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The Diagnostic Biomarkers for Early Detection the Prevalence of Diabetic Nephropathy in Type 2 Diabetic Mellitus Patients: Systematic Review

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ABSTRACT
Diabetic nephropathy (DN) is one of the most prevalent diabetic microvascular complications, and it is the prime cause of renal failure with its consequences of hemodialysis, renal transplantation, and finally death. Microalbuminuria diagnostic usefulness in early-stage diabetic nephropathy is limited, because renal damage frequently comes before proteinuria. As a result, there is need for more sensitive and specific biomarkers for the early detection and prevent development of DN. This systematic review aims to evaluate the diagnostic value of various biomarkers in the early prediction of DN in patients with type 2 diabetes mellitus (T2DM). A comprehensive literature search was conducted using databases such as PubMed, Scopus, and Web of Science. We only considered studies involving human populations for inclusion in our analysis. Animal and *in vitro* studies were excluded from this review. Our analysis of 14 observational studies identified several biomarkers, like Nephrin, Wnt/beta-catenin proteins, Monocyte chemoattractant protein-1(MCP-1), and Transforming growth factor-β (TGF-β), which show significant promise for early detection of DN. Implementing these biomarkers in clinical practice could significantly improve outcomes for patients with DN by facilitating early diagnosis and timely management.
Keywords: Diabetes mellitus type 2, Diabetic Nephropathy, Nephrin, Monocyte chemoattractant protein-1, Transforming growth factor-Beta, Wnt/beta catenin

INTRODUCTION

Diabetes mellitus (DM), is a complex and heterogenous group of chronic metabolic diseases that are characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the kidneys **(1).** Type1 diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin to control blood sugar levels **(2)** .Type 2 diabetes, is a metabolic disorder that is characterized by high blood glucose due to insulin resistance in the target tissues coupled with pancreatic cell dysfunction and is the major form of DM, accounting for 90-95% of all cases of DM **(3)**. Diabetes remains the main form and the cause for the renal disease **(4).**

Diabetic nephropathy (DN) is one of the major micovascular complications that is the most common cause of end-stage renal disease (ESRD). DN is also known as diabetic kidney disease (DKD), which is distinguished by an increase in urine albumin excretion (microalbuminuria) and/or a decreased estimated glomerular filtration rate (eGFR) or both. As it is estimated that up to 25% of newly diagnosed patients with T2DM have already developed one or more complications of DM **(5)**.

Microalbuminuria is used as the gold standard for early detection of DN. Its can defined by two ways: either by measuring urinary albumin excretion rate (UAE), between 30-300 mg/24 hours, or as an albumin/ creatinine ratio (ACR)

of 30-300 mg /g, or by excretion of 20–200 mg/l of albumin in the spot urine samples **(6, 7)**.

The molecular pathophysiology of DN include complex interactions between hyperglycemia-induced metabolic, hemodynamic and inflammatory factors. These factors alter the function and morphology of blood vessel walls and interact with adjacent cells leading to renal endothelial dysfunction, which plays a crucial role in the development of DN. Early changes in DN include increases in kidney size, glomerular volume and GFR, followed by the accumulation of glomerular extracellular matrix, increased urinary albumin excretion, glomerular sclerosis and tubular fibrosis **(8, 9).** Currently, no biomarkers are available can predict whether individuals with T2DM will develop severe kidney disease. Consequently, additional laboratory biomarkers are needed for early DN diagnosis, before the onset of microalbuminuria. Recent research has identified several novel and significant biomarkers that can predict DN earlier and with greater specificity. These biomarkers reflect kidney injury as a result of oxidative stress, glomerular and tubular damage, renal inflammation **(10, 11).**

Nephrin, a 180-KD trans-membrane protein that has been found as an essential biomarker for predicting diabetic kidney disease and the severity of podocyte injury. Nephrin is necessary for the proper functioning of the renal filtration barrier which forms the main component of slit diaphragm. Decrease in nephrin expression has been suggested to podocyte loss and linked to the progression of kidney disease **(12).** Several studies showed that nephrinuria was associated with higher urine albumin concentrations and diabetes status, thus; given that hyperglycemia is likely to cause damage to renal vasculature and glomerular filtration barrier over time **(13).**

Monocyte Chemotactic Protein-1 (MCP-1) also known as Chemokine Ligand2 (CCL2) has been reported to interact with several CC chemokine receptors **(14)**. **MCP-1,** is produced by mesangial cells, podocytes, tubular epithelial cell and monocytes in response to various proinflammatory stimuli. During inflammation, MCP-1 promote recruitment of inflammatory cells such as monocytes/macrophages into the kidney via interaction with its cell surface receptor **(15).** MCP-1, play a major role in the progression of renal inflammatory diseases, which recruits and activates inflammatory cells and activated macrophage to secrete factors such as transforming growth factor- beta **(15).**

