Physical Education, Health and Social Sciences

https://journal-of-social-education.org

E-ISSN: 2958-5996

P-ISSN: 2958-5988

Potential Biomarkers for Early Detection of Diabetic Nephropathy: A Narrative Review

Nadia Rasheed[1], Dr. Salah Shah[2], Dr. Naveed Babar[3], Sidra Iqbal[4]

[1]PhD Scholar, Superior University Lahore, naddiya24@gmail.com
[2]Assistant Professor, salehshah83@gmail.com
[3]Professor, Dean, Faculty of Allied Health Sciences, Superior University Lahore Pakistan, naveed.babur@superior.edu.pk, Orcid id:0000-0002-5437-2497
[4]HOD MLT, Superior University Lahore Pakistan, Sidra.iqbal@superior.edu.pk

DOI: https://doi.org/10.63163/jpehss.v3i3.582

Abstract

Diabetic Nephropathy shows the predominant cause of renal failure in diabetics. It is also a significant contributor to clinical mortality which is characterized by the progressive decrement in renal morphology and physiology because of sustained hyperglycemia. As the disease progress, many patients ultimately require renal replacement therapy for end stage renal disease (ERSD). For this reason, early diagnosis and prompt interventions are crucial to limit disease progression, enhance clinical outcomes and conserve quality of life. The recognition of biomarkers for the early detection of DN is of predominant importance. In recent years, the process of recognition of novel biomarkers which offers valuable insights into the onset and progression of DN has been significantly increased. This review gives a comprehensive evaluation of emerging biomarkers associated with diabetic nephropathy.

Introduction

The pathogenesis of diabetic nephropathy (DN) is complex and multifactorial, progressing via many stages and primarily driven by hyperglycemia-induced inflammatory processes that effect both hemodynamic and metabolic routes. Hemodynamic variations contribute to increased intraglomerular pressure and activation of vasoactive hormonal systems and metabolic changes lead to mesangial cell enlargement and structural remodeling of renal tissue. These processes lead up to inflammation, endothelial dysfunction, and fibrosis. Early diagnostic indicators of DN commonly include glomerular filtration rate (eGFR) and albuminuria. These markers also have prognostic utility in predicting cardiovascular events and mortality, broadening their relevance beyond kidney-specific outcomes.[1] A major limitation of depending on these markers is the growing prevalence of non albuminuric DN in which patients show renal impairment without albuminuria.[3] Moreover, it often reflects an advanced stage of kidney damage, followed by expeditious progression to end-stage renal disease (ESRD) in the cases of albuminuria. It is significantly identified that proteinuria does not reliably pave the way for functional decrement in all cases. This indicates that injury to the tubulointerstitial compartment may occur independently of glomerular destruction. Furthermore, serum creatinine levels and in consequence, the estimated glomerular filtration rate (eGFR) are affected by determinants i.e, muscle mass and dietary protein intake that can decrease their reliability. It is importantly relevant in individuals with Type 2 Diabetes Mellitus (T2DM) in which eGFR estimates founded on the CKD-EPI equation may be less precise. In recent years, significant advances have been made in illuminating the molecular mechanisms of DN and in recognizing related biomarkers. The aim of

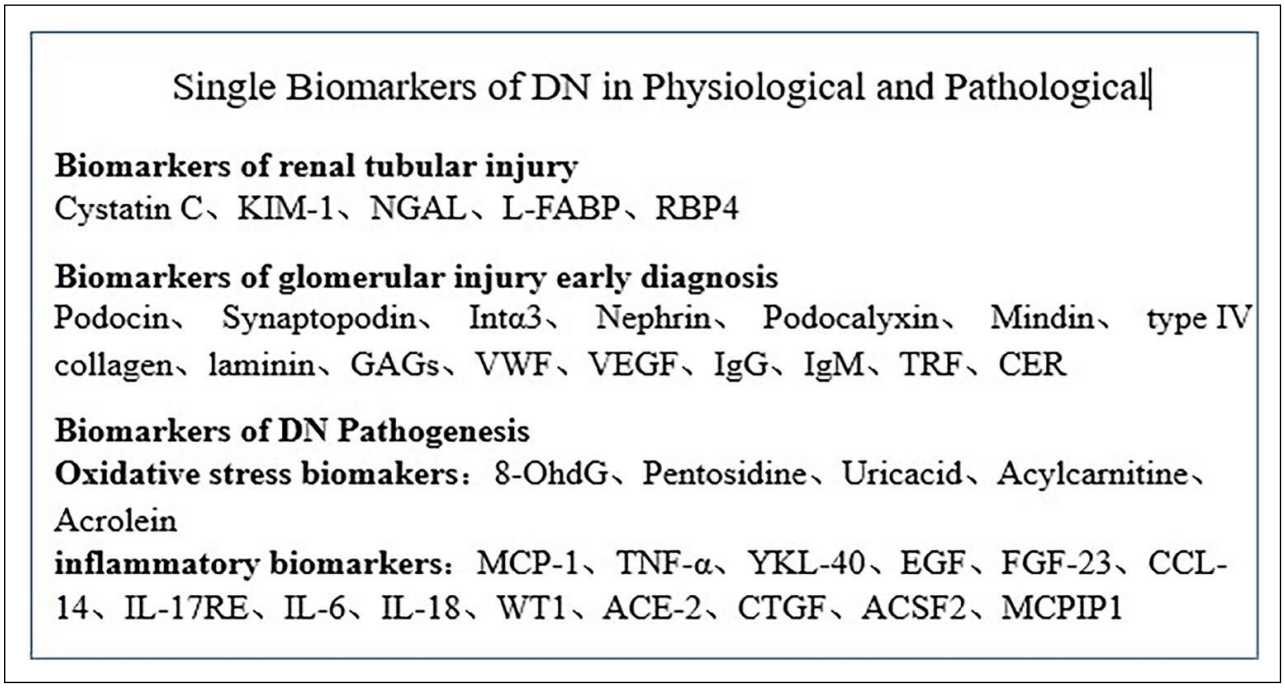
this review is to provide in depth analysis of contemporary biomarkers of DN, scanned via the optics of disease physiology, pathology, pathogenesis, and omics-based approaches.

Physiological and Pathological Biomarkers of DN

Diabetic nephropathy (DN) results in both morphological and functional variations in the kidney, primarily effecting the glomeruli and tubulointerstitial compartments. Analyzing the molecules involved in renal destruction may help predict the progression of DN.

Figure 1 summarizes the individual biomarkers associated with DN under physiological and pathological conditions.

Figure1: Single Biomarkers of DN



Biomarkers of Renal Tubular Injury

Research indicates that tubular injury in diabetic patients can occur prior to glomerular injury, and the extent of tubulointerstitial damage may play a crucial role in the deterioration of renal function.[3] Consequently, tubular biomarkers hold significant importance for the early diagnosis of diabetic nephropathy. *Cystatin C.* Cystatin C (CysC) is a low-molecular-weight protein consisting of 122 amino acids, synthesized and released into plasma by all nucleated cells at a constant rate. This small, positively charged protein is freely filtered through the glomerular membrane and is subsequently completely reabsorbed and degraded in the proximal tubule, without being secreted back into circulation. Consequently, CysC is typically absent in urine.[4–8] As a member of the cysteine protein inhibitor family, CysC serves as the most abundant and potent endogenous inhibitor of both intracellular and extracellular enzyme activity, playing a significant role in various pathological processes, including cardiovascular disease and inflammation.[6] Recent studies have identified CysC as a valuable biomarker for tubular injury, aiding in the quantification and classification of different stages of DN.[9] Research conducted by Jeon[10] et al demonstrated that CysC levels increase with advancing stages of

