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Review

Biomarkers in diabetic nephropathy: A comprehensive review of their role in early detection and disease progression monitoring

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ABSTRACT

Diabetic nephropathy (DN) is a primary contributor to end-stage renal disease (ESRD), arising from intricate pathways that include glomerular hypertension, inflammation, and oxidative stress. Conventional indicators like albuminuria and serum creatinine frequently identify renal impairment only at advanced stages, constraining early intervention. This thorough review assesses both established and novel biomarkers, including those signalling tubular injury (e.g., KIM-1, NGAL), inflammation (e.g., TNF-α, MCP-1), oxidative stress, and extracellular matrix turnover for their capacity to identify diabetic nephropathy at earlier stages, track disease progression, and forecast outcomes. The study examines the increasing significance of multi-biomarker panels, advanced technologies such as proteomics, and machine learning methodologies in improving diagnostic precision and individualised risk evaluation. This study highlights the necessity of incorporating innovative biomarker methodologies to develop early, accurate, and personalised diagnostic tools aimed at alleviating the impact of DN and enhancing patient outcomes. This study is a significant resource for physicians and researchers seeking to enhance the diagnosis and management of diabetic kidney disease.

1. Introduction

Diabetes mellitus (DM) is a chronic disease caused by insufficient insulin production or utilization. Its global prevalence has increased significantly, making it a major cause of non-communicable diseases worldwide [1]. DM elevates blood glucose levels and leads to complications such as cardiovascular disease, stroke, peripheral vascular disease, retinopathy, neuropathy, and end-stage renal disease (ESRD) [2] (Fig. 1). Among these, DN is a common and severe microvascular complication, affecting about one-third of diabetic patients and contributing significantly to kidney failure.

DN develops through complex mechanisms involving glomerular hypertension, oxidative stress, and inflammation. Additional risk factors include hypertension, genetic predisposition, and lifestyle. Managing blood glucose and blood pressure, along with kidney-protective drugs like ACE inhibitors or ARBs, helps slow disease progression. Hyperglycemic kidney disease, linked to juvenile and adult-onset diabetes, affects around 30 % of individuals with hyperglycemia and is a major cause of ESRD [3]. Albuminuria, historically used to indicate chronic kidney disease (CKD) when exceeding 0.5 g/24 h [4], typically appears 10–20 years into DN progression [5]. Although rare in children [6], DN often presents with proteinuria, a key prognostic marker [7].

Studies report that up to 80 % of insulin-dependent diabetics with microalbuminuria may develop advanced nephropathy within 10–15 years, and 75 % may progress to DN over 20 years if untreated [8]. However, newer data suggest lower progression rates (15–30 % over 5–10 years) [9,10]. Albuminuria has limitations—it does not appear in all DN cases and may emerge after substantial kidney damage [11,12].

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Despite significant progress, several controversies and research gaps remain. There is limited consensus on the predictive value and standardization of many novel biomarkers, and their clinical applicability is yet to be validated through large-scale studies. Furthermore, the lack of uniform diagnostic thresholds and variations in biomarker expression among populations complicate interpretation. Thus, early detection through novel biomarkers is critical. This review focuses on 37 emerging genetic, protein, and metabolic markers, highlighting the need for large, prospective studies. A more refined diagnostic approach, integrating sensitive biomarkers and novel technologies, is vital for early DN detection and effective management.

2. Pathology of diabetic nephropathy

The pathology of DN is characterized by complex and progressive changes in the glomeruli, tubulointerstitial tissue, and renal vasculature. The initial hyperglycemic damage sets off a cascade of events that leads to glomerulosclerosis, fibrosis, inflammation, and eventually, renal failure. Early detection and management of DN are essential to slowing or preventing its progression, highlighting the importance of regular monitoring for kidney function in diabetic patients. The pathophysiology of DN involves multiple mechanisms triggered by high blood sugar levels. These mechanisms include the production of advanced glycation end products (AGE), activation of protein kinase C (PKC), and the generation of reactive oxygen species (ROS). Increasing evidence suggests that ROS plays a significant role in the development and progression of diabetic kidney disease (DKD) [13]. Animal studies have shown the impact of antioxidant therapy; however, conclusive evidence regarding its therapeutic efficacy is still lacking.

CKD pathophysiology has been associated with excessive ROS production through nicotinamide adenine dinucleotide (NADPH) oxidase (NOx). Hyperglycemia-induced distribution of PKC, particularly PKC-alpha, to kidney surfaces has been linked to increased NADPH-dependent superoxide generation and elevated levels of vascular endothelial growth factor (VEGF) in the kidney, plasma, and urine [14]. Inhibition of NOx with the compound Pocynin has been shown to reduce diabetes-related increases in proteinuria and glomerulosclerosis [15]. Similarly, eliminating NOx or PKC-alpha in hyperglycemic rodents or AGE-treated mesangial cells resulted in decreased cytosolic superoxide formation and PKC activation, while VEGF levels increased [16]. The biomarkers and mode of action for diabetes are shown in Fig. 2.

Recent studies have highlighted the role of adenosine monophosphate-activated protein kinase (AMPK) signaling in the pathology of DN. Activation of AMPK leads to downstream activation of the mammalian target of rapamycin complex 1 (mTORC1), which in turn stimulates extracellular signal-regulated kinase (ERK)/beta-catenin and Transforming Growth Factor-beta/Suppressor of Mothers against decapentaplegic (TGFβ1/Smad) signaling pathways. These molecular events drive epithelial-mesenchymal transition (EMT), promoting extracellular matrix deposition, tubular hypertrophy, and increased matrix protein synthesis. Furthermore, animal models with podocyte-specific deletion of tuberous sclerosis complex 1 (a negative regulator of mTORC1) exhibit podocyte injury, proteinuria, and mesangial expansion, hallmarks of DKD pathogenesis [17].

3. Biomarkers in diabetic nephropathy

In recent years, biomarker research has become integral to understanding kidney diseases, specifically those impacting the glomerulus. Numerous experts categorize biomarkers based on their sources and roles in pathophysiological processes, primarily focusing on aspects like renal disease, oxidative stress, inflammation, and overall renal function [18]. Specific biomarkers, including chemokines, cytokines, and oxidative stress indicators [19], have emerged as key in identifying disease progression and severity. A complementary categorization system classifies these biomarkers into renal, tubular, and other molecules, enhancing specificity in kidney disease profiling. This review adopts these classification systems, as summarized in Table 1, to systematically examine relevant biomarkers.

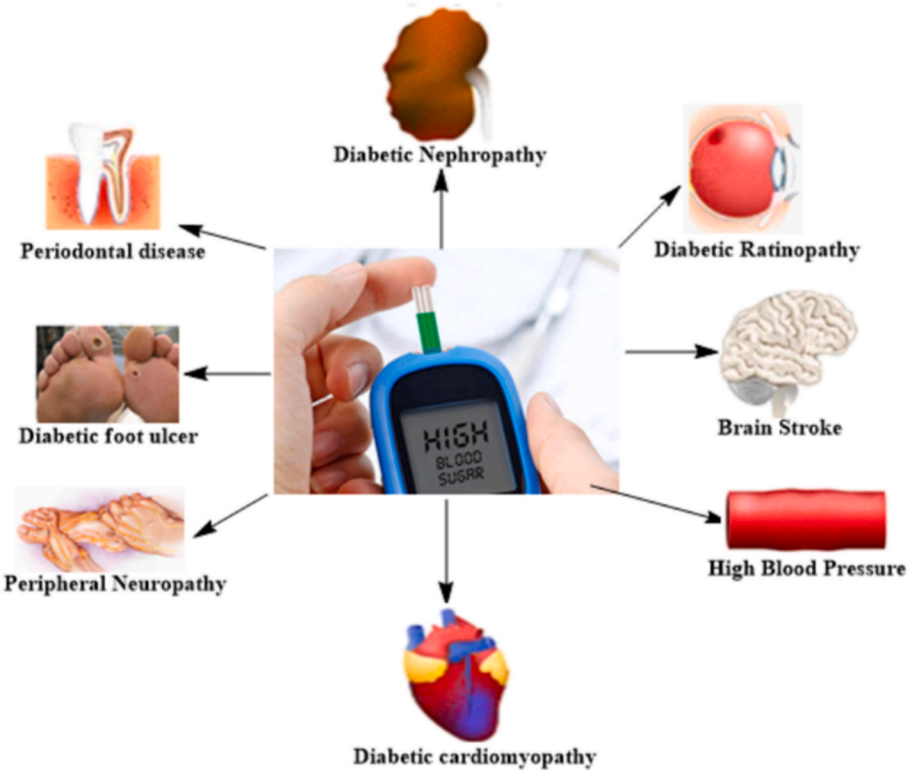

Fig. 1. Complications caused by the Diabetes.

