Nephron

Clinical Practice: Mini-Review

Nephron 2025;149:29–35
DOI: 10.1159/000540307

Received: January 19, 2024
Accepted: July 8, 2024
Published online: July 29, 2024

Systems Biology and Novel Biomarkers for the Early Detection of Diabetic Kidney Disease

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Keywords
Biomarker · CKD273 · Diabetic kidney disease · Outcomes · Treatment

Abstract
Diabetic kidney disease is the most common driver of chronic kidney disease (CKD)-associated mortality and kidney replacement therapy. Despite recent therapeutic advances (sodium glucose co-transporter 2 [SGLT2] inhibitors, finerenone), the residual kidney and mortality risk remains high for patients already diagnosed of having CKD (i.e., estimated glomerular filtration rate <60 mL/min/1.73 m^2 or urinary albumin:creatinine ratio >30 mg/g). The challenge for the near future is to identify patients at higher risk of developing CKD to initiate therapy before CKD develops (primary prevention of CKD) and to identify patients with CKD and high risk of progression or death, in order to intensify therapy. We now discuss recent advances in biomarkers that may contribute to the identification of such high-risk individuals for clinical trials of novel primary prevention or treatment approaches for CKD. The most advanced biomarker from a clinical development point of view is the urinary peptidomics classifier CKD273, that integrates prognostic information from 273 urinary peptides and identifies high-risk individuals before CKD develops.

Unmet Needs of Chronic Kidney Disease Diagnosis

Chronic kidney disease (CKD) is one of the fastest-growing global causes of death according to the Global Burden of Disease (GBD) consortium, expected to become the fifth global cause of death by 2040 and the second in countries with long life expectancy before the end of the century [1]. Diabetic kidney disease (DKD) is the main contributor to this negative trend which might be explained by failure at multiple levels, including suboptimal biomarkers for early detection of kidney disease and risk of progression.

This narrative review aimed to familiarize physicians with emerging biomarkers in CKD and the role of system biology in the identification of biomarkers to guide the early diagnosis and treatment of CKD, with a focus on DKD. A PubMed search for "biomarkers AND kidney AND diabetes" was completed by the authors' opinions and expertise to produce a manuscript fitting the text and reference space limitations set by the journal.

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Current CKD Definition

The Kidney Disease: Improving Global Outcomes (KDIGO) consensus defines CKD as abnormalities of kidney structure or function present for more than 3 months with implications for health. Criteria include low glomerular filtration rate (GFR <60 mL/min/1.73 m^2) or evidence of kidney damage such as pathological albuminuria (urinary albumin/creatinine ratio [UACR] ≥30 mg/g); abnormal urine sediment, histology, or imaging; abnormalities due to tubular disorders; or kidney transplantation [2]. The cut-off values for albuminuria and GFR indicate an increased risk of CKD progression and premature all-cause or cardiovascular death, among other risks. CKD can be also diagnosed with normal eGFR in patients without albuminuria if there are any tubular, genetic or imaging findings, i.e., autosomal dominant polycystic disease or Fabry disease [3]. However, referral to nephrology is usually deferred until UACR >300 mg/g or GFR <30 mL/min/1.73 m^2, limiting the potential benefits of any intervention.

