kidney Structure in Type 2 Diabetes". *Journal of the American Society of Nephrology* 30.6 (2019): 1049-1059.

5. Liu H., *et al*. "Early renal structural changes and potential biomarkers in diabetic nephropathy". *Frontiers in Physiology* 13 (2022): 1020443.

6. Kumar D., *et al*. "Excreted albumin of diabetic microalbuminuria cases exhibits pseudo esterase activity: A new way to explore microalbuminuria, perhaps with more information". *Clinical Chim Acta* 565 (2025): 119947.

7. Magee GM., *et al*. "Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis". *Diabetologia* 52.4 (2009): 691-697.

8. Heerspink HJL., *et al*. "Dapagliflozin in Patients with Chronic Kidney Disease". T*he New England Journal of Medicine* 383.15 (2020): 1436-1446.

9. Kim JH., *et al*. "Addition of nonalbumin proteinuria to albuminuria improves prediction of type 2 diabetic nephropathy progression". *Diabetology and Metabolic Syndrome* 9 (2017): 68.

10. Leong A., *et al*. "Long-term intra-individual variability of albuminuria in type 2 diabetes mellitus: implications for categorization of albumin excretion rate". *BMC Nephrology* 18.1 (2017): 355.

11. Kumari M., *et al*. "Microalbuminurea detection: the future challenges". *Acta Scientific Medical Sciences* 3.8 (2019): 1.