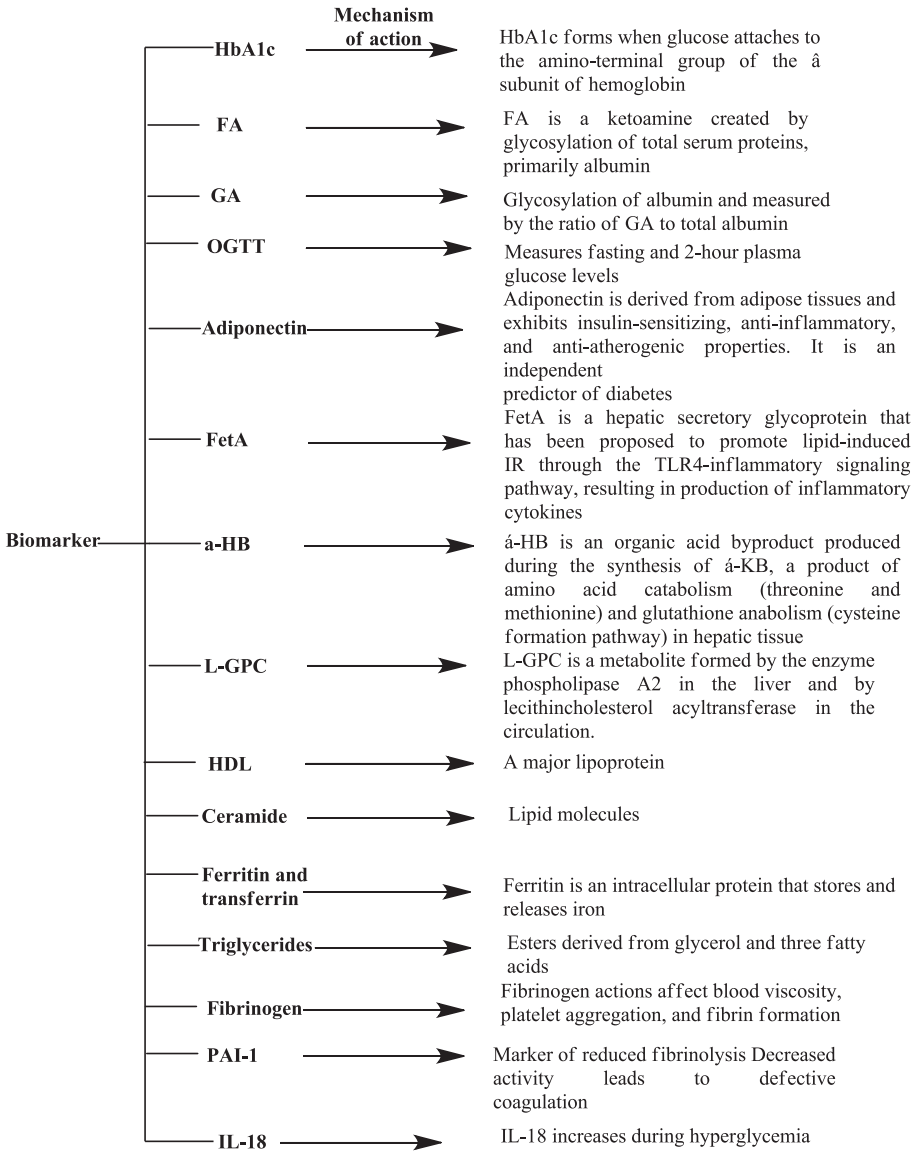

Fig. 2. Specific bViomarkers and mode of action for diabetes.

3.1. *Urinary biomarkers for DN*

DN is a progressive kidney disease caused by diabetes, which can lead to CKD and eventually kidney failure. Early diagnosis of DN is crucial to delay progression, and urinary biomarkers play a key role in detecting early stages of DN. Here are some notable urinary biomarkers used in DN diagnosis and monitoring:

3.1.1. *Albumin*

Albumin biomarkers, especially in the form of albuminuria, are critical in diagnosing and monitoring DN, a common complication of diabetes that affects the kidneys. The most abundant blood protein in the body is Human Serum Albumin (HSA), which is a 65 kDa protein synthesized in the liver. Albumin has several key functions, including regulating oncotic pressure, acting as an acid/base buffer, and facilitating the transport of endogenous substances, chemical messengers, nutrients, and pharmaceutical drugs [20]. In healthy individuals, only a small amount of albumin is processed in the glomerulus, while the majority is reabsorbed by the tubules [21,22].

Increased urine albumin excretion (UAE) is a well-recognized biomarker of glomerular injury [23,24]. Additionally, it is known that tubular dysfunction can independently lead to albuminuria by reducing the reabsorption of filtered albumin [25]. UAE readings below 30 mg/dayor 20 micro/min are considered normal levels of protein in urine. This threshold has been established based on the fact that 95 % of "normal individuals" fall below this assessment [26]. However, it has been demonstrated that even individuals in the "high normal" range of UAE have an increased risk of heart incidents and kidney injury [27–29]. In patients with adult-onset diabetes, baseline albuminuria is a strong predictor of chronic renal failure [30]. The American Diabetes Association recommends annual UAE screening for all individuals with type 1 diabetes with less than five years of disease duration, as well as for all newly diagnosed individuals with type 2 diabetes [31].

However, urinary albumin also has its limitations and disadvantages as a biomarker. Urinary albumin has been widely used to assess different therapeutic options, as well as to diagnose and classify DKD. It has been utilized to indicate the progression or reduction of diabetic renal ailments in various large-scale clinical trials [32,33]. However, as mentioned earlier, patients with normal albuminuria have also shown gradual renal deterioration and histologic changes in the kidneys. It has been suggested that an increase in urine albumin excretion rate (AER) occurs before the onset of kidney failure in DKD. However, some studies,

Table 1
Biomarkers in diabetic nephropathy.

Category	Biomarkers
Glomerular Biomarkers	Transferrin, Albumin, IgG (immunoglobulin G), Ceruloplasmin, Type-4 Collagen, Laminin, GAGs (glycosaminoglycans), Fibronectin
Tubular Biomarkers	NGAL (neutrophil gelatinase-associated lipocalin), KIM-1 (kidney injury molecule 1), NAG (N-acetyl-β-D-glucosaminidase), Cystatin, L-FABP (liver-type fatty acid-binding protein), α-1-Microglobulin, RBP (retinol-binding protein)
Oxidative Stress	8oHdG (8-oxo-7,8-dihydro-2-deoxyguanosine), Pentosidine, Lipid injury, AOPP (advanced oxidation protein products), HNE (4-hydroxy-2-nonenal), Malondialdehyde, Superoxide Dismutase
Inflammation Biomarkers	TNF-α (tumor necrosis factor α), IL-1β (interleukin-1β), IL-8 (interleukin-8), IP-10 (interferon gamma-induced protein), MCP-1 (monocyte chemoattractant protein 1), G-CSF (granulocyte colony-stimulating factor), AGEs (advanced glycation end products), Eotaxin, RANTES (regulated on activation, normal T cell expressed and secreted)
Miscellaneous Biomarkers	VEGF (vascular endothelial growth factor), Podocalyxin, Nephrin, H-FABP (heart fatty acid-binding protein), Orosomucoid, L-PGDS (lipocalin-type prostaglandin D synthase)

including a recent one [34], have shown a discrepancy between elevated urine protein levels and decreased glomerular filtration rates (GFRs).

A broader glomerular filtration barrier and advanced stages of HbA1C (glycated hemoglobin) have been identified as independent predictors of the development of significant albuminuria and DN, but not AER, in individuals with juvenile hyperglycemia and lower levels of albuminuria [35]. Individuals with moderate proteinuria and sustained estimated GFRs have been found to have diffuse glomerular lesions, interstitial fibrosis, loss of tubular epithelial cells, interstitial inflammation, and plaque buildup in arterial walls, particularly in those with adult-onset diabetes [36].

3.1.2. Transferrin

Transferrin has gained interest as a biomarker in DN due to its role in iron metabolism and oxidative stress. DN, a leading cause of CKD in diabetes, involves progressive kidney damage, and transferrin levels and modifications can reflect the extent of renal impairment and oxidative injury in DN. Transferrin, despite having the same molecular mass as human serum albumin, has a higher isoelectric point (point of zero charge) [37]. The relationship between microalbuminuria and transferrin in urine and early tubular damage has been evaluated in urinalysis studies focusing on DKD [38]. The presence of both micro proteinuria and transferrin in urine is associated with compromised microvascular permeability and tubular function, as observed in renal disease confirmed by biopsy. This condition is also related to increased levels of additional biomarkers such as Protein HC, B2M, and NAG [39]. While some reports suggest a connection between microalbuminuria and endothelial damage in arteriosclerotic vascular disease (ASVD), the relationship between transferrin in urine and endothelial damage is less clear and has not been extensively studied in patients with adult-onset diabetes in the early stages of chronic renal failure [40].

Elevated levels of transferrin-to-creatinine ratio (TRF/Cr) may be observed initially in adult-onset diabetic individuals, and it could serve as a specific indicator for predicting the development of diabetes-related complications [41]. Urinary transferrin has been linked to the presence of atherosclerotic plaques in the arterial intima layer in individuals with adult-onset diabetes who do not have renal failure. This suggests that urinary transferrin may have the potential to detect cardiovascular risk in individuals with early-stage kidney disease who do not exhibit microalbuminuria [42]. In a recent study, the levels of transferrin and inflammatory cytokines were found to be potential markers for the early onset of advanced DKD [43].

3.1.3. Immunoglobulins

Immunoglobulin G (IgG) biomarkers have garnered attention for their potential role in diagnosing and managing DN, a common complication of diabetes that affects the kidneys. Immunoglobulin G (IgG) is a protein produced by immune cells that generates a large number of specific antibodies. It has a molecular mass of 150 kDa, which is greater than that of albumin. In individuals with diabetes, the excretion of IgG in the urine is higher compared to control subjects, and it can predict the development of urinary albumin enlargement in hyperglycemic individuals with normal levels of albuminuria [44]. One study found significant associations between daytime changes in systolic blood pressure (SBP) and urine excretion of IgG in hyperglycemic individuals, but not in control subjects. This suggests that urine excretion of IgG may be a more sensitive prognostic marker of mesangial differential stress compared to proteinuria in hyperglycemic individuals with normal protein levels in the urine [45]. Among all the antibodies, IgG2 showed the highest increase, suggesting that specific subclasses of antibodies could serve as novel molecular markers in the early stages of DKD, separate from albumin levels [46].

IgG4-related disease, a specific isoform of IgG, has been used as a diagnostic marker for glomerular burden reduction. Urine discharge of IgG4-related disease was found to be increased in individuals with microalbuminuria, while both IgG and urine discharge of IgG4-related disease were elevated in individuals with overt proteinuria compared to those with normal levels of proteinuria [47]. A comprehensive review, including multiple studies, indicated that immunoglobulin G (IgG) could be a valuable marker for predicting the onset of end-stage renal disease (ESRD) [48].

3.1.4. Caeruloplasmin

Caeruloplasmin is a copper-binding protein in the blood that has antioxidant properties and plays a role in iron metabolism. It is a potential biomarker for DN, a kidney-affecting diabetes complication. Chronic high blood sugar damages the kidneys, causing protein leakage in urine and kidney failure. The complex negative charges of 151 kDa blood metalloprotein ceruloplasmin make glomerular capillary extraction difficult. Urinary ceruloplasmin has been found in diabetics with normal proteinuria, and elevated levels predict microproteinuria [49,50]. In individuals with adult-onset diabetes compared to those without DKD, the urine levels of ceruloplasmin to creatinine ratio were found to be higher. This ratio showed a sensitivity of 91.4 % and a specificity of 61.4 % in diagnosing DKD [51]. Additionally, concentrations of protein HC and NAG were also elevated in these individuals, suggesting that ceruloplasmin could serve as a molecular marker for assessing interstitial nephritis damage in DKD [52].

In DN, caeruloplasmin exacerbates oxidative stress by catalysing the oxidation of ferrous ions, hence facilitating the production of reactive oxygen species (ROS) in renal tissues. The heightened oxidative stress harms glomerular and tubular cells, intensifying inflammation and fibrosis. Increased caeruloplasmin levels are associated with endothelial dysfunction and the advancement of renal damage in diabetes, which further hinders kidney filtration and encourages extracellular matrix formation. Caeruloplasmin's function in regulating oxidative damage positions it as a possible biomarker for oxidative stress-associated renal injury in DN.