chronic kidney disease (CKD), from stage I to III, and correlate positively with the albumin/creatinine ratio, particularly during the transition from normal albuminuria to microalbuminuria. Furthermore, Xu[11] et al confirmed the association of elevated CysC levels with the progression of DN. Notably, serum CysC levels are independent of muscle mass and remain unaffected by age, presenting distinct clinical advantages over creatinine (Cr). Both serum CysC and Cr exhibit a hyperbolic relationship with GFR, allowing their inclusion in the same pre- dictive equation for GFR.[8] CysC is particularly advantageous for patients experiencing muscle mass loss or degenerative muscle diseases, proving to be a more accurate biomarker.[9] Thus, utilizing serum CysC as a biomarker for the early diagnosis of acute kidney injury (AKI) can effectively reflect early changes in renal function and a decrease in estimated GFR. *KIM-1.* KIM-1 is a 38.7-kDa type I transmembrane glycoprotein expressed on the parietal membrane of renal proximal tubular (PT) cells. It is shed from these cells during AKI and contributes to tubular epithelial hyperplasia.[12] Elevated concentrations of urinary KIM-1 (uKIM-1) are associated with further damage to the tubulointerstitium, leading to increased fibrosis and inflammation.[13,14] Notably, estimates of uKIM-1 levels can occur prior to the elevation of serum creatinine, serving as predictors of AKI; thus, KIM-1 has been utilized as a biomarker in studies investigating drug nephrotoxicity.[14] Presently, KIM-1 is the most extensively studied biomarker for DN.[15] Clinical studies have demonstrated a gradual increase in uKIM-1 values among patients with T1DM and T2DM, particularly those exhibiting microalbuminuria.[16,17] In a nested case-control study involving 380 participants and a prospective cohort study with 1156 participants, serum KIM-1 (sKIM-1) levels were independently associated with a heightened risk of decreased eGFR in patients with either early or advanced DN.[18] Similarly, a case cohort study of 894 individuals with DN and renal insufficiency demonstrated that higher sKIM-1 levels correlated with an increased risk of DN progression.[19] Additionally, KIM-1 may be linked to the risk of developing DN in children and adolescents diagnosed with T1DM; however, further prospective cohort studies are necessary to elucidate this relationship.[20] Moreover, fully printed photonic crystal microarrays can quantitatively detect uKIM-1 levels in less than 10 min.[21] Beyond its role in AKI, KIM-1 serves as a valuable tool for detecting CKD progression and guiding therapeutic interventions for patients at risk of CKD.

Neutrophil Gelatinase-Associated Lipocarrierin, NGAL.

NGAL, a 25 kDa protein that belong to the lipocalin family, is synthesized by neutrophils and epithelial cells in various tissues, including the kidney. This protein is released into circulation and subsequently filtered through the glomerular membrane, with reabsorption occurring in the proximal tubule.[9,22] NGAL has been extensively validated as a reliable biomarker for AKI,[23] and prospective analyses have demonstrated a strong association between urinary NGAL (uNGAL) levels and the histopathological severity of inflammatory kidney injury in patients with DN.[24] Significant elevations in serum NGAL (sNGAL) and uNGAL have been observed in individuals with normal to micro-massive albuminuria T2DM,[20,25] indicating that tubular and glomerular injuries may occur in the early stages of DN, thereby enabling the detection of early nephropathy prior to the onset of proteinuria. A meta-analysis further supports the potential diagnostic value of uNGAL for DN.[26] He et al[27] conducted a meta-analysis involving 19 studies, suggesting that both sNGAL and uNGAL could assist in the classification of DN and possess diagnostic utility in normoalbuminuric nephropathy. In a study of 300 subjects with Type 2 Diabetes Mellitus, both uNGAL and sNGAL were predictive of albuminuria and could serve as noninvasive tools for diagnosing, grading, and monitoring the progression of DN.[28] Furthermore, Duan et al[29] identified an optimal cut-off value for the uNGAL-to-creatinine ratio of 60.685 ng/mg, which was recognized as an independent risk factor for DN in patients with CKD and DM, exhibiting high

specificity (90.5%). Additionally, another study involving T2DM patients found that NGAL levels were positively correlated with renal function tests, including creatinine, blood urea nitrogen, and albuminuria. The sensitivity and specificity of uNGAL at a cut-off point of 565 ng/mL were reported to be 97.5% and 100%, respectively, underscoring the accuracy of both uNGAL and sNGAL as biomarkers for the early diagnosis of DN.[30] These findings imply that NGAL could serve as a non-invasive tool for diagnosing, staging, and monitoring the progression of DN, while also offering additional diagnostic value in patients with nephropathy characterized by similar levels of albuminuria. However, large-scale prospective studies are essential to validate the application of NGAL as a biomarker for routine clinical practice.[31]

Hepatic Fatty Acid-Binding Protein, L-FABP. L-FABP is a 14-kDa intracellular protein predominantly synthesized in the cytoplasm of proximal tubule (PT) cells, where it plays a crucial role in the metabolism of long-chain fatty acids. This protein is essential for maintaining fatty acid homeostasis, as fatty acids within the cytoplasm bind to L-FABP. A loss of intraglomerular fatty acid-binding albumin can lead to excessive accumulation of intraglomerular fatty acids, which induces inflammatory responses and manifests as tubular lesions in CKD. The upregulation of the L-FABP gene accelerates fatty acid metabolism and mitigates inflammation, functioning as a protective response.[32] In a three-year follow-up study involving 48 patients with Type 1 Diabetes Mellites (T1DM), uL -FABP emerged as an early marker of DN, correlating with disease progression over time, independent of albuminuria.[33] A cross-sectional study comparing patients with T2DM and nondiabetic individuals found that changes in uL-FABP levels during renal impairment preceded alterations in urinary albumin levels, suggesting that uL-FABP is a more reliable indicator than the albumin-to-creatinine ratio (ACR).[34]Hhong et al[35] reported significantly elevated L-FABP levels in elderly patients with T2DM, which were closely associated with the onset and progression of type 2 DN. Furthermore, a meta-analysis conducted by H ang et al[36] indicated that uL-FABP could serve as a potential biomarker for detecting all stages of DN and for predicting the progression and severity of the condition in patients with both T1DM and T2DM. A 12-year follow-up study corroborated these findings, demonstrating a significant increase in uL-FABP, a 50% reduction in GFR, and a decrease in the incidence of cardiovascular disease among patients with T2DM.[37] The assessment of uL-FABP in individuals with T2DM appears to be a promising tubular marker for predicting the incidence of cardiovascular disease and renal impairment. However, a 14-year follow-up study by Panduru et al, which involved 2329 individuals with T1DM found that uL-FABP was an independent predictor of stroke and mortality in this population, but did not predict other cardiovascular endpoints.[38] Furthermore, Hirowatari[39] et al reported that uL-FABP levels were significantly reduced following the administration of sodium-glucose cotransporter 2 inhibitors, indicating that uL-FABP may serve as a marker for the therapeutic efficacy of DN treatment. Additionally, Mohsen et al proposed that the DPP4 inhibitor saxagliptin may reduce albuminuria by mitigating tubular injury, suggesting that uL-FABP could be a valuable marker for monitoring the efficacy of gliptins in the management of DN.[40] Importantly, advancements in clinical decision-making, such as the development of chemiluminescence rapid quantitative tests[41] and microchip immunoassays,[42] have facilitated the rapid, cost-effective, and high-sensitivity quantitative detection of biomarkers like uL-FABP, which is beneficial for precise and frequent monitoring of renal function.

Retinol-Binding-Protein-4, RBP4. RBP4 is a low-molecular-weight transporter that facilitates the transport of vitamin A (retinol) in the bloodstream. Elevated RBP4 levels have been associated with the onset of metabolic diseases, as RBP4 promotes inflammation and oxidative stress through the activation

of immune cells and releasing pro-inflammatory cytokines.[43] Furthermore, RBP4 is regarded as a potential diagnostic marker for renal impairment due to its ability to detect tubular damage early and to sensitively reflect the extent of injury to the renal proximal convoluted tubules.[44] Evidence indicate that elevated RBP4 levels can be identified in the early stages of T 2 DN, with urinary RBP4 (uRBP4) and microalbumin levels significantly higher in the diabetic cohort compared to both the control group and those with nephropathy.[45] A retrospective study involving 1946 patients with T2DM, with or without DN, found that elevated uRBP4 was linked to an increased risk of DN in T2DM patients, as well as worsening albuminuria and declining renal function in those with DN.[46] Additionally, Javed reported a significant correlation between RBP4 levels and creatinine clearance.[47] Xing et al established that RBP4 levels are positively correlated with urinary albumin concentration, achieving a sensitivity of 85.7% and a specificity of 56.2%. This study, which included a cohort of 135 T2DM patients, proposed that RBP4 could serve as a bio- marker for the early diagnosis of DN[48]. Furthermore, a prospective study involving 438 T2DM patients found that RBP4 was positively correlated with the degree of renal impairment, effectively identifying DN in this population.[49]RBP4 also reflects the onset of diabetic retinopathy[50] and is regarded as a promising biomarker for predicting cardiovascular disease. Moreover, medicinal plants that target RBP4 may aid in the treatment of cardiometabolic diseases.[51] For instance, a study involving patients with prediabetes or early T2DM who were supplemented with mulberry leaves for 12 weeks revealed that the down-regulation of RBP4 is associated with improved insulin resistance. Collectively, these findings suggest that RBP4 is a valuable biomarker for both the prevention and treatment of early DN.[52] Collectively, it may serve as an effective marker for identifying the early onset of DN and for predicting the progressive stages of renal impairment in individuals with both T1DM and T2DM.