The Blind Spot in CKD

By the time CKD is diagnosed based on GFR criteria, over 50% of the functioning kidney mass has been lost. While albuminuria may allow an earlier diagnosis of CKD, the UACR criterion to diagnose CKD is still a late event, around 5- to 10-fold higher than physiological albuminuria levels. Moreover, most CKD patients are diagnosed based on eGFR rather than on UACR criteria. Thus, there is a blind spot in the current CKD definition, in which kidney damage is progressing but we lack biomarkers to diagnose it [4]. This is illustrated by autosomal dominant polycystic kidney disease, in which there is a tool sonography that allows the diagnosis of CKD decades before patients meet eGFR or UACR criteria. The need for earlier markers of kidney damage or of increased risk of CKD is driven by the observation that sodium glucose co-transporter 2 inhibitors (SGLT2i) and at least some glucagon-like peptide 1 receptor agonists (GLP1ra) such as the twincretin tirzepatide slow the progressive loss of eGFR patients within type 2 DM (T2DM) independently of whether they meet diagnostic criteria for CKD [5], i.e., they may be used for primary prevention of CKD in persons who do not yet have CKD but who are at high risk of CKD. Such early intervention is associated with better outcomes in terms of severe kidney events of on-treatment eGFR slopes than interventions initiated when CKD has already been diagnosed [6]. SGLT2i decrease glomerular hyperfiltration and albuminuria and protect proximal tubular cells from albuminuria and glucose toxicity, preserving the expression of the anti-aging and kidney protective protein Klotho [7]. The molecular mechanisms of kidney protection by GLP1ra are less well characterized, but they decrease excess body weight and improve control of blood pressure. However, early biomarkers are needed to identify persons with ongoing kidney injury who are thus more likely to benefit from intervention.

Current Biomarkers for CKD

Ideal biomarkers are non-invasive, easily quantifiable and have reproducible results. Beyond serum creatinine (sCr), used to estimate GFR and albuminuria, few biomarkers are in clinical use to assess kidney injury or function. Serum cystatin C may also be used to estimate eGFR. However, it is more expensive than sCr, and, thus, not as widely used despite providing better information on the risk of death, likely because it also increases in the presence of inflammation.

KIM-1 and neutrophil gelatinase-associated lipocalin (NGAL) are markers of acute kidney injury (AKI) used in the first hours of injury. [TIMP2]*[IGFBP7] (NephroCheck) and NGAL are FDA approved for AKI [8]. However, increased kidney gene expression and urinary levels have also been reported in the context of CKD [8, 9]. Increased urinary injury molecule 1 (KIM-1) is observed in patients with CKD and macroalbuminuria, but it did not improve prediction of mortality or disease severity. NGAL is expressed in injured kidneys, but urinary NGAL did not predict kidney outcomes in persons with CKD.

Systems Biology in the Future of CKD Biomarkers

Beyond sCr and UACR, and in some centers, cystatin C, none of the previously described biomarkers are currently used routinely in clinical practice due to the lack of evidence from randomized clinical trials with solid conclusions that can inform clinical decision-making. In this regard, it is unlikely that a single biomarker will provide additional actionable risk stratification. However, multiple combined biomarkers may better stratify risk as it has been shown for polygenic risk scores. Systems biology (genomics, proteomics, metabolomics, and others) provides a non-biased approach to biomarker identification among hundreds or thousands of potential biomarkers, i.e., it may be devoid of a priori knowledge on

disease pathophysiology, allowing for the discovery of previously unsuspected players or associations [4].

The Surrogate Markers for Micro-and Macrovascular Hard Endpoints for Innovative Diabetes Tools consortia (SUMMIT) used Luminex analysis and mass spectrometry to identify 7 serum biomarkers that combine metabolites and proteins with a strong correlation with progression to kidney failure, including KIM-1, α1-antitripsin, C16-acylcarnitine, FGF-21, and uracil [10]. Additionally, a combination of 12 serum biomarkers, including KIM-1 and beta-2-microglobulin could predict GFR decline beyond clinical criteria [11]. Indeed, serum KIM-1 and beta-2-microglobulin predicted eGFR decline as well as the larger panel. Increased serum levels of extracellular matrix (ECM)-related proteins, such as WFDC2 and MMP-7, were associated with kidney function decline in patients with T2DM with and without albuminuria (Table 1) [12]. The SYSKID consortia used systems biology to identify 9 predictor biomarkers for CKD progression [13]. These serum biomarkers had adjusted R2 values of 15% for patients with normal eGFR (≥60 mL/min/1.73 m^2) and 34% for patients with declined eGFR (<60 mL/min/1.73 m^2) when used alone. When combined with molecular and clinical predictors, the adjusted R2 value increased to 35% and 64% for patients with normal eGFR or low eGFR, respectively, enhancing the prognostic value compared to clinical prediction alone [13].