3.1.5. Type IV collagen

Type IV collagen, a key structural protein in the basement membranes of kidneys, is increasingly studied as a biomarker for DN. This biomarker assesses DN kidney damage and progression. The mesangial matrix, glomerular, and tubular basement membranes expel type IV collagen. Normal albuminuria and micro proteinuria adult-onset diabetics had advanced urine type IV collagen (U-Col4) compared to strong controls. High proteinuria was strongly associated with this level, but not glycated hemoglobin [53]. Earlier studies indicated that U-Col4 was more responsive than urine protein as an indicator for primary

hyperglycemic renal disease, and a subsequent investigation revealed that U-Col4 excretion increased with microproteinuria and showed a positive interaction with creatinine clearance [54,55]. A paradoxical follow-up survey found that U-Col4 levels were higher in moderately increased albuminuria patients than in those with normal albumin levels, and they correlated with predicted GFR and urine protein elimination rate. U-Col4 levels at baseline may indicate a decline in kidney function in adult-onset diabetics without albuminuria, but not a steady progression to hyperglycemic renal disease [56]. Type IV collagen being the integral to the pathophysiology of DN, a predominant contributor to CKD in individuals with diabetes. As a fundamental structural element of the glomerular basement membrane (GBM), it supports the integrity and selective permeability of the filtration barrier. In diabetes, chronic hyperglycemia induces the overexpression and aberrant accumulation of type IV collagen, mostly via pathways associated with advanced glycation end products (AGEs) and transforming growth factor-beta (TGF-β). This results in glomerular basement membrane thickening, mesangial matrix enlargement, and ultimately glomerulosclerosis. Increased concentrations of type IV collagen in blood or urine have been suggested as early indicators for DN, frequently identifiable prior to the emergence of microalbuminuria. Consequently, addressing the signalling mechanisms that govern type IV collagen synthesis and deposition presents a promising avenue for therapeutic intervention in DN.

3.1.6. Laminin

Laminin is a glycoprotein that plays a crucial role in maintaining the integrity of the extracellular matrix and is involved in cell adhesion, migration, and differentiation. In the context of DN, laminin biomarkers have gained attention for their potential to reflect kidney damage, fibrosis, and the progression of the disease. Laminin is a bulky (800 kDa) heterotrimeric protein composed of α-β-γ chains and arranged in a cross configuration. It forms proteoglycan manacles and is called laminin. In a healthy adult glomerular basement membrane, the primary isoform of laminin is laminin-α5-β2-γ1, which interacts with Col4 through 255 entactin [57]. Laminin is a component of the basal lamina layer of the glomerulus. Its urinary excretion is elevated in adult-onset diabetes with normal albuminuria, and it is associated with the excretion of NAG and alpha-1microglobulin. Laminin-deficient mice exhibit severe albuminuria and typically succumb within three to five weeks. The glomerular basement membrane appears structurally disordered in the absence of laminin-β2 [58]. Micro coria-congenital nephrotic syndrome, which encompasses congenital nephrotic syndrome and various ophthalmic and neurological symptoms, is a condition caused by mutations in the laminin-β2 gene [59,60]. Micelacking laminin-α5 exhibit glomerular basement membrane disintegration, podocyte clustering, and the failure of glomerular endothelial cells (GEnCs) and Goormaghtigh cells to form a parallel loop with Henle's loop, known as vasa recta [61]. Therefore, laminin is essential for the formation of the basement membrane. However, several studies have also demonstrated that urine laminin excretion is higher in patients with diabetes compared to their healthy counterparts, even before the onset of microalbuminuria [62,63]. Individuals with type 2 diabetes mellitus (T2DM) who develop nephropathy show a significantly higher laminin/albumin ratio compared to those without DKD, highlighting the discriminatory significance of urine laminin in diabetic and non DKDs [64].

3.1.7. Glycosaminoglycan

GAGs are involved in renal fibrosis, glomerular filtration barrier integrity, and inflammation, making them potential biomarkers for DN. GAG dysregulation is linked to DN, which damages the kidneys. The complex network of proteins, carbohydrates, plasma membrane, and extracellular matrix contains 13–30 kDa glycosaminoglycans (GAGs). GAGs regulate cell growth and differentiation, interleukin-1 production, cell-to-matrix attachment, and cell-to-cell communication and cooperation. They also influence basement membranes [65].

Heparin sulfate has been identified as the primary anionic component of the Glomerular Basement Membrane (GBM) and is the most abundant glycosaminoglycan present in the GBM [66,67]. In diabetes, there is a decrease in the amount of heparin sulfate within the extracellular matrix of the glomerular and tubular cells, as well as the GBM. This decrease in heparin sulfate affects the structural integrity of the glomerular tuft and may be partially responsible for the proteinuria that is characteristic of DN [68]. When hyperglycemia occurs, glomerular endothelial cells produce less GAG, which reduces the amount of heparin sulfate in the glycocalyx and allows for the increased passage of albumin across the glomerular capillary wall without disrupting the inter endothelial junctions [69]. Furthermore, systemic damage to the extracellular matrix is associated with decreased albumin excretion in urine [70]. Urine indicators of tubular injury, such as ß-2-Mmicroglobulin (B2M), 2-acetamido-2-deoxy-beta-D-glucopyranose (NAG), and Uromodulin, are also found in the tubular basal laminae (TBL) and have been linked to urinary GAGs excretion [71,72]. B2M is a low molecular weight protein, approximately 11.8 kDa, that constitutes the light chain of major histocompatibility complex class I molecules present on the surface of nearly all nucleated cells. It is incessantly released into the bloodstream and readily filtered by the renal glomeruli. Under typical circumstances, B2M is nearly entirely reabsorbed and metabolised by the proximal tubules, leading to low concentrations in the urine. However, in conditions such as DN, characterised by tubular dysfunction or damage, reabsorption is compromised, resulting in increased urine B2M levels. Elevated serum B2M may indicate a reduction in GFR, acting as a marker of overall renal function. B2M is recognised as an inflammatory marker and has been associated with cardiovascular risk in diabetes individuals. B2M's significance in both tubular damage and diminished filtration renders it a promising biomarker in diabetic nephropathy. The TBL is a specialised extracellular matrix layer that supports renal tubular epithelial cells and preserves cell polarity. It is essential in the selective reabsorption and secretion functions of the nephron. In diabetic nephropathy, persistent hyperglycemia and related metabolic stress result in thickening and structural modifications of the tubular basal lamina. These alterations compromise tubular integrity, hinder solute management, and lead to tubulointerstitial fibrosis. In diabetic nephropathy, damage to the tubular basal lamina occurs early and coincides with disease progression and deteriorating renal function. A recent study in diabetics with good glycemic control found a correlation between urine GAG excretion and the severity of glomerular basement membrane (GBM) lesions, while in individuals with more advanced renal impairment, it was associated with tubulointerstitial nephritis [73,74]. Additionally, there is a connection between urinary GAG excretion and diabetic neuropathy [75]. Conflicting data exists regarding the relationship between urinary GAG excretion and diabetic eye disease. Even though some studies have shown an association, it has been demonstrated that urine GAG output is not a standalone risk factor for diabetic eye problems [76–78]. In type 2 diabetics, there is an association between blood pressure and urinary GAG excretion [79–82], but inconsistent outcomes have been reported in relation to diabetes duration [83–85].

3.1.8. Fibronectin

Fibronectin is an extracellular matrix protein that plays a role in cell adhesion, migration, and wound healing. It has been studied as a potential biomarker for DN, a common complication of diabetes that affects the kidneys. Fibronectin, a plasma glycoprotein with a molecular mass of 440 kDa, is primarily produced by fibroblasts and endothelial cells and plays a role in cell attachment to vascular endothelium [86]. In patients with diabetes, higher levels of fibronectin production have been observed, and studies have shown correlations between plasma levels of fibronectin, retinopathy, and microalbuminuria [87]. Regarding the glomerular basement membrane, studies have found higher levels of urine fibronectin in patients with adult-onset diabetes compared to healthy controls, as well as in patients with lower levels of albumin in urine compared to normal levels [88]. However, the potential use of

plasma fibronectin as an early diagnostic marker for DN may be limited due to the weak positive correlation between urine albumin levels and plasma fibronectin levels. Furthermore, studies have demonstrated elevated levels of urine fibronectin in insulin-dependent diabetes patients with excessive albumin in urine and in type 2 diabetes patients with low levels of albuminuria but high levels of albumin in urine [89,90].

3.1.9. Lipocalin-type prostaglandin D2 synthase

In the context of DN, L-PGDS has emerged as a potential biomarker due to its involvement in kidney inflammation and fibrosis. DN is characterized by chronic inflammation, oxidative stress, and fibrosis, and L-PGDS may be implicated in the pathogenesis of these processes. Lipocalin-type prostaglandin D2 synthase (L-PGDS) is a polypeptide belonging to the lipocalin superfamily that is responsible for producing prostaglandin D2. Unlike albumin, it has specific chemical characteristics and a smaller size (molecular weight 20–31 kDa), allowing it to pass more easily through the glomerular capillary barriers [91]. In patients without diabetes, L-PGDS is present in the peritubular interstitial but not in the tubular cells. However, in diabetic patients, it can be found in the renal tubules [92]. Increased urinary excretion of L-PGDS has been reported in patients with diabetes and any type of renal disease, except for IgA nephropathy, compared to controls. It has shown sensitivity rates of 67 % and 86 % and specificity rates of 93 % to identify renal disease [93]. L-PGDS is considered more accurate than other urine indicators of tubular damage such as B2M (beta-2 microglobulin),2-acetamido-2-deoxy-beta-D-glucopyranose, and blood creatinine. However, it is less accurate than urinary albumin excretion (UAE) in detecting renal disease [94]. It is believed to be more useful in the early stages of renal disease rather than in advanced stages, as reduced GFR affects L-PGDS excretion [95]. L-PGDS is generally more accurate than urinary Col4 (collagen type 4), B2M, serum creatinine, and 2-acetamido-2-deoxy-beta-D-glucopyranose in predicting proteinuria [96]. In hyperglycemic patients, the presence of complex L-PGDS elimination is independently associated with a history of heart diseases [97].

3.2. Tubular biomarkers

Tubular biomarkers are molecules or proteins found in blood, urine, or other bodily fluids that indicate kidney tubule damage, dysfunction, or injury. Kidney tubules filter blood, resorb nutrients, and excrete waste into urine. Disease, trauma, or other conditions can damage these structures, releasing biomarkers into the bloodstream or urine. Tubular cell-related kidney diseases can be diagnosed and monitored using these biomarkers.