Transforming growth factor–beta (TGF-β), Is secreted protein that perform many cellular functions including the control of cell growth, cell proliferation, and apoptosis. TGF-β, is protein that function to modulate or regulate extracellular matrix production and also stimulate glomerular mesangial and epithelial cells to produce extracellular matrix proteins. TGF-β, is one of the growth factors which are implicated in diabetic nephropathy pathogenesis, which cause mesangial extension by promoting glomerular mesangial hypertrophy and by inducing the extracellular matrix expansion **(16).**

Wnt /beta catenin, are a large family of secreted glycoproteins that play a central role in embryonic development , differentiation, cell motility, and cell proliferation **(17)**. Wnt signaling pathways work in a combinatorial with other pathways, including transforming growth factor-β pathways. Alterations in Wnt/ β- catenin signaling is involved in congenital defects of the kidney and urinary tract, renal carcinoma, obstructive nephropathy,chronic allograft nephropathy diabetic nephropathy **(18).** When there is decrease in the secretion of Wnt proteins leads to decreased translocation of β-catenin to nucleus. The down-regulation of Wnt/β-catenin signaling leads to detrimental effects on kidney including increased apoptosis of mesangial cells and increased deposition of fibrous tissue in mesangium. On the other hand, it is documented that diabetes leads to overactivation of Wnt1/β-catenin signaling, which promotes podocyte injury and deposition of extracellular matrix in mesengium, which is the hallmarks of DN **(19)**

Materials and Methods

This systematic review was planned according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines **(20)**. All the steps including searching, selection of final included papers, and quality assessment of articles were performed by authors independently, and any discrepancies were resolved through discussion or consultation with a third reviewer.

Search strategy

We conducted a literature review using PubMed, Google Scholar, and Web of Science to see if the biomarkers could

detect early DN detection more effectively. The following keywords were searched individually or in conjunction with others: “diabetic nephropathy”, “Advanced biomarkers”, “inflammation”, “serum”, “plasma”, and “diagnostic” in the title, keywords, and abstract. The search terms were connected by ‘AND’ and ‘OR’ Boolean operators.

Inclusion and exclusion criteria

We included cross-sectional, cohort, and case-control studies published in English from 2013 to 2024. These studies involved adult participants (aged 18 years and older) diagnosed with T2DM. Additionally, we ensured that the studies provided sufficient data on diagnostic performance and met quality appraisal standards. Studies with nonrelated topics or nonsufficient reported data, reviews, abstracts, and articles that were not in English were excluded. We only considered studies involving human populations for inclusion in our analysis. Animal and in vitro studies were excluded from our review.

Study selection

The articles that were found were exported to EndNote Reference Manager X7, and subsequently, duplicates were removed. Based on the eligibility criteria, two independent reviewers screened the articles by title and abstract, followed by full-text screening. During the study selection process, disagreements were resolved through consensus from the third reviewer.

Data extraction

The data from the selected studies were extracted based on a prespecified data extraction form, which included the following data variables: first author, year of publication, country of study, study design, study population (T2DM patients), details on the type of biomarkers (urinary or serum), results,.

Outcome measurements

Diabetic nephropathy is defined as a derangement in renal function with an estimated GFR <60 ml/min/1.73 m3, and kidney damage by estimation of albuminuria >30 mg/dl **(21).**

Results

The initial database search yielded a total of 555 articles. Figure 1, illustrates the comprehensive study selection process. After removing duplicates and screening titles and abstracts, 14 studies were ultimately included based on our inclusion criteria. Since all the included studies were observational, their methodological quality was assessed by the nine-star Newcastle Ottawa Scale (NOS), which consists of three major aspects: selection, comparability, and exposure or outcome. Table 1 includes characteristics and outcomes extracted from included studies.