Biomarkers of Glomerular Injury

The glomeruli serve as the primary sites of damage in DN. This progressive DN is characterized by several pathological changes, including the loss of podocyte foot processes, thickening of the glomerular basement membrane, and expansion of mesangial cells within the glomeruli. Collectively, these alterations lead to a reduction in glomerular surface area and impaired glomerular filtration.[53]

Table 1 summarizes the biomarkers associated with current glomerular injury.

Table:1 Biomarkers associated with glomerular injury.

Glomerular damage	Podocyte injury	Glomerular basement membrane damage	Glomerular endothelial injury	Glomerular filtration ecreased
biomarkers	podocin[54] synaptopodin[55,56] integrin alpha 3 (Intα3)[57] nephrin[58] podocalyxin[59] and mindin[60]	type IV collagen[37] laminin[61] glycosaminoglycans(GAGs)[62]	von Willebrand factor (VWF)[63] vascular endothelial growth factor (VEGF).[63]	immunoglobulin G(IgG)[64] immunoglobulin M(IgM)[65] transferrin (TRF)[66] ceruloplasmin (CER)[67]
comment		early diagnosis		

DN Pathogenesis Biomarkers

Oxidative Stress Biomarkers

Reactive oxygen species (ROS) are the primary contributors to oxidative stress, which is associated with disease progression. In the kidneys, ROS predominantly generated by mitochondria and the nicotinamide adenine dinucleotide phosphate oxidase (NOX) family. Additionally, oxidative

stress arises from advanced glycation end-products (AGEs) induced by hyperglycemia during the later stages of non-enzymatic glycation of sugars and proteins. This hyperglycemia-induced oxidative stress leads to several detrimental outcomes, including DNA damage, lipid peroxidation, mitochondrial dysfunction, and the infiltration of inflammatory cells, ultimately culminating in renal cell damage.

8-OHdG. 8-Hydroxy-2'-deoxyguanosine (8-OHdG) is a byproduct of DNA damage resulting from oxidative stress in living cells, particularly in the context of DN. It is excreted in urine through nuclease activity and can also be detected in plasma.[13,68] Cohort studies involving patients with T1DM have indicated that elevated plasma levels of 8-OHdG are independently associated with an increased risk of kidney disease, implying its potential utility in monitoring the progression of DN.[69] Wakeel et al demonstrated that urinary 8-OHdG is a reliable marker of oxidative DNA damage in T1DM patients with diabetic retinopathy.[70] Furthermore, urinary excretion of 8-OHdG may serve as an independent predictor of disease progression and the onset of both microvascular and macrovascular complications. However, Serdar et al reported that urine 8-OHdG measurement did not effectively predict progressive DN when compared to uACR.[71] Consequently, further research is warranted to elucidate the clinical significance of these biomarkers and to explore the role of novel therapeutic agents in diabetes management.

Pentosidine. Pentosidine, a product of higher sugar oxidation, is formed through the covalent binding of amino groups to glucose. Machowska et al observed that plasma pentosidine levels correlate with low GFR, oxidative stress, and inflamma- tion, serving as independent predictors of mortality in patients with CKD.[72] Furthermore, Perkins et al reported that patients with microalbuminuria exhibited approximately a two-fold increase in pentosidine excretion and an early decline in GFR compared to those with normal albuminuria.[73] In diabetic patients, elevated pentosidine levels have been identified as independent predictors of diabetic retinopathy, cardiovascular disease, and all-cause mortality.[74] Collectively, these findings suggest that measuring pentosidine levels in both urine and serum may aid in identify patients at risk for early GFR decline and could serve as a promising biomarker for both microvascular and macrovascular complications associated with diabetes.

Uric acid. Uric acid, a byproduct of purine metabolism, has been demonstrated to independently predict the progression of DN. Numerous clinical studies have concentrated on the relationship between uric acid levels and DN prognosis. In a cohort study involving 277 patients with T1DM, elevated serum uric acid levels were identified as predictors of persistent massive albuminuria.[75] Similarly, among a cohort of 422 patients with T2DM who had been diagnosed for at least 15 years, initial hyperuricemia emerged as an independent risk factor for DN progression.[76] A four-year follow-up study by Cosmo et al revealed a significant association between serum uric acid levels and albuminuria; furthermore, the cumulative incidence of GFR decline was notably higher in patients with hyperuricemia, which was identified as an independent risk factor for progression in T2DM patients.[77] Additionally, a significant correlation exists between urinary lactate levels and biomarkers indicative of renal tubular injury and epithelial stress, suggesting that elevated urinary lactate levels could serve as potential bio- markers for the risk of renal disease progression.

Collectively, this evidence indicates that serum uric acid may function as an independent predictor for the subsequent development of massive albuminuria in patients with both T1DM and T2DM.

Acylcarnitine. Acylcarnitine, an esterification product of carnitine, plays a crucial role in fatty acids oxidation and is significantly associated with an increased risk of T2DM.[78] Mirzoyan et al[79] demonstrated that in cases of hyperlipidemia, the development of diabetes correlates with a diminished capacity of the kidneys to oxidize fatty acids and amino acids. Sulaj et al[80] pro- posed that

acylcarnitine has historically been an important diagnostic marker for congenital fatty acid oxidation disorders. Mu et al[81] found that short- and medium-chain acylcarnitines were less prevalent, while longer acylcarnitines were more abundant in the late stages of DN, typically observed in diabetes with normal albuminuria and microalbuminuria. The increase in long-chain acylcarnitines is believed to compensate for the adaptive oxidation of fatty acids in the early stages of DN, whereas the reduction of long-chain acylcarnitines in advanced DN stages is attributed to incomplete fatty acid oxidation. Consequently, acylcarnitine may serve as a predictive marker for the risk of DN. Hassan et al[82] emphasized the importance of monitoring plasma free amino acid and acylcarnitine profiles children with T1DM, particularly those testing positive for JAK2 (V617F), to facilitate the early diagnosis of DN. Li and Xuerui et al[83] conducted an analysis of clinical data from 1032 participants with T2DM, measuring levels of 25 acylcarni- tine metabolites in fasting plasma via mass spectrometry. Their findings indicated that certain plasma acylcarnitine metabolites were elevated in T2DM patients with DN, and incorporating acylcarnitine into traditional risk models enhanced the predictive value for DN. Esmati et al[84] employed flow injection tandem mass spectrometry (FI-MS/MS) to simultaneously quantify amino acids and carnitine/acylcarnitines in patients with T2DM, meeting analytical performance requirements within a brief timeframe. The concurrent detection of amino acid and acylcarnitine profiles serves as prospective tandem bio- markers for DN, offering valuable insights for predicting the risk of DN at the time of initial diagnosis. While acylcarnitines have demonstrated a strong predictive capacity for DN, further clinical data and scientific research are necessary to enhance the acylcarnitine risk model.

Acrolein. Acrolein, An α, β-unsaturated aldehyde, is endogenously produced during lipid peroxidation. It forms highly reactive conjugates with proteins, leading to alterations in protein function. Renal fibrosis is a hallmark of DN, and it has been demonstrated that acrolein modification at Cys358 in PKM2 results in its inactivation, which is implicated in the pathogenesis of DN.[85] Currently, there are very few reports on acrolein involving DN biomarkers.

Inflammatory Biomarkers

Monocyte Chemoattractant Protein-1, *MCP-1.* MCP-1, also known as C-C motif chemokine ligand 2 (CCL2), is a pro-inflammatory cytokine synthesized by monocytes, cortical tubular epithelial cells, and podocytes. It is responsible for mediating the migration of monocytes and macrophages to tissues via the nuclear factor-κB pathway. MCP-1 has been implicated in various renal pathologies, including inflammation, glomerular injury, tubular atrophy, and fibrosis.[86] Notably, excessive renal inflammation can lead to a rapid decline in renal function, and elevated levels of MCP-1 have emerged as a promising biomarker for predicting progressive decline in non-DN renal function.[87]

In a median follow-up period ranging from 4.2 to 7.1 years, Menez et al found that 266 patients (30.8%) experienced a composite CKD outcome following cardiac surgery. The suggesting indicates that uMCP-1 is independently associated with CKD post-surgery, and suggests its potential as a noninvasive indica- tor of tubular injury.[88] Similarly, Fufaa et al found a significant correlation between uMCP-1 concentrations and changes in renal interstitial volume, as well as disease progression in normotensive patients with albuminuria and T1DM.[89] In a cohort of 75 patients with T2DM exhibiting varying degrees of DN, uMCP-1 levels were observed to increase with albuminuria, demonstrating a sensitivity of 92% and a specificity of 100% for early diagnosis.[90] Additionally, in a prospective study involving 83 high-risk patients with T2DM and DN, Satirapoj et al showed that uMCP-1 was positively associated with early declines in DN GFR, independent of conventional risk factors.[91] A case-cohort study of 894 participants with T1DM and T2DM reported that high levels of MCP-1 were also associated with an increased risk of DN

progression.[19] Overall, MCP-1 proves to be a valuable biomarker for detecting the incidence or progression of CKD in patients undergoing cardiac surgery as well as for stratifying long-term CKD risk in other recognized clinical settings for kidney injury.[87] These observations suggest that MCP-1 as a promising inflammatory marker for diagnosing early progressive renal dys- function and for assessing long-term CKD risk.