3.2.1. Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule- 1(KIM-1), and N-acetyl Glucosamine (NAG) or acetamino-2deoxy-β-d-glucose

The lipocalin family includes 25 kDa neutrophil gelatinase-associated lipocalin. The polypeptides regulate cell death and immunity while binding and transporting small hydrophobic compounds.

3.2.1.1. Neutrophil gelatinase-associated lipocalin. NGAL is mostly found in PMN leukocyte granules but is also expressed at low levels in other organs [98,99]. This biomarker is promising for diagnosing and treating acute renal failure [100]. Tubular cell proliferation regulation may not protect [101]. Human obesity, insulin resistance, and hyperglycemia are linked to NGAL [102]. Diabetics had higher urine NGAL than healthy controls [103]. Urinary NGAL and supraphysiological GFR correlate with initial hyperglycemia [104]. Even after controlling for systolic blood pressure, blood glucose, and hyperglycemia duration, elevated NGAL levels reduced the estimated GFR in adult-onset diabetes with albuminuria [105]. Insulin-dependent diabetes without proteinuria and adult-onset diabetes with decreased estimated GFR increased urinary NGAL and HAVCR1 [106].

NGAL is a sensitive biomarker for renal injury and is significant in DN. In DN, hyperglycemia and oxidative stress induce damage to tubular epithelial cells, resulting in elevated production and secretion of NGAL into the urine and circulation. Increased NGAL levels indicate early tubular damage prior to notable alterations in glomerular filtration rate, rendering it an important biomarker for the early identification and assessment of diabetic nephropathy development. Moreover, NGAL is involved in regulating inflammation and cellular iron transport, which may affect renal healing and fibrosis. The fast increase of NGAL after renal injury and its stability in biological fluids render it a viable instrument for the clinical evaluation of diabetic kidney disease.

3.2.1.2. Kidney injury molecule-1 (KIM-1). The KIM-1, are crucial in the aetiology and early identification of DN. KIM-1 is a transmembrane protein that is significantly upregulated in proximal tubular epithelial cells after renal damage. In DN, hyperglycemia and oxidative stress cause tubular injury, resulting in the upregulation and excretion of KIM-1 in the urine. Increased urine KIM-1 levels indicate proximal tubular injury prior to notable glomerular damage or deterioration in renal function, rendering it a sensitive biomarker for the early identification of DN. KIM-1 indicates tubular cell damage and also facilitates tubular healing by enhancing the phagocytosis of apoptotic cells and debris. Prolonged elevated levels of KIM-1 signify continuous tubular inflammation and fibrosis, facilitating the advancement of DN. Consequently, the assessment of KIM-1 can facilitate early diagnosis, prognosis, and therapy evaluation in DKD. KIM-1 did not show significant differences among the three hyperglycemic subsets (normal urine protein levels, low urine protein levels, and evident urine protein), although it was not associated with the albumin/creatinine ratio [107].

3.2.1.3. N-acetyl-β-D-glucosaminidase (NAG). The hydrolytic enzyme NAG is primarily found in the renal tubules. Its large molecular mass (140 kDa) prevents it from being filtered through the glomerular membrane into the urine, so its presence in urine indicates tubular abnormality. Various tubulointerstitial disorders lead to increased urinary NAG activity. Even in patients with normal urine albumin levels, NAG excretion is higher in individuals with hyperglycemia compared to controls [108]. In patients with type 2 diabetes and both micro- and macrovascular complications, there is a significant increase in urinary NAG excretion [109]. These findings suggest that tubular damage frequently occurs in the early stages of type 2 diabetes, and urine NGAL, HAVCR1, and NAG may serve as promising early indicators of kidney damage in individuals with DKD. Furthermore, in addition to being indicators of renal tubular injury, a recent study found that the average levels of, NAG, and NGAL/creatinine ratio were highest in hyperglycemic individuals with high levels of urine protein. Moreover, the NGAL/creatinine ratio was strongly correlated with mortality and ESRD [110].

In DN, hyperglycemia and oxidative stress induce tubular damage, resulting in the excretion of NAG in the urine. Increased urine NAG levels signify proximal tubular injury and have been demonstrated to manifest earlier than conventional measures such as proteinuria. NAG functions as an early biomarker for identifying tubular dysfunction and active kidney injury in diabetic nephropathy due to its sensitivity. Monitoring urine NAG can aid in evaluating disease progression and the efficacy of therapeutic interventions in DN.

3.2.2. Cystatin C

Cystatin C is a promising biomarker, especially in evaluating kidney function and detecting early kidney damage. It is increasingly being used in clinical practice to provide a more accurate assessment of renal health, particularly in situations where creatinine-based assessments may fall short. Cystatin C, a 13 kDa cysteine protease antagonist that is freely filtered through the renal microvasculature, is a unique molecular marker of kidney damage. Cystatin C has been associated with a lower

estimated GFR and increased risk of adult-onset diabetes [111]. An experiment involving Zucker diabetic fatty rats (ZDF) demonstrated elevated levels of cystatin 3, while kidney biopsy did not show evident damage in the ZDF rats. Cystatin C levels continued to rise as renal damage progressed, highlighting the importance of early detection and accurate evaluation of DKD [112]. Cystatin 3 levels were identified as an independent predictor of a GFR below 60 mL/min/1.73 m2 in individuals with adult-onset diabetes and normal proteinuria, suggesting that cystatin 3 may be a useful molecular marker for early detection of DKD [113]. Furthermore, it should be noted that cystatin 3 and other low molecular-mass polypeptides are screened and subsequently reabsorbed in the proximal tubule. In DKD, urinary cystatin 3 levels increase regardless of serum cystatin 3, indicating tubular injury rather than capillary damage [114]. Limited studies have examined the association of cystatin 3 with clinical indicators, although it has been shown that this particular molecular marker is elevated in individuals with hypertension, consistent with previous research [115].

Cystatin C has now emerged a sensitive and dependable biomarker of renal function, especially significant in the context of DN. In DN, initial renal impairment frequently transpires prior to notable alterations in serum creatinine concentrations. Cystatin C levels, however, commence to increase early, indicating even slight reductions in GFR. Cystatin C provides a more precise estimation of GFR in diabetic patients than creatinine, as it is not substantially influenced by muscle mass, age, or sex. Furthermore, raised blood cystatin C is linked to diminished kidney function and heightened cardiovascular risk, which is frequently enhanced in diabetes. Cystatin C is posited to modulate protease activity in the kidney, potentially influencing the regulation of extracellular matrix turnover, which is disrupted in DN.

3.2.3. Liver-Type fatty binding protein (L-FABP)

L-FABP, a 14 kDa minor fragment expressed in kidney proximal tubular cells, has been shown to be an excellent biomarker for the early detection of acute renal damage [116]. It is released into the urine in response to low blood oxygen levels, preventing waste from leaving the blood and entering the urine [117]. It has been hypothesized that L-FABP in the kidneys acts as an endogenous antioxidant that protects against tubulointerstitial damage [118]. In the presence of CKD, urinary excretion of L-FABP is also increased. Urine L-FABP (uL-FABP) excretion has been demonstrated to correlate with functional and structural tubular damage as evidenced by immunohistochemical markers in kidney biopsy tissues [119]. This correlation has been validated in various disease processes such as minimal-change nephrotic syndrome, lupus nephritis, and DN, which are characterized by significant proteinuria leading to tubular injury and CKD [120]. The association between urine L-FABP levels and the severity of ESRD has been documented in two studies on juvenile-onset hyperglycemia and five studies on adult-onset hyperglycemia [121]. Urine L-FABP levels increased with the progression of type 1 diabetes and were higher in individuals with normal protein levels in urine compared to healthy controls [122]. These findings suggest that urinary L-FABP accurately reflects the severity of DKD and may serve as a suitable biomarker for early diagnosis [123]. However, one study reported inconsistent results [124]. Another investigation found that urine L-FABP levels were higher in individuals with normal albumin levels in urine compared to healthy controls, and the results varied depending on the degree of albuminuria. Increased urine L-FABP was not associated with a reduction in GFR in the subgroup of patients with normal microalbuminuria [125]. All of these studies suggest that urine L-FABP may have predictive value for DN progression or as a target for therapeutic intervention, but further multicenter clinical trials involving diverse populations are needed to establish its clinical relevance [126]. It is important to note that all of these investigations were conducted on patients without albuminuria, suggesting that L-FABP may bevaluable in the early stages of hyperglycemic renal diseases but not in advanced stages [127].

3.2.4. Alpha 1-Microglobullin (Protein HC)

Alpha-1-microglobulin (α1M or Protein HC) is a liver-produced low-molecular-weight glycoprotein. Plasma and urine contain it, which has been studied as a biomarker for kidney function conditions. It is used in clinical practice to monitor kidney health and diagnose renal diseases earlier than other biomarkers. Protein HC, a 27 kDa protein complex, is easily purified by the nephrons and recycled by the proximal tubules. Urinary 1-microglobulin excretion may help screen DKD. In 33.6 % of patients with normal urine protein, 53.6 % of patients with less albumin, and 64.5 % of macro-proteinuria patients, urinary 1-microglobulin levels were elevated. These findings suggest that Protein HC stages may help diabetics detect kidney disease early. Protein HC is linked to glycemic control, hardness, regulation, and proteinuria, suggesting it can assess kidney damage in adult-onset diabetes [128].

In another study, 45.2 % had increased Protein HC discharge, 23.1 % had less albumin in their urine, 9.6 % had more, and 27.2 % had a GFR of 60 mL/min/1.73 m2. These findings suggest that Protein HC may be a marker for DKD in adult-onset diabetes before albuminuria and GFR decline [129].

In an alternative study, 27.9 % and 23.5 % of non-insulin-dependent diabetes patients with normal proteinuria exhibited increased urinary 1-Protein HC and 2-Protein HC levels, respectively [130].

3.2.5. Pentosidine

Pentosidine is a biomarker for advanced glycation end-products (AGEs), which are formed by non-enzymatic protein, lipid, and nucleic acid glycation. AGEs contribute to aging and the pathophysiology of diabetes, cardiovascular disease, and kidney dysfunction. Cross-linking between sugar molecules like glucose or fructose and protein lysine residues creates pentosidine. AGE polymerization and concentration are marked by pentosidine, a metabolic component. Diabetics had higher urinary pentosidine levels than healthy controls. Diabetics with renal disease had higher urine and plasma pentosidine thresholds. Serum pentosidine levels are linked to ESRD, diabetic eye disease, high blood pressure, and high triglycerides, indicating its role as an indicator of diabetic microvascular complications. Studies have shown that diabetics with high urine protein excrete more pentosidine than controls [131].