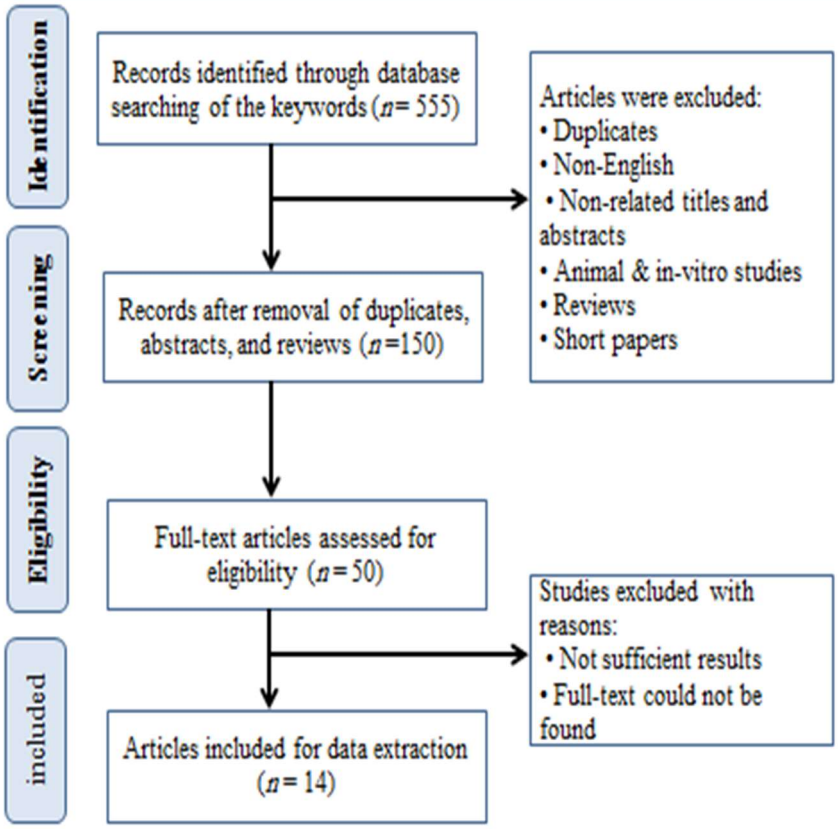

Figure 1: Flowchart of study selection

Discussion

DN remains a significant complication of diabetes mellitus and is a leading cause of the end-stage renal disease, and early detection is crucial for preventing progression to end-stage renal disease. Various studies have investigated advanced biomarkers to identify early indicators of DN across different populations and geographical regions. This systematic review explored a comparison between the routinely biomarkers and advanced biomarkers in the early detection of renal damage, associated with DN in T2DM. We gathered 14 articles that looked at the efficacy of biomarkers in the human population [Table 1]. Characteristics of these biomarkers that involved in the systematic review [Table 2].

The collected data from these 14 studies illustrate the potential of various biomarkers for diagnosing DN at different stages of its progression. Early markers such as nephrin, MCP-1, TGF-β and wnt/beta catenin protein are crucial for early intervention. The integration of these biomarkers into clinical practice could greatly enhance the ability to detect DN early, allowing for timely and targeted management strategies.

Table 1: Extracted data and summary of the results in the systematic review.

Study/Year/ Country	Study type	Population	Biomarkers	Results/ Conclusions
(Aljorani *et al.*, 2023)/ Iraq (22)	Cross-sectional	100 patients with T2DM&DN Normoalbuminuria (n=50) Microalbuminuria (n=50)	Nephrin	Nephrin is specific and sensitive indicators of early-stage diabetic nephropathy-associated renal damage.
(Ganesh et al.,2022)/	Case-Control	140 patients with T2DM&DN Normoalbuminuria (n=40)	Nephrin, UACR	urinary nephrin elevated in T2DM patients with Normoalbuminuria than urinary