Tumor Necrosis Factor -α, *TNF-α.* TNF-α has been identified as a notable inflammatory marker that predicts the progression of DN.[92] A meta-analysis by Qiao et al[93] demonstrated a significant elevation in TNF-α levels among patients with T1DM compared to healthy controls. Furthermore, Sharad et al established a robust correlation between microalbuminuria and the activity of soluble serum TNF-α receptors and the IL-6 pathway in T1DM patients, indicating the critical role of TNF-α in disease progression.[94] Umapathy et al reported that a gradual increase in normal-micro-massive albuminuria in T2DM is associated with the rs1800629 polymorphism in the TNF-α gene.[95] Additionally, Khaloo et al found that elevated TNF-α levels were linked to diabetic retinopathy in T2DM, achieving an area under the curve (AUC) of 0.84.[96] Consequently, the assessment of TNF-α emerges as a promising biomarker for predicting cardiovascular disease and progressive renal function impairment. The TNF-α receptor is a type 1 transmembrane protein distinguished by cysteine-rich motifs present in glomeruli and tubular cells. It comprises two types: TNF-α receptor 1 (TNFR1, 55 kDa) and TNF-α receptor 2 (TNFR2, 75 kDa). TNF-α binds to these receptors and is also detected in its soluble form within the systemic circulation.[13] Studies have indicated that soluble TNF-α receptor 1 (sTNFR1)[97] and soluble TNF-α receptor 2 (sTNFR2)[19] sever as significant predictors of DN progression in patients with T2DM, with sTNFR1 emerging as the most robust prognostic biomarker.[98] Paykov et al reported that serum levels of TNF receptors were independently associated with decreased renal function in T2DM and ESRD.[99] In a nested case-control and prospective cohort study, elevated plasma levels of TNFR-1 and TNFR-2 were linked to a heightened risk of DN progression, independent of age and other laboratory parameters.[18] Moreover, circulating levels of sTNFR have been shown to independently predict progressive renal function decline and a ten-year risk of ESKD in cohorts of patients with T1DM and T2DM.[100] In contrast, Martin et al reported that sTNFR1 predicts of short- to medium-term mortality; but not of progressive renal function decline in an elderly cohort of T2DM patients with CKD. They also noted that the parallel assessment of uACR could provide complementary prognostic information.[101] Furthermore, sTNFR1 and sTNFR2 are emerging as promising biomarkers for forecasting progressive impairment of renal function.

YKL-40. YKL-40, also known as chitinase 3-like-1 (CHI3L1), is a 40-kDa glycoprotein secreted by various cell types that pro- tects renal tubular cells from apoptosis.[102] AKI is a prevalent syndrome among critically ill patients, and elevated levels of YKL-40 are associated with poorer clinical outcomes. Biomarkers are essential for in the early recognition and management of AKI, potentially enhancing patient outcomes.[103] Urinary YKL-40 levels correlate with the severity and mortality of AKI during hospitalization, and its elevation is considered a promising urinary biomarker for AKI diagnosis. It demonstrates comparable diagnostic efficacy in identifying patients with AKI at or above KDIGO stage 2 within 24 h; however, further studies are warranted to validate its clinical applicability.[103,104] A single-center, prospective cohort study involving 249 AKI patients indicated that urinary YKL-40 levels were associated with disease progression and/or mortality, thereby enhancing clinically determined risk reclassification.[105] Additionally, Conroy et al identified YKL-40 as an independent risk factor for mortality in AKI related to malaria pathogenesis, highlighting its potential as a biomarker for AKI.[106] Elevated serum YKL-40 concentrations have also been

documented in patients with T2DM.[107] In a case-cohort study involving 894 T2DM participants, higher YKL-40 levels were linked to an increased risk of DN progression.[19] The integration of YKL-40 with other AKI biomarkers, such as NGAL, may facilitate a more comprehensive assessment of progression risk.[108] However, additional research is required to establish the universal applicability of YKL-40 and its relationship with long-term AKI outcomes.

EGF. Epidermal growth factor (EGF) is a 6-kDa mediator that regulates and stimulates the proliferation, migration, and differentiation of mesenchymal cells, particularly within epithelial tissues. It is expressed predominantly in the distal tubules and plays a crucial role in the proliferation and survival of renal tubular cells, typically being excreted in the urine. Recent data suggest that urinary EGF serves as a reliable noninvasive indicator of functionally normal tubular volume and the status of tubular repair following AKI.[109] Norvik et al demonstrated that lower levels of urinary EGF (uEGF) were associated with a rapid decline in GFR and an increased risk of CKD events in the general population, based on a median follow-up of a large sample size (n = 5883) over an average of six years. These findings align with observations in CKD and high-risk populations, indicating that uEGF can be uti- lized as a broadly applicable tubular-specific biomarker for assessing clinical risk.[110] Additionally, the uEGF/MCP-1 ratio is independently linked to rapid renal progression in patients with DN.[91] Lower urinary EGF levels correlate with increased interstitial fibrosis and tubular atrophy, while higher EGF levels are associated with improved treatment responses and remission in various glomerular diseases.[111] Therefore, the therapeutic use of exogenous EGF may not be an appropriate strategy for long-term treatment.

FGF-23. Fibroblast growth factor 23 (FGF-23), a 28 kDa hormone, is crucial for regulating renal phosphate excretion and maintaining mineral balance.[112] Phosphate homeostasis is compromised when the GFR declines.[113] An observational study involving 60 patients with stages III-V CKD found that elevated phosphate levels correlated with increased FGF-23/ Klotho ratios, suggesting that these ratios may serve as risk factors for evaluating CKD patients and as protective indicators for treatment as well as prognosis.[113] Additionally, a separate study of 60 CKD patients undergoing hemodialysis revealed significant associations between FGF-23 and levels of creatinine, urea, phosphorus, and calcium.[112] A systematic review and meta-analysis conducted by Castillo et al indicated that aerobic physical exercise can decrease FGF-23 levels and slow the progression of CKD.[114] Furthermore, several studies have elucidated the mechanisms underlying the upregulation of FGF-23 in AKI, establishing that quantitative changes in FGF-23 may serve as a reliable biomarker for predicting adverse outcomes and prognosis in AKI patients.[115,116] FGF-23 is a potential marker for DN, but there are currently few research reports on DN.

Other Inflammatory Factor Biomarkers. Recent studies have updated our understanding of inflammatory factor biomarkers in DN. For instance, Hostet et al[102] demonstrated that elevated urinary levels of C-C motif chemokine ligand 14(CCL-14) are associated with renal impairment, identifying it as the most reliable predictor of AKI severity and persistence. Furthermore, the expression levels of renal interleukin-17 receptor E (IL-17RE) have been correlated with albuminuria and the severity of DN.[117] Interleukin-6 (IL-6) is recognized for its dual role in inflammation and glycemic control, making it a promising biomarker and therapeutic target for both DN and T2DM.[118] Additionally, decreased serum levels of IL-18 have been linked to the development of DN in the Pakistani population.[119] The overexpression of Wilms' tumor 1(WT1) in podocytes has been shown to induce podocyte injury associated with DN.[120] Moreover, angiotensin-converting enzyme-2 (ACE-2) and connective tissue growth factor (CTGF) have emerged as early and reliable predictors of disease progression in DN.[121] Lysine lactylation and acyl-CoA synthetase family member 2 (ACSF2), which are implicated in the pathogenesis of metabolic and inflammatory

diseases, may also contribute to the progression of DN.[122] Notably, a reduction in MCPIP1 has been identified as an independent risk factor for renal progression in patients with DN. Additionally, centrally administered dapagli- flozin has been reported to exert anti-inflammatory effects by upregulating MCPIP1 levels in microglia and altering lipid metabolism in kidneys affected by DN,[123] These findings suggest that MCPIP1 levels may serve as a valuable biomarker for assessing the efficacy of dapagliflozin in the treatment of DN.disease outcomes, based on individual molecular profiles.