3.2.6. Hydroxy-2 deoxyguanine (8-OHdG)

A complex biomarker used to assess disturbance in the balance between the productions of reactive oxygen species (free radicals) in the human body is 8-hydroxy-2′-deoxyguanine (8-OHdG). In a recent study, the formation of 8-OHdG and oxidative stress were found to be significantly elevated in the cortex and nipples of streptozocin-induced high blood sugar mice compared to control mice. However, after insulin therapy, these levels were reduced, suggesting a potential link between DNA damage, oxidative stress, and 8-OHdG. This finding indicates that 8-OHdG could be a sensitive molecular marker to assess oxidative stress and DNA impairment [132].

The etiology of DN involves the activation of protein kinase C isoforms, high levels of hexose sugars such as glucose being converted into sugar alcohols, and the generation of glycotoxins. Early research suggested that pentosidine may serve as a urinary marker for DN, as it was significantly higher in individuals with adult-onset glycemic individuals with overt kidney disease and correlated with urine 2MG discharge, which is the excretion of Beta-2 microglobulin (β2MG) in the urine [133]. Urinary levels of 8-OHdG and 8-oxodG, byproducts of oxidative DNA damage, may serve as indicators of overall oxidative stress [134]. Type 2 diabetic patients were found to excrete higher amounts of 8-OHdG in their urine compared to healthy controls, and higher levels of urine 8-OHdG were associated with elevated HbA1c levels and the severity of kidney injury [135]. Recent research suggests that individuals with higher urinary excretion of 8-oxodG, compared to those with intermediate or lower elimination, may have a higher risk of developing ESRD, indicating that urine 8-oxodG could be a valuable

biological marker for predicting the progression of ESRD [136]. In summary, 8-OHdG is a critical marker in research focused on oxidative stress and DNA damage, offering valuable insights into the cellular consequences of environmental or metabolic factors that contribute to disease.

3.2.7. Malondialdehde (MDA)

Malondialdehyde (MDA) is a biomarker commonly used to measure oxidative stress and lipid peroxidation in biological systems. MDA is a reactive aldehyde produced as a byproduct of the degradation of polyunsaturated fatty acids (PUFAs) in cell membranes, particularly in response to oxidative damage. It is often used as an indicator of cellular damage and oxidative stress, as it forms adducts with proteins and DNA, potentially leading to mutations, inflammation, and disease development. However, recent research has uncovered the presence of highly mutagenic impurities generated during the production of MDA, which may contribute to its observed biological activity [137]. Given that MDA is naturally formed in animal tissue, it is crucial to determine its mutagenic and carcinogenic potential. To ensure highly pure MDA for biological testing, three complementary approaches have been developed. These include chromatographic purification of MDA's sodium salt and sublimation of MDA's free acid. The latter method, specifically designed to produce stable MDA in non-acidic conditions, is unique [138].

A cross-sectional study demonstrated significantly higher serum MDA levels in diabetics with and without complications, along with other measures [139]. Another recent study indicated a surge in MDA levels among adult-onset diabetes patients, particularly those undergoing insulin treatment. The association between long-term diabetes and MDA biomarker levels suggests the involvement of lipid peroxidation in the etiology of glycemic difficulties [140].

3.2.8. Superoxide dismutase

Oxidative stress is considered a significant factor in the development of vascular complications in cases of type 2 diabetes [141]. Changes in the levels of antioxidants, including superoxide dismutase (SOD), can contribute to the vulnerability of tissues to oxidative stress, leading to diabetes-related issues [142]. Epidemiological research suggests that the increased incidence of vascular diseases, independent of hyperglycemia, plays a significant role in explaining diabetic mortality [143].

A *meta*-analysis was conducted, involving eight articles divided into nine groups. The perfect group consisted of 106 individuals, the Caucasian and mixed females set had 105 individuals, and the white males collection included 99 individuals. Data from eight studies, representing nine groups, were combined to demonstrate a statistical improvement in superoxide dismutase levels [144].

3.3. Biomarkers of inflammation

Biomarkers of inflammation are substances or molecules in the body that can be measured to assess the presence or degree of inflammation. These biomarkers are typically used in clinical settings to help diagnose, monitor, and predict various inflammatory conditions. These biomarkers can be measured in blood, serum, or other bodily fluids and used to monitor disease progression, guide treatment decisions, and assess the effectiveness of therapies aimed at reducing inflammation.

3.3.1. Tumor necrosis factor alpha (TNF-α)

Tumor necrosis factor-alpha (TNF-α) is an important inflammatory mediator in the pathogenesis of renal damage. It induces programmed cell death, injuries, extracellular matrix deposition, increased protein absorptivity, and reduced GFR. While white blood cells are the primary source of TNF-α (cachectin), intrinsic kidney cells can also produce and contribute to kidney damage [145].

Initial research has shown significantly higher levels of cachectin release in individuals with adult-onset diabetes and both smaller and larger albuminuria compared to healthy controls. Furthermore, cachectin levels increase with the severity of renal disease [146]. Other studies have reported elevated levels of urinary and serum TNF-α in individuals with diabetic renal ailments compared to those with normal protein excretion and control subjects. Cachectin levels in urine and serum have also been found to be significantly associated with urinary protein excretion, suggesting that cachectin may serve as a primary indicator of renal injury in individuals with diabetes [147].

Urinary excretion of TNF-α in type 2 diabetes patients is increased and has been linked to the severity of renal injury, both in the glomerular and tubulointerstitial compartments. This implies that TNF-α plays a role in the development and progression of renal damage. TNF receptors 1 and 2 (TNFR1 and TNFR2) have been found to be upregulated and associated with an increased risk of ESRD. Although both markers show significant connections, TNFR1 has a stronger association with the development of DKD, leading to ESRD. Elevated circulating TNFR levels in individuals with adult-onset diabetes, at the onset or early stages, are powerful indicators of eventual progression to ESRD in patients with or without albuminuria [148].

In DN, TNF-α induces renal inflammation, oxidative stress, and cellular death, resulting in structural and functional impairment of the kidneys. It enhances glomerular permeability, leading to proteinuria, and promotes the synthesis of additional pro-inflammatory and profibrotic mediators, including interleukins and TGF-β, which expedite mesangial growth and glomerulosclerosis. TNF-α also promotes leukocyte infiltration into renal tissues, intensifying chronic inflammation and fibrosis. Increased TNF-α levels are associated with the severity of renal impairment, serving as both an indicator of disease advancement and a possible therapeutic target in DN.

3.3.2. Interleukin18 (IL-18)

Interleukin 18 (IL-18) is a pro-inflammatory cytokine produced by vascular endothelial cells or activated macrophages, and it promotes the production of interferon-c (IFN-γ) [149]. Therefore, IL-18 serves as a marker of inflammation resulting from endothelial damage and is a predictor of future cardiovascular events [150]. In obesity, activated adipocytes generate adipocytokines, which contribute to organ and microangiopathy and damage [151]. Oxidative damage promotes the conversion of free fatty acids (FFA) to lipid peroxides, leading to renal microcirculation problems. The liver fatty acid binding protein (LFABP) binds to cytotoxic lipid peroxides released, and increased urinary LFABP indicates renal injury due to kidney stress [152].

Activated macrophages infiltrate the kidneys, causing nephropathy and glomerular injuries, and contribute to the production of IL-18 during kidney development [153]. Thus, the elevated levels of IL-18 indicate an additional mechanism of glomerular damage caused by infiltrating cells, in addition to the impact on regular endothelial cells and activated macrophages. Analyzing the trend of changes in each complication's pathological condition may help clarify the involvement of one or more of these factors. A recent study suggested that serum IL-18 and its gene haplotypes can serve as markers in patients with DN [154]. Another study demonstrated that circulating IL-18 is a specific biomarker for atherosclerosis-prone patients at increased risk of heart disease, stroke, and adult-onset diabetes [155]. In summary, IL-18 can be a valuable biomarker for diagnosing, monitoring, and predicting the progression of a wide range of diseases, including autoimmune disorders, cardiovascular diseases, cancers, infectious diseases, and metabolic disorders. Its role in inflammation makes it a key player in understanding disease pathogenesis and therapeutic outcomes.

3.3.3. Ip-interferon gamma Induced-Protein

Interferon-gamma (IFN-γ)-induced proteins, often referred to as IP (Interferon-gamma-induced proteins), are a group of biomarkers that are upregulated in response to IFN-γ signaling. IFN-γ is a cytokine crucial for immune responses and inflammation regulation, primarily produced by immune cells like T cells and natural killer cells. When cells are exposed to IFN-γ, they express various proteins involved in immune

responses, cellular defense, and inflammation. IP-10, initially discovered as an interferon-inducible chemotactic cytokine, is now classified as a pro-inflammatory chemokine. It plays a role in modulating immune responses by stimulating and attracting various white blood cells, including T lymphocytes, eosinophils, leukocytes, and NK cells, through binding to CXCR3. Small-inducible cytokine B10 (IP-10) is released by a wide range of cells, including leukocytes, enterocytes, vascular endothelial cells, basal cells, fibrocytes, mesenchymal stromal cells, accessory cells, astroglia, and liver cells [156].

Elevated levels of IP-10 have been found in the early stages of insulin-dependent hyperglycemia [157]. Furthermore, recent research has shown that intrahepatic and circulating IP-10 levels are associated with obesity and glycemic resistance in patients with chronic HCV infection and HCV/HIV co-infection [158]. In a recent study, IP-10 was identified as an independent risk factor for developing hepatic inflammation, insulin resistance, and eventual diabetes, along with chemokine (C–C motif) ligand 2 (CCL2) and cachectin levels, as well as Homeostatic Model Assessment of insulin resistance [159].