India (23)		Microalbuminuria (n=40) 40 healthy subjects as control		albuminuria.
(Kostovska et al.,2020)/Macedonia (24)	Cross-sectional	90 patients with T2DM&DN Normoalbuminuria (n=56) Microalbuminuria (n=25) Macroalbuminuria (n=9) 30 healthy subjects as control	Urinary nephrin, urinary ACR	Urinary nephrin is earlier, more specific and sensitive marker than microalbumin in early detection of DN.
(Rangaswamaiah *et al.,*2022)/India (25)	Case-control	60 patients with T2DM&DN Normoalbuminuria (n=30) Microalbuminuria (n=30) 30 healthy subjects as control	Nephrin, Microalbumin	urinary nephrin significantly elevated in normo albuminuria only when compared to urinary ACR and it is positive association with kidney damage.
(Haddad and Albrahimi,2023)/ Iraq (26)	Case-control	50patients with T2DM 50 patients with DN 30 healthy subjects as control	TGF-β1	There was a significant difference between serum TGF-β1 in diabetic patients with nephropathy, diabetic patients without nephropathy and controls.
(Abbas *et al.*, 2022)/ Iraq (10)	Case-control	60 patients with T2DM&DN Normoalbuminuria (n=20) Microalbuminuria (n=20) Macroalbuminuria (n=20) 60 healthy subjects as control	TGF-β	Increased levels of TGF-β play a role in pathogenesis of diabetic nephropathy
(Duaibel *et al.,* 2022)/ Iraq (27)	Case-control	150 patients with T2DM&DN Mild nephropathy (n=50) Moderate nephropathy (n=50) Severe nephropathy (n=50) 150 healthy subjects as control	MCP-1	MCP-1 biomarkers is highly related to the degree of proteinuria in diabetic patients
(Scurt et al.,2022)/Germany (28)	Case-control	360 patients with T2DM &DN Microalbuminuria (n= 172) Normoalbuminuria (n= 188)	Serum and Urine MCP-1	MCP-1 is a marker and possibly a mediator of early diabetic nephropathy.
(Mahmoud *et al.,*2021)/ Egypt (29)	Case-control	54 patients with T2DM 27 healthy subjects as control	MCP-1.	MCP-1 level is increased in type 2 Diabetic patients and significantly increased with the progression of diabetes complications
(Shaker and Sadik 2013)/ Egypt (30)	Cross-sectional	60 patients with T2DM Normoalbuminuria(n=20) Microalbuminuria(n=20) Macroalbuminuria (n=20) 20 healthy subjects as control	MCP-1, TGF- β	TGF-β and MCP-1 can be used as the markers for detection of progression of DN.
(Klimontove *et al.,* 2018)/ Russia (31)	Cross-sectional	156 patients with T2 DM 24 healthy subjects as control	Wnt protein	Higher Wnt level in patients with diabetes, and the higher plasma concentration of WISP1 is associated with insulin resistance
(Paez *et al.,* 2020)/Mexico (32)	Cross-sectional	80 patients with chronic kidney disease	Wnt protein	There were negative correlations between serum Wnt5a concentrations and eGFR at each stage of CKD
(Salh *et*	Cross-	136 patients with T2DM&DN	HbA1c,UAC	The incidence of albuminuria in elderly patients

al.,2024)/ Iraq (7)	sectional	Normoalbuminuria (n=82) Microalbuminuria (n=37) Macroalbuminuria (n=17)	R	with T2DM was high in patients with poor diabetes control, a long duration of diabetes,
(Huang *et al*.,2021)/China (33)	Cross-sectional	309 patients with T2DM	Insulin resistance	Higher insulin resistance levels were observed as risk factors for diabetic nephropathy in T2DM patients

MCP-1:Monocyte chemoattractant protein-1; TGF-β:Transforming growth factor-beta; HbA1c: Glycated hemoglobin; FBS: Fasting blood sugar; UACR: Urinary Albumin creatinine ratio; T2DM:Type 2 diabetes mellitus; DN: Diabetic nephropathy; eGFR: estimated glomerular filtration rate; CKD: Chronic kidney disease; WISP1: Wnt inducible signaling pathway protein;

Table 2: Characteristics of Protein Biomarkers in the Systematic review

Biomarker	M. Wt.	Physiological source	Physiological role
MCP-1 (34)	11–13 kDa	Produced by fibroblasts, epithelial, smooth muscle cell, mesangial, monocyte, with the common source is monocyte/ macrophages	Plays an important role in the macrophages and monocytes recruitment.
TGF- Beta (35)	220-235 kDa	Produced by lymphocytes, Monocytes/ Macrophages, and platelets.	Cause mesangial extension by promoting renal cellular hypertrophy and inducing the extracellular matrix expansion
Nephrine (36)	185 KDa	Integral component for the glomerular podocyte	Form an integral part of podocytes, together with endothelial cells and the basement form the glomerular filtration barrier.
Wnt/Beta catenin (37)	90 kDa	Produced by mesenchymal cells	Contribute to cell development under normal physiological conditions.

Several studies have highlighted the efficacy of biomarkers in detecting early DN. For instance, Aljorani *et al.,* 2023 (22) found elevated levels of nephrin in normoalbuminuric subjects, as well as the negative correlation between nephrin concentration with eGFR and the high diagnostic sensitivity and specificity of this marker in patients with DN, serum and urinary levels of these markers could be very important markers for early detection of DN. Furthermore, these findings show that this indicator have a higher diagnostic value in the early identification of DN than microalbuminuria. Similarly, Ganesh *et al.,*2022 (23) demonstrated that nephrin levels are strongly and positively associated with nephropathy in T2DM patients and it has greater potential to be an early predictor biomarker of nephropathy than albumin creatinine ratio. Kostovska *et al.,*2020 (24) identified that nephrin has greater diagnostic value in early detection of DN compared to microalbumin. Rangaswamaiah *et al.,*2022 (25) concluded significantly elevated levels of urinary nephrin might be used for early diagnosis and prognostic marker for nephropathy in type 2 diabetes mellitus.