Conclusion

Diabetic nephropathy (DN) investigation is increasingly improving and the recognition of new biomarkers provides promising tools for early diagnosis, disease monitoring, and therapeutic targeting. This findings shows a complete overview of recently recognized biomarkers for DN , analyzing them through multidimensional perspectives which confine physiology, pathology, underlying mechanisms, and emerging technologies.

Future research should emphasize on integration of various biomarkers into cohesive prognostic and diagnostic techniques, allowing personalized treatment strategies to improve patient outcomes and survival. These novel biomarkers should also be identified as possible inclusion criteria or surrogate endpoints in randomized clinical trials (RCTs). Larger, well-designed researches are required, integrating renal biopsy specimens alongside urine, plasma, or serum samples from the same patients to build a robust evidence base. Moreover, the establishment of standardized protocols for sample collection, processing, and analysis across research units is pivotal to ensure reproducibility and comparability of results.

References

Duolin W, Yijun L, Ping L, et al. Interaction between estimated mild glomerular filtration rate and albuminuria on cardiovascular disease risk in patients with Type 2 Diabetes Mellitus. Chin J Diabetes Mellitus. 2024;16(07):746-754. DOI: 10.3760/cma.j. cn115791-20240408-00163

Penno G, Solini A, Orsi E, et al. Non-albuminuric renal impairments a strong predictor of mortality in individuals with type 2 diabetes: the renal insufficiency and cardiovascular events (RIACE) Italian multi center study. Diabetologia. 2018;61(11): 2277-2289. DOI: 10.1007/s00125-018-4691-2

Porrini E, Ruggenenti P, Mogensen CE, et al. Non-proteinuric pathways in loss of renal function in patients with type2 diabetes. Lancet Diabetes Endocrinol. 2015;3(05):382-391. DOI: 10.1016/ S2213-8587(15)00094-7

Lin CH, Chang YC, MingChuang L. Early detection of diabetic kidney disease: present limitations and future perspectives. World J Diabetes. 2016;7(14):290-301. DOI: 10.4239/wjd.v7.i14.290

Lequn /, Dan /, Shunlin X, et al. Current status and influencing factors for physicians in different departments prescribing novel hypoglycemic agent with cardiovascular benefits. Natl Med J China. 2023;103(08):578-584. DOI: 10.3760/cma.j. cn112137-20220615-01319

Rico Fontalvo J, Aroca Martinez G, Daza Arnedo R, et al. Novel biomarkers of diabetic kidney disease. Biomolecules. 2023; 13(04):633. DOI: 10.3390/biom13040633

Xu Yk, Ding Y, Li Xc, et al. Cystatin C is a disease-associated protein subject to multiple regulation. Immunol Cell Biol. 2015;93(05):442-451. DOI: 10.1038/icb.2014.121.

van Deventer HE, Paiker JE, Katz IJ, et al. A comparison of cystatinC and creatinine based prediction equations for the estimation of glomerular filtration rate in black South Africans. Nephrol Dial Transplant. 2011;26(05):1553-1558. DOI: 10.1093/ ndt/gfq621

Ibrahim Y, Staib M, Younes Ibrahim M. Biomarkers and kidney diseases: a brief narrative review. J Lab Precis Med. 2022;7:20.

La Jeon Y, Kim MH, Lee WI, et al. Cystatinc as an early marker of diabetic nephropathy in patients with Type2 diabetes. Clin Lab. 2013;59(11-12):1221-1229. DOI: 10.7754/Clin.Lab.2013.
120804

Xu LL, Gao W, Chen /M, et al. Relationships between diabetic nephropathy and insulin resistance, inflammation, Trx, Txnip, CysC and serum complement levels. Eur Rev Med Pharmacol Sci. 2020;24(22):11700-11706. DOI: 10.26355/eurrev_202011_
23815

Brozat JF, Harbalioglu N, Hohlstein P, et al. Elevated Serum KIM-1 in sepsis correlates with kidney dysfunction and the severity of multi-organ critical illness. Int J Mol Sci. 2024; 25(11):5819. DOI: 10.3390/ijms25115819

Jung CY, Yoo TH. Pathophysiologic mechanisms and potential biomarkers in diabetic kidney disease. Diabetes Metab J. 2022; 46(02):181-197. DOI: 10.4093/dmj.2021.0329

Swaminathan SM, Rao IR, Shenoy SV, et al. Novel biomarkers for prognostic diabetic kidney disease progression. Int Urol Nephrol. 2023;55(04):913-928. DOI: 10.1007/s11255- 022-03354-7

Khonsha F, Valilo M, Nejabati HR, et al. Biomarkers for Diabetic Nephropathy with a Focus on Kidney Injury Molecule-1 (KIM-1). Curr Diabetes Rev. 2023;19. DOI: 10.2174/ 1573399819666230328151108

Hammoud MS, Baban RS, Ali SH. Evaluation of UrinaryKidneyInjuryMolecule-1(kim-1) as prognostic biomarker in children with type-1 diabetic nephropathy. Biochem Cell Arch. 2021;21(01):715-719.

de Carvalho JAM, Tatsch E, Hausen BS, et al. Urinary kidney injury molecule-1 and neutron philglatinase-associated lipocalin as indicators of tubular damage in normoalbuminuric patients with type 2 diabetes. Clin Biochem. 2016;49(03):232-236. DOI: 10.1016/j.clinbiochem.2015.10.016

Coca SG, Nadkarni GN, Huang Y, et al. Plasma biomarkers and kidney function decline in early and established diabetic kidney disease. J Am Soc Nephrol. 2017;28(09):2786-2793. DOI: 10. 1681/ASN.2016101101

Schrauben SJ, Shou H, /hang X, et al. Association of multiple plasma biomarker concentrations with progression of prevalent diabetic kidney disease: findings from the chronic renal insufficiency cohort (CRIC) study. J Am Soc Nephrol. 2021;32(01): 115-126. DOI: 10.1681/ASN.2020040487

Trutin I, Bajic /, Turudic D, et al. Cystatin C, renal resistance index, and kidney injury molecule-1 are potential early predictors of diabetic kidney disease in children with type 1 diabetes. Front Pediatr. 2022;10. DOI:10.3389/fped.2022.962048

Liu Y, He X, Lian /, et al. Rapid and sensitive detection of urinary KIM-1 using fully printed photonic crystal microarrays. Nano Res. 2024;17(05):4329-4337. DOI:10.1007/s12274-023-6335-1

Abbasi F, Moosaie F, Khaloo P, et al. Neutrophil gelatinase-associated lipocalin and retinol-binding protein-4 as biomarkers for diabetic kidney disease. Kidney Blood Pressure Res. 2020;45(02):222-232. DOI: 10.1159/000505155

Jung CY, Yoo TH. Novel biomarkers for diabetic kidney disease. Kidney Res Clin Pract. 2022;41(suppl 2):S46-S62. DOI: 10. 23876/j.krcp.22.084

Garg P, Shetty M, Krishnamurthy V. Correlation of urinary neu- trophil gelatinase with the histopathological extent of kidney damage in patients with diabetic nephropathy. Saudi J Kidney Dis Transpl. 2023;34(SUPPL 1):S112-S121. DOI:10.4103/sjkdt.

sjkdt_95_22

Kaul A, Behera MR, Rai MK, et al. Neutrophil gelatinase- associated lipocalin: as a predictor of early diabetic nephropathy in Type2 diabetes Mellitus. Indian J Nephrol. 2018;28(01):53-60. DOI: 10.4103/ijn.IJN_96_17

Huijing L, Wei L, Jin /, et al. Meta-analysis of the value of urinary NGAL in the diagnosis of diabetic nephropathy. Int J Lab Med. 2022;43(15):

1863-1868. DOI: 10.3969/j.issn.1673-4130.2022.15.016

He P, Bai M, Hu J, et al. Significance of neutrophil gelatinase- associated lipocalin as a biomarker for the diagnosis of diabetic kidney disease: a systematic review and meta-analysis. Kidney Blood Pressure Res. 2020;45(04):497-509. DOI: 10.1159/000507858