3.3.4. Monocyte Chemoattractant-1(MCP-1)

Monocyte chemoattractant denotes chemicals, primarily Monocyte Chemoattractant Protein-1 (MCP-1), that draw monocytes, a category of white blood cells, to areas of inflammation or tissue damage. MCP-1 is a chemokine that interacts with receptors on monocytes, directing their migration from the circulation into afflicted organs. In conditions such as diabetic nephropathy, increased MCP-1 levels facilitate monocyte infiltration into the kidneys, resulting in inflammation, fibrosis, and the advancement of renal damage. MCPs are crucial in beginning and maintaining inflammatory responses in diverse clinical situations. MCP-1 is a member of the CC cytokine family and is produced by various cell types, including Polkissen cells, glomerular endothelial cells (GEC), tubular epithelial cells, and macrophages, in response to inflammatory cytokines such as lymphokines, leukocyte pyrogenic cytokines, cachectin, and interferon-gamma. Previous studies have investigated the role of MCP-1 in DKD and have identified it as a crucial determinant. In renal disease, there is recruitment and accumulation of macrophages. Urine levels of MCP-1 are elevated in DN and other inflammatory kidney disorders [160]. In one study, significantly higher levels of uMCP-1 were observed in patients with macro proteinuria ($P < 0.001$) and micro proteinuria ($P < 0.01$) compared to hyperglycemic individuals with normal albuminuria and healthy controls ($P < 0.001$). A correlation analysis showed a significant association between uMCP-1 and the protein/creatinine ratio ($R = 0.968$, $P < 0.001$). Furthermore, uMCP-1 levels were positively correlated with serum urea ($R = 0.461$, $P = 0.001$), serum creatinine ($R = 0.475$, $P = 0.001$), and inversely correlated with GFR (GFR) ($R = –0.983$, $P < 0.001$). ROC curve analysis for the early detection and diagnosis of DKD showed that a cutoff value of 110 pg/mg for urine MCP-1 had 100 % specificity and 92 % sensitivity. MCP-1 may serve as a predictive marker for the progression of diabetic renal disease, although further research is needed to determine the role of urinary MCP-1 in individuals with normal proteinuria and micro proteinuria in the context of diabetes [161]. In summary, MCP-1 is a valuable biomarker in assessing inflammation-related diseases, and its levels provide insights into disease activity and progression in various pathological conditions.

3.3.5. Granulocyte colony-stimulating factor

Granulocyte Colony-Stimulating Factor (G-CSF) is a polypeptide growth factor that affects the production of neutrophilic granulocytes. This physiological process occurs on a vast scale in vivo and serves as an essential component of the host's defensive system. In order to replace normal losses, an adult of normal size will produce approximately 120 billion granulocytes every day. During stressful situations like infection, this production capability can be enhanced by at least tenfold. G-CSF is expected to play a role in both the basal regulation of neutrophil production and the regulation of neutrophil recruitment. It acts as the primary regulator of neutrophil responses to inflammatory stimuli. Additionally, G-CSF appears to impact various biological functions, including proliferation, neutrophil functions, and cell distribution [162]. Following G-CSF treatment, there was a significant reduction in ovarian and endometrial damage and fibrosis scores. G-CSF's actions in rat models offer the potential for improved treatment of human conditions such as early ovarian failure and uterine abnormalities associated with diabetes mellitus [163]. G-CSF itself can be measured, but its biomarkers typically refer to indicators that can help track its effects or activity in the body.

3.3.6. Eotaxin

Eotaxin is a small glycoprotein present in the airways of asthma patients, acting as a chemokine to attract inflammatory cells. As a CC cytokine, eotaxin induces the movement of eosinophils from small blood capillaries in the lungs by interacting with the CC chemokine receptor CCR3 on the leukocyte cell membrane [161].

In a study involving six uncontrolled non-insulin diabetic subjects (HbA1c levels > 7.5 %) and 20 non-glycemic subjects with chronic gum disease, the concentrations of 14 chemokines were measured in the gingival crevicular fluid (GCF) of both diabetic and non-diabetic patients in healthy and diseased areas. Eotaxin concentrations were higher in the healthy and diseased areas of diabetic participants compared to non-glycemic subjects. This finding suggests that uncontrolled non-insulin-dependent diabetes modifies the levels of various chemokines, favoring a pro-inflammatory profile at both healthy and pathological gum disease sites, which may contribute to the increased susceptibility of diabetic individuals to periodontal breakdown [164].

Another study analyzed 44 native renal biopsies from individuals with DN and 23 control cases. In terms of eotaxin expression in situ, the DN group exhibited a significant increase ($P = 0.0012$). The results indicate that in DN patients, eotaxin contributes to the production of cytokines and chemokines in situ, potentially playing a crucial role in the development of interstitial inflammation and the decline of their estimated GFR (eGFR) [165].

3.3.7. Orosomucoid

Orosomucoid is a glycoprotein that plays a role in inflammatory processes. In patients with insulin-dependent diabetes, urinary levels of orosomucoid are higher in those with normal albuminuria compared to controls. These elevated levels are associated with an increase in microalbuminuria and macroalbuminuria in these patients [166]. Similarly, patients with type 2 diabetes excrete more orosomucoid in their urine, along with immunoglobulin G, ceruloplasmin, and transferrin [167].

Orosomucoid has been identified as a significant independent factor in diabetic microvascular complications and as an early marker of renal injury [168]. The rate of urinary orosomucoid excretion in individuals with adult-onset diabetes is predictive of cardiovascular mortality [169]. In the early stages of type 2 DKD, there is an increase in urine orosomucoid levels, making it an important marker for detecting DN and initiating early treatment [170].

Only 20 years ago, the field of chemokines was revolutionized by the discovery of the chemokine RANTES (now known as CCL5) [171]. This discovery led to the identification of numerous other chemokines and chemokine receptors, providing insights into the mechanisms of chemotaxis, immune response to infection and inflammation, and immunological communication [172].

3.3.8. Rantes

RANTES, or CCL5, plays a crucial role in attracting various immune cells, including thymocytes, accessory cells, eosinophils, large granular lymphocytes, macrophages, and granulocytes, to sites of infection and inflammation. Although initially thought to be produced exclusively by T cells, it is now known to be produced by a wide range of cell types. RANTES exhibit positive functions by guiding immune cells to areas of

infection and injury and can also have direct antibacterial effects through the production of nitric oxide in macrophages [173].

However, RANTES can also have negative effects on inflammatory processes, contributing to conditions such as joint inflammation, atopic dermatitis, kidney damage, colitis, and other diseases associated with inflammation and tissue damage [174]. It has been implicated in arterial stiffness, hypertension, asthma, nasal polyps, endometriosis, kidney disease, and potentially even Alzheimer's disease. Additionally, RANTES has been linked to the initiation or progression of certain cancers, such as prostate and breast cancer [175].

Genetic variations in the RANTES promoter (28G genotype) and the chemokine receptor type 5 (organizer 59029A genotype) have been identified as potential risk factors for DKD in patients with adult-onset diabetes [176]. Another study found that increased serum levels of RANTES in individuals with insulin-dependent diabetes are closely associated with postprandial (acute) hyperglycemia, suggesting its potential role in the early stages of DN [177].

3.4. Glomerular biomarkers

Glomerular biomarkers in blood or urine can indicate glomerular disease presence, severity, or progression. These biomarkers help diagnose kidney diseases, track treatment efficacy, and predict outcomes. These biomarkers and other clinical indicators help nephrologists diagnose, stage, and monitor glomerular diseases, improving outcomes prediction and treatment optimization.

3.4.1. Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a crucial regulator of physiological processes such as vasculogenic during embryonic development, muscular development, and reproductive functions. However, VEGF has also been implicated in the pathological formation of new blood vessels in various diseases, including cancer, ophthalmic disorders, and other conditions [178].

In a recent study, the role of glycemic Endothelial Nitric Oxide Synthase Knockout Mice in the progression of DKD was identified [179]. Early research has also found a connection between VEGF, its receptor, gestational diabetes, and the development of preeclampsia [180].

Furthermore, another recent study highlighted that serum levels of VEGF-A, with a significant contribution from platelet-derived vascular permeability factor, better reflect diabetic susceptibility than blood VEGF-A levels [181].

3.4.2. Podocalyxin

Podocalyxin is a sialomucin protein that shares similarities with CD34 and endoglycan. It is expressed during cellular migration and tissue development within the hematopoietic system, particularly in regions of blood cell production. It is also present in subsets of leukemia, breast, prostate, hepatic, pancreatic, and renal cancers. It is frequently associated with more aggressive variants of these cancers [182].

A study has identified that urinary podocalyxin serves as a more sensitive and specific marker for DKD compared to microalbuminuria [183]. Urinary podocalyxin may prove to be a valuable and more accurate diagnostic indicator for the early detection of DKD compared to the measurement of microproteinuria [184].

3.4.3. Nephrin

In podocytes, nephrin plays a critical role in maintaining the proper structure of the slit diaphragm. The podocyte slit diaphragm depends on nephrin. It activates podocyte cell signaling pathways by interacting with podocyte and slit diaphragm proteins. Nephrin deficiency during development can cause congenital kidney syndromes in children. Adult kidney diseases like diabetic and HIV-associated kidney disease decrease nephrin expression. The kidney and several other organs express nephrin, but its role outside the renal system is unknown. Further research is needed to determine if nephrin could be a renal disease treatment target [185].

The presence of nephrin in urine, which is commonly observed in patients with normal levels of proteinuria, suggests that it may contribute to the development of microproteinuria [186]. If further research confirms that urinary nephrin can serve as an indicator of preclinical DKD, it could provide valuable insights into podocyte dysfunction in the disease and potentially lead to the identification of novel early treatment targets [187].

In DN, nephrin is crucial for preserving the integrity of the slit diaphragm between podocyte foot processes, which is vital for effective glomerular filtration. Damage or downregulation of nephrin disrupts the filtration barrier, leading to elevated proteinuria, a characteristic of DN. The absence of nephrin disrupts podocyte functionality and induces podocyte apoptosis, hence hastening glomerulosclerosis and the course of the disease. Consequently, nephrin insufficiency is strongly correlated with the extent of renal impairment in DN.

3.4.4. Retinol-Binding protein 4 (RBP4)

Kanai discovered and characterized retinol-binding protein 4 (RBP4), a small plasma protein weighing approximately 21 kDa [188]. The protein is primarily produced in the liver (as a hepatokine) and to a lesser extent by adipocytes (20–40 %, as an adipokine) and immune cells, particularly macrophages [189]. RBP4 is well-known for its role as a transporter of retinol (vitamin A alcohol, ROH) and has also been found to have fatty acid transport capabilities [190], Under normal conditions, the concentration of RBP4 in plasma remains relatively constant and is approximately 34 mg per 100 mL of plasma in individuals with normal kidney function [191].

A majority of RBP4 molecules (86 %) are bound to retinol (holo-RBP4) and tightly associated with transthyretin (TTR), forming a 76 kDa complex. This large size of the "retinol transport unit" limits the renal clearance of RBP4 and ensures adequate retinol levels in the plasma. However, the retinol-free component of RBP4 (apo-RBP4) undergoes glomerular filtration, effective reabsorption, and degradation in the kidney's proximal tubules [192]. Only a small amount of plasma RBP4 (0.1 mg/24 h, 0.025 %) escapes reabsorption and degradation, eventually being excreted in the urine [193]. From a clinical perspective, the urinary portion of RBP4 (urinary RBP4 or uRBP4) is of particular importance because its elevation in urine indicates tubular damage and reflects the presence of proximal tubular dysfunction [194].