Haddad and Albrahimi,2023 (26) revealed that the serum level of serum TGF-β1was significantly higher in poorly

controlled diabetic patients. The study found that there was a significant positive association between the levels of serum TGF-β1with the disease duration. Also Abbas *et al*., 2022 (10) found the importance of transforming growth factor-beta marker in DN pathogenesis which is powered by their correlation with albuminuria and high specificity and sensitivity through ROC analysis, and thus the possibility use as biochemical marker in DN.

Duaibel *et al.,* 2022 (27) observed that MCP-1 was significantly correlated with patients who had diabetic nephropathy, so there is a susceptibility association between it and the incidence of this disease among Iraqi patients. Scurt *et al*.,2022 (28) found that serum and urinary MCP1 levels are elevated in early DN, and these are likely to be markers and mediators of renal disease in diabetes at early stages, suggesting a role in onset and progression of diabetic kidney disease. Mahmoud *et al.,*2021 (29) revealed that MCP-1 level can be used as a predictor marker in early stage of diabetic complications in type 2 diabetic patients, as it showed significant positive correlation with the level of proteinuria

Shaker and Sadik 2013 (30) suggest that the progression of DN is associated with increased levels of serum TGF- β1 and urinary MCP-1 that are closely linked to renal damage and the degree of glycemic control.

Klimontove *et al.,* 2018 (31) found that subjects with type 2 diabetes serum levels of circulating WISP1 are associated with adiposity and adipose tissue dysfunction.

Paez *et al.,* 2020 (32) demonstrated that there was a negative correlation between the serum concentrations of wnt protein and the clinical stages of chronic kidney disease. In addition, its was play an important role in the progression to end-stage kidney disease.

Salh *et al.,*2024 (7) show that albuminuria in elderly patients with T2DM was high in patients with poor glycemic control, a long duration of diabetes, and comorbidity conditions (mainly hypertension). Accordingly, patient education may play a key role in controlling albuminuria risk factors and enhancing early screening of albumin in to prevent further kidney damage.

Huang *et al.,*2021 (33) found that higher insulin resistance levels implied a higher risk for diabetic nephropathy in normal-weight patients with T2DM, and these correlations were not obvious in overweight and obese patients with T2DM.

The biomarkers introduced in this study offer several advantages over traditional proteinuria measurement for the early detection and management of DN:

Early Detection: Nephrin, MCP-1, TGF-beta, and Wnt protein : These biomarkers can detect DN earlier than proteinuria, often before any significant albumin is present in the urine. This early detection allows for timely intervention to prevent or slow disease progression.

Sensitivity and Specificity: Nephrin, MCP-1, TGF-beta: These biomarkers provide higher sensitivity and specificity compared to proteinuria. They can detect subtle changes in renal function and inflammation, offering more precise diagnostic information.

Different Pathophysiological Processes:, MCP-1, and TGF-beta: These markers provide insights into different aspects of DN pathophysiology, including inflammation, whereas proteinuria primarily reflects glomerular damage.

Limitations of this study

Apart from the emergence of various new biomarkers that provide promising results, some studies have limitations, such as too few samples and too short follow-up periods In addition, the results of one study to another are not always similar and consistent, which is due to the use of different analysis methods and conditions (38). Other factors, such as lifestyle and population ethnicity, must also be considered when presenting research results. Researchers are still using albuminuria and eGFR values as final parameters in research related to diabetic nephropathy. To date, no new biomarkers have been found that have a prognostic ability beyond albuminuria and eGFR values. However, some experts claim that new biomarkers can better describe disease progression than albuminuria and eGFR value (39).

Conclusion

The studies reviewed indicate robust potential for various biomarkers in the early detection of DN. Key serum biomarkers

such as, Nephrin, MCP-1, TGF-beta, and Wnt protein have shown significant promise. All the biomarkers discussed in this systematic review showed promising results for predicting diabetic nephropathy because they correlate with albuminuria, eGFR, or both. These could be categorized as glomerular biomarkers (Nephrin); inflammatory biomarkers (MCP-1, wnt proteins and TGF-beta); The use of single biomarkers or biomarker panels in clinical practice is still very limited

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Availability of data and materials

All data generated during this study are included in this published article.

Author contributions

Alyaa Kadhim contributed to the study conception and design. The first draft of the manuscript was written by Alyaa Kadhim and Huda Farhan, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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