Megallaa MH/, Abdel Salam MS, Saad NLM, et al. NGAL (Neutrophil gelatinase-associated lipocalin) as an early biomarker of nephropathy in patients with type 2 diabetes. Alexandria J Med. 2023;59(01):52-58. DOI:10.1080/20905068.2023.2230051

Duan S, Chen J, Wu L, et al. Assessment of urinary NGAL for differential diagnosis and progression of diabetic kidney disease. J Diabetes Complicat. 2020;34(10):107665. DOI: 10. 1016/j.jdiacomp.2020.107665

Kashgary A, /aki MES, Elwahab AMA, et al. Study of neutrophil gelatinase associated lipocalin and kidney injury molecule-1 in patients with Type 2 Diabetes Mellitus nephropathy. Clin Lab. 2024;70(03):563-570. DOI:10.7754/Clin.Lab.2023.230824

Serwin N, Cecerska Heryc E, Pius Sadowska E, et al. Renal and inflammation markers-renalase, cystatin C, and NGAL levels in asymptomatic and symptomatic SARS-CoV-2 infection in a one- month follow-up study. Diagnostics. 2022;12(01):108. DOI: 10. 3390/diagnostics12010108

Xu Y, Xie Y, Shao X, et al. L-FABP: a novel biomarker of kidney disease. Clin Chim Acta. 2015;445:85-90. DOI: 10.1016/j.cca. 2015.03.017

Dayem AE, Soha M, Bohy E, et al. Follow up of value of the intrarenal resistivity indices and different renal biomarkers for early identification of diabetic nephropathy in type 1 diabetic patients. Open Access Maced J Med Sci. 2017;5(02):188-192. DOI: 10.3889/oamjms.2017.034

Ngan DTT, Gia Binh N, Lan LTH, et al. Evaluation of urinaryl- fabpasanearl ymarker for diabetic nephropathy in type 2 diabetic patients. J Med Biochem. 2020;39(02):224-230. DOI: 10.2478/ jomb-2019-0037

Kaiyi /, Baoren L, /uwen /, et al. Correlation between urine NGAL, L-FABP and RBP and type 2 diabetic nephropathy in the elderly. Int J Lab Med. 2020;41(10):1226-1229. DOI: 10. 3969/j.issn.1673-4130.2020.10.019

/hang L, Xue S, Wu M, et al. Performance of urinary liver-type fatty acid-binding protein in diabetic nephropathy: A meta- analysis. Front Med (Lausanne). 2022;9. DOI: 10.3389/fmed. 2022.914587

Araki S, Haneda M, Koya D, et al. Predictive effects of urinary liver-type fatty acid-binding protein for deteriorating renal function incidence of cardiovascular disease in Type2 diabetic patients without advanced nephropathy. Diabetes care. 2013;36(05): 1248-1253. DOI: 10.2337/dc12-1298

Panduru NM, Forsblom C, Saraheimo M, et al. Urinary liver-type fatty acid binding protein is an independent predictor of stroke and mortality in individuals with type 1 diabetes. Diabetologia. 2017;60(09):1782-1790. DOI: 10.1007/s00125-017-4328-x

Hirowatari K, Kawano N. Association of urinary liver-type fatty acid-binding protein with renal functions and anti-hyperglycemic drug use in type 2 diabetic nephropathy patients. Int Urol Nephrol. 2023;55(08):2111-2118. DOI: 10.1007/s11255-023-03532-1

Mohsen M, Elberry AA, Rabea AM, et al. A new clinical utility for tubular markers to identify kidney responders to saxagliptin treatment in adults with diabetic nephropathy. Can J Diabetes. 2022;46(02):134-141.e2. DOI: 10.1016/j.jcjd.2021.07.004

Sun T, Qu S, Huang T, et al. Rapid and sensitive detection of L-FABP for prediction and diagnosis of acute kidney injury in critically ill patients by chemiluminescent immunoassay. J Clin Lab Anal. 2021;35(11). DOI: 10.1002/jcla.24051

Kasama T, Sun M, Kaji N, et al. Microchip immunoassays for monitoring renal function: rapid, low-cost, and highly sensitive quantification of urinary biomarkers of diabetic nephropathy. Micromachines (Basel). 2021;12(11):1353. DOI: 10.3390/ mi12111353

Chang CL, Li YR, Wang /Y, et al. Serum retinol binding protein 4 as a potential biomarker for sarcopenia in older adults. J Gerontol Ser A Biol Sci Med Sci. 2023;78(01):34-41. DOI: 10.1093/gerona/ glac151

Cao X, /hong G, Jin T, et al. Diagnostic value of retinol-binding protein 4 in diabetic nephropathy: a systematic review and meta- analysis. Front Endocrinol (Lausanne). 2024;15. DOI: 10.3389/ fendo.2024.1356131

/hou X, Liu S, Yang B, et al. Urinary or osomucoid and retinol binding protein levels as early diagnostic markers for diabetic kidney Disease. BMC Nephrol. 2023;24(01). DOI: 10.1186/ s12882-023-03363-3

Sarula Y, /haoli H, Xin. Clinical study on serum25-hydroxy vitamin D and retinol binding protein4 in type 2 diabetic nephropathy. Chin J Clin Nutr. 2021;29(02):82-89. DOI: 10. 3760/cma.j.cn115822-20210130-00026

Javed A, Khurshid R, Niazi F, et al. The association between retinol-binding protein 4, fasting blood glucose and creatinine clearance and the risk of diabetic nephropathy. Pak J Med Health Sci. 2019;13(03):601-603.

/hibo X. Study on the value and correlation of retinol-binding protein in the early diagnosis of type 2 diabetic nephropathy [D]. Jinlin, Changchun University of Traditional Chinese Medicine; 2023. DOI: 10. 26980/d.cnki.gcczc.2023.000743

Huang J, Liu J, Liu W. Correlations of Serum retinol-binding protein and stromal cell-derived factor-1 with renal function in patients with diabetic kidney disease. Clin Lab. 2024;70(01): 11-17. DOI: 10.7754/Clin.Lab.2023.211254

Song JJ, Han XF, Chen JF, et al. Correlation between glycated hemoglobin A1c, urinary micro albumin, urinary creatinine, β2 micro globulin, retinol binding protein and diabetic retinopathy.

World J Diabetes. 2023;14(07):1103-1111. DOI: 10.4239/wjd. v14.i7.1103

Oluwamodupe C, Adeleye AO. Targeting retinol-binding protein 4 (RBP4) in the management of cardio metabolic diseases. Cardio Vasc Toxicol. 2023;23(9-10):285-294. DOI: 10.1007/ s12012-023-09803-8

Fongsodsri K, Thaipita kwong T, Rujimongkon K, et al. Mulberry-Derived 1-deoxynojirimycin prevents Type 2 Diabetes Mellitus progression via modulation of retinol-binding protein 4 and haptoglobin. Nutrients. 2022;14(21):4538. DOI: 10.3390/ nu14214538

Lassen E, Daehn IS. Molecular mechanisms in early diabetic kidney disease: glomerular endothelial cell dysfunction. Int J Mol Sci. 2020;21(24):9456. DOI: 10.3390/ijms21249456

Kerley RN, McCarthy C. Biomarkers of glomerular dysfunction in pre-eclampsia - A systematic review. Pregnancy Hypertens Int J Womens Cardiovasc Health. 2018;14:265-272. DOI: 10.1016/j. preghy.2018.03.002

Ning L, Suleiman HY, Miner JH. Synaptopodin is dispensable for normal podocyte homeostasis but is protective in the context of acute podocyte injury. J Am Soc Nephrol. 2020;31(12):2815-2832. DOI: 10.1681/ASN.2020050572

Wang R, Yao C, Liu F. Association between Renal Podocalyxin Expression and Renal Dysfunction in Patients with Diabetic Nephropathy: A Single-Center, Retrospective Case-Control Study. BioMed Res Int. 2020;2020:1-8. DOI: 10.1155/2020/ 7350781

Hayek SS, Koh KH, Grams ME, et al. A tripartite complex of suPAR, APOL1 risk variants and αvβ3 integrin on podocytes mediates chronic kidney disease. Nat Med. 2017;23(08):945-953.