Urinary RBP4 levels have been found to be significantly elevated (even $>$ 104-fold) in various pathological conditions affecting the kidneys directly or indirectly, such as glomerular diseases, prediabetes, DN, renal allograft dysfunction, CKDs, preeclampsia, leukemia, and others [195]. In the absence of clinical evidence of kidney diseases, increases in urinary RBP4 secretion can identify subclinical kidney disease and may play a role in the initial assessment and subsequent monitoring of DKD in patients with lupus [196].

In multiple stepwise linear regression analyses, both uric acid and estimated glomerular filtration rate (eGFR) showed strong associations with serum RBP4. These findings suggest that reduced kidney clearance in early DKD affects RBP4 and indirectly supports the hypothesis of a relationship between metabolic syndrome, uric acid, and insulin resistance [197].

3.4.5. Advanced glycated end products

Prolonged exposure to hyperglycemia is now recognized as the primary causative factor in the development of diabetes complications [198]. Glucose has a wide range of transient and reversible effects on cellular activity [199], as well as irreversible effects that can lead to chronic and cumulative dysfunction [200]. A recent study suggests that the rapid progression of DN may be associated with three key AGEs: carboxymethyl lysine (CML), carboxyethyl lysine (CEL), and pentosidine. These AGEs could potentially serve as early indicators of DN [201]. Urinary excretion of proteins modified by AGEs has also been proposed as a useful marker of proteinuria in individuals with both insulin-

dependent and non-insulin-dependent diabetes, indicating the need for further investigation in larger diabetic cohorts [202–204].

3.4.6. Interleukin-6(IL-6)

In 1986, pro-inflammatory cytokine was found as a B lymphocyte that initiates Immunoglobulin G synthesis [205]. The cytokines of the IL-6 family have a wide range of physiological and pathological roles. Some of their roles overlap, for example, both a pro-inflammatory cytokine and adipose-genesis inhibitory factor promote the preparation of sever-stage protein in hepatocytes, and adiposeness inhibitory factor, a pro-inflammatory cytokine, are all implicated in the osteoclast synthesis stimulates bone breakdown [206]. However, one research discovered that urine pro-inflammatory cytokine levels did not differ meaningfully among proteinuria phases, with only a slight rise among individuals with micro proteinuria and normal proteinuria [207]. Despite the fact that a recent systematic analysis indicated that pro-inflammatory cytokine might be one of the reliable molecular markers for forecasting the advancement of DKD although the results are inconsistent, More research is needed to validate the use of IL6 in the initial findings of DKD [208].

3.4.7. MicroRNAs (MiRNAs)

MicroRNAs (MiRNAs) are pervasive, rapidly growing, non-coding, single-stranded (ss) RNA transcripts that operate as post-transcriptional controllers of gene expression by inhibiting polypeptide translation and/or promoting messenger RNA (mRNA) degradation. MiRNAs are believed to affect the expression of at least 60 % of all protein-coding genes, and changes in miRNA expression patterns have been observed in a variety of pathophysiological conditions. Currently, there is a significant focus on MiRNAs as both novel biomarkers and potential therapeutic targets [209].

It has been discovered that new MiRNAs are associated with histological abnormalities and serve as useful indicators of renal injury, enabling the sensitive, specific, and noninvasive diagnosis of DN and lupus nephritis [210]. The results of various studies have indicated that targeting DNA-associated genes is useful in monitoring and conducting community trials in DKD. Five highly important and consistently dysregulated MiRNAs have been identified, and future research efforts should focus on determining their potential impact on DKD, as well as their clinical utility as biomarkers and treatment mediators for diabetic renal disease [211].

3.4.8. Proteomites

Diabetes and its complications are complex, requiring a comprehensive and unbiased clinical approach such as proteomics. Proteomics, which involves the systematic study of peptide identity, quantity, and function, has recently been applied to the study of diabetic renal disease. Proteomic research in DN has uncovered new mechanisms of diabetic kidney pathophysiology and potential urine markers for DN. Recent advancements in proteomic techniques have also facilitated the identification of the role of advanced glycation end products (AGEs) in impaired mitochondrial respiration, as well as the rapid development of mass spectrometric methods for peptide and protein markers of DKD and markers of pharmacologic therapies. Although proteomic investigations in DN are relatively recent, they have shown significant promise [212].

Further, proteomics plays an essential role for biomarker development as it facilitates the thorough examination of proteins expressed in cells, organs, or body fluids across diverse physiological and pathological states. In conditions such as DN, proteomic methods facilitate the identification of particular protein alterations that manifest early in disease progression, frequently prior to the onset of clinical symptoms. Employing techniques like mass spectrometry and protein microarrays, researchers may concurrently identify, quantify, and characterise millions of proteins, uncovering novel biomarkers that more precisely indicate kidney injury, inflammation, or fibrosis compared to established indicators. Moreover, proteomics elucidates molecular pathways and protein interactions implicated in disease mechanisms, offering insights into prospective treatment targets. The elevated sensitivity and specificity of proteomic biomarkers enhance diagnosis, prognosis, and treatment monitoring, facilitating the advancement of personalised medicine. Proteomics is a crucial instrument that expedites biomarker identification, deepens comprehension of disease mechanisms, and aids in the formulation of tailored therapies.

In a recent study, ten micrograms of urine albumins were collected from 190 groups, including 20 healthy individuals, 20 individuals with normal urinary protein levels, 18 individuals with microalbuminuria in glycemic patients, and 132 individuals with autopsy-confirmed kidney disease (including 65 with diabetic renal disease, 10 with glycemic CKD, and 57 with non-glycemic chronic kidney ailments). These samples were analyzed using supervised learning methods. The classification system achieved a 75 % accuracy in identifying patients with albuminuria, 87.5 % accuracy in identifying those with proteinuria, and 87.5 % accuracy in identifying those with DKD when applied to a blinded validation set. Importantly, it was able to distinguish DKD from chronic renal disease in both glycemic and non-glycemic individuals. Among the most significant predictors of the classification model, two proteins, ubiquitin, and β2-microglobulin, were discovered and validated. These findings indicate the presence of a distinct urinary proteomic marker capable of reliably classifying adult-onset diabetes patients with diabetic familial idiopathic nephrotic syndrome [213].

Research demonstrates that proteomic assessments can identify biological markers for renal dysfunction in urine, which is an essential step in advancing treatment plans and understanding pathogenic mechanisms [214].

3.4.9. Alpha-Klotho (Klotho)

Alpha-Klotho (Klotho) and fibroblast growth factor 23 (FGF23) were initially discovered separately and later classified as novel phosphatonins and anti-aging proteins, respectively [215]. Interestingly, fibroblast growth factor 23 null mice exhibit nearly all the characteristics of Klotho null mice, suggesting that Klotho and fibroblast growth factor 23 may share similar signaling pathways, particularly in the regulation of mineral metabolism [216]. It has been suggested that plasma Klotho levels could serve as an early indicator for predicting renal impairment in patients with non-insulin-dependent diabetes, and the levels of Klotho and FGF-23 may have clinical utility as markers for anticipating fracture occurrences [217].

3.4.10. Copeptin

Copeptin is an important hormone in humans. While measuring traditional AVP levels can be difficult and lead to pre-analytical errors, it is important for fluid balance and vascular tone. Copeptin, a 39-amino acid glycopeptide that makes up the C-terminal portion of the AVP precursor, has become a reliable and sensitive surrogate marker for AVP release, similar to C-peptide for insulin release. Copeptin is useful for diagnosing diabetes insipidus and monitoring sepsis and cardiovascular conditions [218]. Copeptin can also be utilized for diagnosing atherosclerosis in individuals with type 1 diabetes. A cross-sectional study revealed higher serum copeptin concentrations in type II diabetics, particularly those with nephropathy, and its correlation with urinary albumin and HbA1c levels suggests that copeptin may serve as a prognostic marker for hyperglycemia and the progression of diabetic renal disease in type II diabetics when considering other risk factors. The strong associations between copeptin levels and glycemic and renal markers, as well as its positive correlation with a history of diabetes mellitus, highlight its importance as an early and consistent diagnostic tool for hyperglycemic kidney disease and its related DKD [219].

3.4.11. E-cadherin

Cadherin expression is dynamic and influenced by cellular signals and development. Sequence similarity divides cadherins into five subfamilies: classical types I and II (E-, P-, N-, and VE-cadherin), unusual (T-

cadherin), macula adherens, protocadherins, and cadherin-related polypeptide Classical cadherins include epithelial, neural or synaptic, placental, vascular-endothelial, retinal, and kidney. E-cadherin is crucial to epithelial cell adherent junction (AJ) formation. It maintains the epithelial barrier by promoting durable, homotypic adhesion between neighboring cells [220]. The absence of E-cadherin leads to the loss of tight junctions and desmosome formation, underscoring its significance in regulating epithelial cell–cell interactions. Serum levels of E-cadherin and osteoblast-specific factor 2 may serve as useful indicators associated with the pathology and stages of DKD [221].

3.4.12. Dipeptidyl peptidase (DPPI)

Dipeptidyl peptidase I is a lysosomal cysteine protease involved in the degradation of granzymes, which are serine endopeptidases exclusively found in the granules of activated cytotoxic white blood cells [222]. A study revealed that the micro-particle-bound form of DPP IV was the predominant form found in urine, and T2DM patients excreted significantly higher levels compared to the control group. In T2DM patients, urine levels of micro-particle-bound DPP IV were positively correlated with urine albumin-to-creatinine ratio (UACR). These findings suggest that the level of microvesicle-bound DPP IV in urine is associated with the severity of diabetic renal disease. Another study demonstrated the potential usefulness of blood soluble DPP-4 levels as a future biomarker for declining kidney function in patients with type 2 diabetes [223].

DPPI is essential for the activation of numerous serine proteases in immunological and inflammatory cells, including neutrophils, mast cells, and cytotoxic T lymphocytes. DPPI modulates the maturation and function of enzymes implicated in immunological defence and inflammatory responses by cleaving dipeptides from the N-terminus of protein substrates. Dysregulation has been associated with chronic inflammatory illnesses, such as DN, in which inflammation leads to kidney damage and fibrosis. Comprehending DPPI's function and regulation may uncover innovative therapeutic targets to alleviate inflammation-induced advancement of DN. The present study's emphasis on DPPI provides significant insights into the molecular mechanisms behind diabetic kidney impairment and prospective therapeutic options.