DOI: 10.1038/nm.4362

Liu J, Guo S, Li H, et al. Effects of glucagon-like peptide-1 recep- tor agonists (GLP-1RAs) on podocytes, inflammation, and oxi- dative stress in patients with diabetic nephropathy (DN). Pak J Med Sci. 2022;38(05):1170-1174. DOI: 10.12669/pjms.38.5.4719

Pelu JE, Kurniawan LB, Widaningsih Y, et al. Analysis of urine podocalyxin in Type 2 Diabetes Mellitus subjects with and without diabetic nephropathy. Indones J Med Lab Sci Technol. 2023;5(01):20-28. DOI:10.33086/ijmlst.v5i1.3933

Sambel IT, Eren E, Bozyigit C, et al. Serum mindin, nephrin and podocalyxin levels in patients with type 1 diabetes: are these new markers to detect the development of nephropathy? Guncel Pediatri J Curr Pediatr. 2022;20(02):147-154. DOI: 10.4274/jcp. 2022.34635

El-Fattah MEA, Rashed LA, Nasr SMM. The role of transferrin and laminin biomarkers in the diagnosis of diabetic nephropathy in type II diabetic patients. J Adv Med Res. 2021:69-80. DOI: 10. 9734/JAMMR/2021/V33I730876

Waseem T, Ahmed M, Rajput TA, et al. Molecular implications of glycosaminoglycans in diabetes pharmacotherapy. Int J Biol Macromol. 2023;247:125821. DOI: 10.1016/j.ijbiomac.2023. 125821

Wang F, Gao XY, /hang R. Change and significance of serum inflammatory factors, vWf, VEGF and adhesion molecules in patients with diabetic nephropathy. J Hainan Med Univ. 2017; 23(16):41-44.

Typiak M, Audzeyenka I, Dubaniewicz A. Presence and possible impact of fcγ receptors on resident kidney cells in health and disease. Immunol Cell Biol. 2022;100(08):591-604. DOI: 10.

1111/imcb.12570

Huang /, Xu J, Ma J, et al. Clinical significance of glomerular IgM deposit in IgA nephropathy: a 5-year follow-up study. Renal Fail. 2024;46(02). DOI: 10.1080/0886022X.2024.2386146

/hao L, /ou Y, /hang J, et al. Serum transferrin predicts end- stage renal disease in Type 2 Diabetes Mellitus patients. Int J Med Sci. 2020;17(14):2113-2124. DOI: 10.7150/ijms.46259

Prabhakar SS, Deshmukh H. Role of ceruloplasmin in diabetic nephropathy. J Am Soc Nephrol. 2022;33(11):664.

Rico Fontalvo J, Aroca G, Cabrales J, et al. Molecular mechanisms of diabetic kidney disease. Int J Mol Sci. 2022;23(15):8668. DOI: 10.3390/ijms23158668

Sanchez M, Roussel R, Hadjadj S, et al. Plasma concentrations of 8-hydroxy-2'-deoxyguanosine and risk of kidney disease and death in individuals with type 1 diabetes. Diabetologia. 2018;61(04): 977-984. DOI: 10.1007/s00125-017-4510-1

Wakeel E, Maged A. A-E-A, Mohamed E-K, et al. Urinary markers of oxidative DNA damage in type 1 diabetic children: relation to microvascular complications. Asian J Pharm Clin Res. 2017;10(10):318-322. DOI: 10.22159/ajpcr.2017.v10i10.18930

Serdar M, Sertoglu E, Uyanik M, et al. Comparison of 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels using mass spectrometer and urine albumin creatinine ratio as a predictor of development of diabetic nephropathy. Free Radical Res. 2012;46(10):1291-1295. DOI: 10.3109/10715762.2012.710902

Machowska A, Sun J, Qureshi AR, et al. Plasma pentosidine and its association with mortality in patients with chronic kidney disease. Plos One. 2016;11(10):e0163826. DOI: 10.1371/journal. pone.0163826

Perkins BA, Rabbani N, Weston A, et al. High fractional excretion of glycation adducts is associated with subsequent early decline in renal function in type 1 diabetes. Sci Rep. 2020; 10(01). DOI: 10.1038/s41598-020-69350-y

Nin JW, Jorsal A, Ferreira I, et al. Higher plasma levels of advanced glycation End products are associated with incident cardiovascular disease and all-cause mortality in type 1 diabetes A 12-year follow-up study. Diabetes Care. 2011;34(02):442-447. DOI: 10.2337/dc10-1087

Hovind P, Rossing P, Tarnow L, et al. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes an inception cohort study. Diabetes. 2009;58(07):1668-1671. DOI: 10.2337/db09-0014

Bartakova V, Kuricova K, Pacal L, et al. Hyper uricemia contributes to the faster progression of diabetic kidney disease in Type 2 Diabetes Mellitus. J Diabetes Complicate. 2016;30(07):1300-1307. DOI: 10.1016/j.jdiacomp.2016.06.002

De Cosmo S, Viazzi F, Pacilli A, et al. Serum uric acid and risk of CKD in type 2 diabetes. Clin J Am Soc Nephrol. 2015;10(11): 1921-1929. DOI: 10.2215/CJN.03140315

Yiwei MA. Study on fatty acids, acylcarnitine and intestinal microbiota and the risk of metabolic diseases in Chinese population [D]. Beijing, University of Chinese Academy of Sciences; 2018.

Mirzoyan K, Klavins K, Koal T, et al. Increased urine acylcarni- tines in diabetic ApoE-/- mice: hydroxytetradecadienoylcarnitine (C14: 2-OH) reflects diabetic nephropathy in a context of hyper- lipidemia. Biochem Biophys Res Commun. 2017;487(01):109-115. DOI: 10.1016/j.bbrc.2017.04.026

Sulaj A, Kopf S, von Rauchhaupt E, et al. Six-Month periodic fasting in patients with type 2 diabetes and diabetic nephropathy: a proof-of-concept study. J Clin Endocrinol Metab. 2022;107(08): 2167-2181. DOI: 10.1210/clinem/dgac197

Mu X, Yang M, Ling P, et al. Acylcarnitines: can they be biomarkers of diabetic nephropathy? Diabetes Metab Syndr Obesity Targets Ther. 2022;15:247-256. DOI: 10.2147/DMSO.S350233

Hassan MH, Galal O, Sakhr HM, et al. Profile of plasma free amino acids, carnitine and acylcarnitines, and JAK2v617f mutation as potential metabolic markers in children with type 1 dia- betic nephropathy. Biomed Chromatogr. 2023;37(12). DOI: 10. 1002/bmc.5747

Li X, Miao Y, Fang /, et al. The association and prediction value of acylcarnitine on diabetic nephropathy in Chinese patients with Type 2 Diabetes Mellitus. Diabetol Metab Syndr. 2023;15(01). DOI: 10.1186/s13098-023-01058-1

Esmati P, Najjar N, Emamgholipour S, et al. Mass spectrometry with derivatization method for concurrent measurement of amino acids and acylcarnitines in plasma of diabetic type 2 patients with diabetic nephropathy. J Diabetes Metab Disord. 2021;20(01):591-599. DOI: 10.1007/s40200-021-00786-3

Kuo CW, Chen DH, Tsai MT, et al. Pyruvate kinase M2 modification by a lipid peroxidation byproduct acrolein contributes to kidney fibrosis. Front Med (Lausanne). 2023;10. DOI: 10. 3389/fmed.2023.1151359

Campion CG, Sanchez-Ferras O, Batchu SN. Potential role of serum and urinary biomarkers in diagnosis and prognosis of diabetic nephropathy. Can J Kidney Health Dis. 2017;4:205435811770537. DOI: 10.1177/2054358117705371

Gao L, /hong X, Jin J, et al. Potential targeted therapy and diagnosis based on novel insight into growth factors, receptors, and downstream effectors in acute kidney injury and acute kidney injury-chronic kidney disease progression. Signal Transduction Targeted Ther. 2020;5(01):2373-2383. DOI: 10.1038/s41392- 020-0106-1

Menez S, Ju W, Menon R, et al. Urinary EGF and MCP-1 and risk of CKD after cardiac surgery. Jci Insight. 2021. DOI: 10. 1172/jci.insight.147464

Fufaa GD, Weil EJ, Nelson RG, et al. Urinary monocyte chemo- attractant protein-1 and hepcidin and early diabetic nephropathy lesions in type 1 diabetes mellitus. Nephrol Dial Transplant. 2015;30(04):599-606. DOI: 10.1093/ndt/gfv012

Shoukry A, Bdeer SEA, ElSokkary RH. Urinary monocyte chemoattractant protein-1 and vitamin D-binding protein as biomarkers for early detection of diabetic nephropathy in Type 2 Diabetes Mellitus. Mol Cell Biochem. 2015;408(1-2):25-35. DOI: 10.1007/s11010-015-2479-y

Satirapoj B, Dispan R, Radinahamed P, et al. Urinary epidermal growth factor, monocyte chemoattractant protein-1 or their ratio as predictors for rapid loss of renal function in type 2 diabetic patients with diabetic kidney disease. BMC Nephrol. 2018;19(01). DOI: 10.1186/s12882-018-1043-x

Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovasc Ther. 2012;30(01):49-59. DOI: 10.1111/j.1755-5922. 2010.00218.x

Qiao Y, Chen Y, Pan Y, et al. The change of serum tumor necro- sis factor alpha in patients with type 1 diabetes mellitus: A systematic review and meta-analysis. Plos One. 2017;12(04): e0176157. DOI: 10.1371/journal.pone.0176157

Purohit S, Sharma A, /hi W, et al. Proteins of TNF-α and IL6

Pathways are elevated in serum of Type-1 Diabetes Patients with Microalbuminuria. Front Immunol. 2018;9. DOI: 10.3389/ fimmu.2018.00154

Umapathy D, Krishnamoorthy E, Mariappanadar V, et al. Increased levels of circulating (TNF-α) is associated with (−308G/A) promoter polymorphism of TNF-α gene in diabetic nephropathy. Int J Biol Macromol. 2018;107:2113-2121. DOI: 10. 1016/j.ijbiomac.2017.10.078

Khaloo P, Qahremani R, Rabizadeh S, et al. Nitric oxide and TNF-α are correlates of diabetic retinopathy independent of hs-CRP and HbA1c. Endocrine. 2020;69(03):536-541. DOI: 10. 1007/s12020-020-02353-x

Saulnier PJ, Gand E, Velho G, et al. Association of circulating biomarkers (adrenomedullin, TNFR1, and NT-proBNP) with renal function decline in patients with type 2 diabetes: a French prospective cohort. Diabetes Care. 2017;40(03):367-374. DOI: 10.2337/dc16-1571

Martin WP, Conroy C, Naicker SD, et al. Multiplex Serum biomarker assays improve prediction of renal and mortality outcomes in chronic kidney disease. Kidney360. 2021;2(08): 1225-1239. DOI: 10.34067/KID.0007552020

Paykov ME, Nelson RG, Knowler WC, et al. Elevation of circulating TNF receptors 1 and 2 increases the risk of end-stage renal disease in American Indians with type 2 diabetes. Kidney Int. 2015;87(04):812-819. DOI: 10.1038/ki.2014.330

Niewczas MA, Pavkov ME, Skupien J, et al. A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes. Nat Med. 219;25(05):805-813. DOI: 10. 1038/s41591-019-0415-5

Martin WP, Tuohy C, Doody A, et al. Parallel assessment of albuminuria and plasma sTNFR1 in people with type 2 diabetes and advanced chronic kidney disease provides accurate prognostication of the risks of renal decline and death. Sci Rep. 2020; 10(01). DOI: 10.1038/s41598-020-71684-6

Hoste E, Bihorac A, AlKhafaji A, et al. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. Intensive Care Med. 2020;46(05):943-953. DOI: 10.1007/ s00134-019-05919-0

Hoste EA, Vaara ST, De Loor J, et al. Urinary cell cycle arrest biomarkers and chitinase 3-like protein 1 (CHI3L1) to detect acute kidney injury in the critically ill: a post hoc laboratory anal- ysis on the FINNAKI cohort. Crit Care. 2020;24(01). DOI: 10. 1186/s13054-020-02867-w

De Loor J, Decruyenaere J, Demeyere K, et al. Urinary chitinase 3-like protein 1 for early diagnosis of acute kidney injury: a prospective cohort study in adult critically ill patients. Crit Care. 2016;20(1). DOI: 10.1186/s13054-016-1192-x

Hall IE, Stern EP, Cantley LG, et al. Urine YKL-40 is associated with progressive acute kidney injury or death in hospitalized patients. BMC Nephrol. 2014;15(1). DOI: 10.1186/1471-2369- 15-133

Conroy AL, Hawkes MT, Elphinstone R, et al. Chitinase-3-like 1 is a biomarker of acute kidney injury and mortality in pediatric severe malaria. Malar J. 2018;17(1). DOI: 10.1186/s12936- 018-2225-5

Wang S, Hu M, Qian Y, et al. CHI3L1 In the pathophysiology and diagnosis of liver diseases. Biomed Pharmacother. 2020;131: 110680. DOI: 10.1016/j.biopha.2020.110680

Ling C, Wenting C, Heding W, et al. The diagnostic value of retinol-binding protein combined with neutrophil gelatinase- associated lipid carrier protein in early diabetic nephropathy. Shanxi J Med. 2023;52(05):323-327. DOI: 10.3969/j.issn. 0253-9926.2023.05.001

Ono K, Maeshima A, Nagayama I, et al. Urinary epidermal growth factor level as a noninvasive indicator of tubular repair in patients with acute kidney injury. Diagnostics. 2024;14(09):947. DOI: 10.3390/diagnostics14090947

Norvik JV, Harskamp LR, Nair V, et al. Urinary excretion of epi- dermal growth factor and rapid loss of kidney function. Nephrol Dial Transplant. 2021;36(10):1882-1892. DOI: 10.1093/ndt/ gfaa208

Kok HM, Falke LL, Goldschmeding R, et al. Targeting CTGF, EGF and PDGF pathways to prevent progression of kidney disease. Nat RevNephrol. 2014;10(12):700-711. DOI: 10.1038/ nrneph.2014.184

Mohammed NA, Ali HH, Hussein AJ. Assessment of FGF-23 level and relationship with PTH and biochemical markers in patients with CKD undergoing hemodialysis. Rev Latino Americana De Hipertension. 2024;19(02):78-83. DOI: 10.5281/ zenodo.10870074

Khairi I, Kasim H, Bakri S, et al. Association between ratio of fibroblast growth factor 23 (FGF-23) to Klotho and phosphate level in chronic kidney disease patient. Acta Biomed. 2024; 95(01). DOI: 10.23750/abm.v95i1.15302

Castillo RF, Perez RG, Gonzalez AL. Beneficial effects of physical exercise on the osteo-renal klotho-FGF-23 axis in chronic kidney disease: a systematic review with meta-analysis. Int J Med Sci. 2024;21(02):332-340. DOI: 10.7150/ijms.90195

Christov M, Neyra JA, Gupta S, et al. Fibroblast growth factor 23 and klotho in AKI. Semin Nephrol. 2019;39(01):57-75. DOI: 10. 1016/j.semnephrol.2018.10.005

Leaf DE, Jacob KA, Srivastava A, et al. Fibroblast growth factor 23 levels associate with AKI and death in critical illness. J Am Soc Nephrol. 2017;28(06):1877-1885. DOI: 10.1681/ASN. 2016080836

Wang J, Wang X, Wang M, et al. Clinical significance of interleukin 17 receptor E in diabetic nephropathy. Int Immunopharmacol. 2023;120:110324. DOI:10.1016/j.intimp.2023.110324

Reddy VKK, Shiddapur G, Jagdale N, et al. Investigating Interleukin-6 Levels in Type 2 Diabetes Mellitus Patients With and Without Diabetic Nephropathy. Cureus J Med Sci. 2024. DOI: 10.7759/cureus.67014

Maqsood M, Sharif S, Naz S, et al. Expression of pro-inflammatory cytokines (IL-6 & IL-18) exacerbate the risk of diabetic nephropathy in the Pakistani population. Mol Biol Rep. 2023;50(04):3249-3257. DOI: 10.1007/ s11033-023-08249-z

Wang P, Yang J, Dai S, et al. miRNA-193a-mediated WT1 sup- pression triggers podocyte injury through activation of the E/H2/β-catenin/NLRP3 pathway in children with diabetic nephropathy. Exp Cell Res. 2024;442(02):114238. DOI: 10.1016/j.yexcr.2024.114238

Ibrahim RK, Ghudhaib KK, Allawi AAD. Early prediction of nephropathy in Iraqi patient with diabetes type II by evaluating some relevant biochemical factors. Baghdad Sci J. 2024;21(05): 1549-1560. DOI: 10.21123/bsj.2023.8008

Chen J, Feng Q, Qiao Y, et al. ACSF2 And lysine lactylation con- tribute to renal tubule injury in diabetes. Diabetologia. 2024; 67(07):1429-1443. DOI: 10.1007/s00125-024-06156-x

Da J, Xu Y, Tan Y, et al. Central administration of Dapagliflozin alleviates a hypothalamic neuroinflammatory signature and changing tubular lipid metabolism in type 2 diabetic nephropathy by upregulating MCPIP1. Biomed Pharmacother. 2023;168:115