Biomarkers play a pivotal role in the early detection, diagnosis, and management of DN. These biomarkers can provide valuable insights into the pathophysiological mechanisms of DKD and help in monitoring disease progression or response to treatment. Table 2 compares various biomarkers commonly associated with DN, their types, relevance, and differentiating features.

The development and validation of biomarkers with optimal sensitivity, specificity, and predictive power are critical. These biomarkers are not only useful for early diagnosis but also for guiding treatment strategies, assessing therapeutic efficacy, and monitoring disease progression. The specificity, sensitivity, and predictive power of biomarkers are vital for their clinical application. Specificity refers to the ability of a biomarker to correctly identify individuals who do not have the disease. A highly specific biomarker reduces the likelihood of false positives, ensuring that those who are diagnosed with DN indeed have the condition. In the case of DN, a sensitive biomarker would help identify those in the early stages of kidney damage, allowing for timely intervention and treatment. Similarly, biomarkers with high predictive value can aid clinicians in determining which patients are at risk of developing more severe stages of nephropathy or those who are likely to benefit most from specific therapeutic interventions.

Although experimental biomarkers such as miRNAs and proteomic markers hold promise for enhancing the diagnosis and management of DN, they are not yet ready to replace conventional clinical tools like urine albumin-to-creatinine ratio (ACR) or GFR in everyday practice. miRNAs are small, non-coding RNA molecules that regulate gene expression and have been identified as potential biomarkers for various diseases, including DN. Several studies have explored the role of miRNAs in DN, with particular interest in their ability to modulate inflammation, fibrosis, and other pathological processes associated with kidney damage. Proteomic markers have shown potential in identifying early changes in kidney function associated with DN. However, like miRNAs, proteomic biomarkers are still largely confined to the research phase.

Table 2
Differences between Various Biomarkers in Diabetic Nephropathy.

Biomarker	Type	Role in DN	Key Features
Albumin (Urinary)	Protein	Early sign of kidney damage; microalbuminuria is a hallmark of DN	Increased levels indicate damage to glomerular filtration
Creatinine (Serum)	Waste product of muscle metabolism	Elevated levels suggest impaired kidney function	High levels indicate decreased kidney clearance
eGFR (Estimated Glomerular Filtration Rate)	Kidney function indicator	Key marker for assessing overall kidney function	Lower eGFR suggests reduced kidney function or early kidney failure
Urea (Serum)	Waste product of protein metabolism	Increased levels suggest reduced kidney function	Elevated urea can indicate both acute and CKD
Cystatin C (Serum)	Inhibitor of cysteine proteases	Sensitive marker for kidney function, especially in early stages of DN	Elevated levels can indicate early kidney dysfunction independent of muscle mass
Transforming Growth Factor-Beta (TGF-β)	Cytokine/ Signaling molecule	Mediates fibrosis and glomerular injury in DN	Elevated levels correlate with progression to ESRD
Soluble Tumor Necrosis Factor Receptor (sTNFR)	Cytokine receptor	Reflects inflammatory response in kidney injury	Increased levels seen in inflammatory and fibrotic processes in DN
Fibroblast Growth Factor-23 (FGF-23)	Phosphaturic hormone	Regulates phosphate homeostasis; higher in kidney injury	Elevated levels are linked to vascular calcification and cardiovascular risk in DN
Neutrophil Gelatinase-Associated Lipocalin (NGAL)	Acute phase protein	Early marker of acute kidney injury and tubular damage in DN	Increased NGAL is sensitive in detecting tubular injury and predicting disease progression
Kidney Injury Molecule-1 (KIM-1)	Cell membrane protein	Sensitive marker for kidney tubular damage	Elevated KIM-1 levels reflect tubular injury and inflammation
Chronic Kidney Disease (CKD)-MBD Markers	Combination of markers	Includes markers like phosphorus, calcium, and parathyroid hormone (PTH)	Used to assess bone-mineral disturbances often seen in DN
MicroRNA (miRNA)	Small non-coding RNA molecules	Regulate gene expression and show promise as diagnostic markers	Altered miR profiles are associated with DN development and progression

3.5. Recent advances in biomarker discovery

Recent advances in scientific technologies have facilitated the discovery of novel biomarkers for diabetic nephropathy (DN), a progressive kidney complication associated with diabetes. These biomarkers offer the potential for early detection, prognosis, and therapeutic targeting. Based on recent literature between 2022 and 2024, biomarkers have been identified across genomic, transcriptomic, metabolomic, and proteomic domains Table 3.

Table 3
Some Recent Biomarkers for Diabetic Nephropathy.

Class	Biomarkers	Year	Ref.
Genomic	Cyp2d22,Slc1a4,Ddah1	2023	[224]
	GABRR1,ELMO1,FRMD3,CARS, MYO16/IRS2,THBS2、NGAL,PIP,TRAF6, ICAM-1,C667T	2022	[225]
	IL-6-634C/G, IL-10-592C/A	2024	[226]
	REDD1	2023	[227]
Transcriptomics	miRNA-21	2024	[228]
	circRNAATG7	2024	[229]
Metabolomics	Methionine and branched-chain amino acids	2023	[230]
	Phenyl sulfate	2023	[231]
	Urine lactate	2023	[232]
	TMA	2023	[233]
	TMAO	2024	[234]
Proteomics	TNF	2022	[235]
	S100A8/A9	2022	[236]
	ACSL1	2023	[237]
	CKD27	2024	[238]

3.5.1. Genomic biomarkers

Several genomic biomarkers have been identified in the last three years, indicating a growing understanding of DN's genetic basis. In 2023, genes such as Cyp2d22, Slc1a4, Ddah1, and REDD1 were associated with DN, suggesting roles in drug metabolism, amino acid transport, and cellular stress responses. In 2022, more extensive genetic profiling uncovered GABRR1, ELMO1, FRMD3, CARS, MYO16/IRS2, THBS2, NGAL, PIP, TRAF6, ICAM-1, and C667T polymorphism. These genes are largely involved in inflammation, fibrosis, and immune regulation. Polymorphisms in IL-6 (−634C/G) and IL-10 (−592C/A), reported in 2024, underscore the role of inflammatory cytokines in DN pathogenesis. Notably, REDDI was identified in 2023, are regulator of stress-activated signaling pathways, providing insight into cellular stress responses in DN.

3.5.2. Transcriptomic biomarkers

Transcriptomic studies have focused on non-coding RNAs as potential biomarkers. In 2024, miRNA-21 and circRNA-ATG7 emerged as promising markers. miRNA-21 is a well-known regulator of fibrosis and inflammation, processes integral to DN progression. While as circRNA-ATG7 is implicated in autophagy and cellular homeostasis, offering a novel link between non-coding RNA and kidney pathology. These markers provide opportunities for non-invasive diagnostic assays and potential therapeutic modulation.

3.5.3. Metabolomic biomarkers

Metabolomic profiling from 2023 to 2024 has revealed key metabolites associated with DN. Methionine and branched-chain aino acids, along with phenyl sulfate, were linked to altered amino acid metabolism in DN. Urinary lactate was also elevated, indicative of hypoxic stress or altered renal energy metabolism. Importantly, trimethylamine (TMA) and trimethylamine-N-oxide (TMAO), identified in 2023 and 2024, respectively, are gut-derived uremic toxins associated with renal and cardiovascular outcomes. These metabolites may serve as indicators of metabolic dysregulation and potential therapeutic targets.

3.5.4. Proteomic biomarkers

Proteomic research has revealed a set of proteins with potential diagnostic and prognostic value. In 2022, TNF and S100A8/A9 were identified, reinforcing the role of inflammation in DN. ACSL1, discovered in 2023, plays a role in fatty acid metabolism and may reflect early metabolic dysfunction. In 2024, CKD273, a urinary proteomic classifier comprising multiple peptide biomarkers, showed promise in predicting DN progression, representing a significant advancement toward personalized nephrology.

4. Conclusion

In conclusion, this review emphasises the increasing significance of new biomarkers in revolutionising the therapeutic management of DN. Conventional indicators like albuminuria and serum creatinine frequently do not identify early renal impairment, resulting in postponed diagnosis and treatment. Emerging biomarkers, such as those linked to glomerular injury (e.g., nephrin, podocalyxin), tubular damage (e.g., NGAL, KIM-1, NAG), oxidative stress (e.g., 8-OHdG, MDA), and inflammation (e.g., TNF-α, IL-18, MCP-1), exhibit enhanced sensitivity and specificity in identifying subclinical renal dysfunction. These indicators not only improve early detection but also elucidate the underlying pathophysiological mechanisms of DN, facilitating more precise disease staging and risk stratification.

The review further emphasises the possibility of combining multi-biomarker panels with sophisticated analytical methods like proteomics and machine learning to enhance diagnosis accuracy, facilitate personalised risk evaluation, and inform therapy choices. Nonetheless, despite their potential, the majority of these biomarkers are still in the experimental stage and necessitate additional validation via extensive, longitudinal investigations before their normal implementation in clinical practice. Emerging biomarkers across genomics, transcriptomics, metabolomics, and proteomics have deepened insights into the complex pathogenesis of diabetic nephropathy. These discoveries point to inflammation, metabolic imbalance, and cellular stress as central mechanisms, paving the way for improved diagnostic tools and personalized treatment strategies.

Overall, this work underlines the necessity for a paradigm change from conventional diagnostics to a more holistic biomarker-driven approach. This strategy can promote early diagnosis, allow for prompt and personalised therapies, and ultimately diminish the progression to end-stage renal disease and its related healthcare costs. This review offers a significant foundation for physicians, researchers, and policymakers seeking to enhance outcomes in diabetic kidney disease *via* precision medicine.

5. Future Prospectus

The prospects of this study involve clinical validation and standardisation of the new biomarkers for the early identification and monitoring of DN development. The use of multi-biomarker panels with sophisticated technologies like proteomics and machine learning may improve diagnosis precision and facilitate personalised treatment approaches. Significant, multi-center investigations are crucial to determine their prognostic significance across varied populations. Ultimately, these developments may facilitate earlier therapies and enhance long-term results in diabetic Nephropathy.

CRediT authorship contribution statement

Zahoor A. Wani: Writing – original draft. **Sumeer Ahmed:** Writing – original draft, Methodology. **Abdullah Saleh:** Writing – review & editing. **Venkateswara Rao Anna:** Investigation, Validation. **Khairi M. Fahelelbom:** Data curation, Resources. **Senthil Kumar Raju:** Formal analysis. **Ahmed Abu-Rayyan:** Writing – review & editing, Conceptualization. **Ajmal R. Bhat:** Writing – review & editing.

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Data availability

Data will be made available on request.

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