Metabolomics may identify small molecules of interest in CKD. In the FinnDiane cohort, urine metabolomics markers, including acylcarnitines, acyl-glycines, and compounds related to tryptophan metabolism distinguished persons with type 1 diabetes (T1DM) and normoalbuminuria who progressed to A1 albuminuria with accuracy of 75% and precision of 73% [21]. A retrospective MRN spectroscopy study identified 142 serum metabolites correlated with eGFR in participants with and without diabetes from four independent cohorts. Some amino acids as glycine and phenylalanine and metabolites as citrate and glycerol had a negative association with eGFR, whereas alanine, valine, and pyruvate had a positive relationship with diabetes [22]. New proteomic platforms have been used to identify a higher number of proteins in large clinical and epidemiological studies [19].

New proteomic platforms have been used to identify a higher number of proteins in large clinical and epidemiological studies [15, 16, 19]. In 4 independent cohorts of T1DM and T2DM patients with and without albuminuria, the SOMAscan platform identified circulating LAYN, DLL1, MAPK11, endostatin, and ESAM as independent predictors of progression to kidney failure [19]. The SOMAscan platform studied 194 inflammatory proteins in 3 independent cohorts of participants with T1DM and T2DM. Kidney risk inflammatory signature (KRIS) composed of 17 plasma proteins, including 6 members of the TNF receptor superfamily, was associated with the risk of developing kidney failure in a 10-year follow-up. The risk conveyed by KRIS was independent of albuminuria for both groups. Additionally, KRIS proteins were thought to contribute to the pathogenesis by promoting inflammation [15]. In a recent study, the OLINK platform measured plasma concentrations of 19 TNF receptors and 6 TNF ligands in individuals with T1DM with albuminuria A2 and A3. Seventeen TNF receptors were associated with progression to kidney failure in participants with A3 albuminuria, and 13 of them were associated with a decline in eGFR also in participants with A2 albuminuria (Table 1) [16].

Recent findings report associations of proinflammatory and profibrotic plasma markers, such as soluble TNF receptors 1 and 2, YKL-40, monocyte chemotactic protein-1, and soluble urokinase-type plasminogen activator receptor, as well as biomarkers of tubular injury with both the initiation and progression of DKD, being higher plasma TNFR-2 concentration most strongly associated with DKD progression [17]. Three elevated plasma proteins, FGF-20, angiopoietin-1, and TWEAK (tumor necrosis factor ligand superfamily member 12), were reported to be associated with "protection" against kidney failure in diabetes [20]. However, the authors likely extrapolated inappropriately from association and prediction studies to pathophysiology. Indeed, the pathogenic role of TWEAK activation of its receptor (TWEAK receptor, also known as Fn14) in multiple conditions, including AKI, CKD and cardiovascular disease [23]. Indeed, activation of the system is driven by increased expression of Fn14, sensitizing to TWEAK activity, in a manner that low circulating TWEAK levels, which are known to be associated with adverse cardiorenal outcomes, serve as evidence of TWEAK/FN14 activation akin to low circulating C3 level evidencing complement activation in glomerulonephritis [23]. In patients with T1DM, the increase of a panel of serum biomarkers (TNFR-1, KIM-1, CD27, syndecan-1, α-1-microglobulin) preceded A1 albuminuria (Table 1) [18].

CKD273: Urinary Peptidomics

Despite the avalanche of novel biomarkers, the urinary peptidomics biomarker CKD273 remains the best-characterized CKD biomarker and received a letter of

Table 1. Some examples of current and potential futures biomarkers for DKD

Biomarker	Description	Advantage	Disadvantage	Approved context of use	Reference
Current biomarkers					
Urine KIM-1	Cell surface receptor in epithelial and lymphoid/myeloid cells	Marker of acute and chronic tubular injury	Not specific for CKD, not adequately studied in CKD	AKI	Reviewed in [9]
Urine NGAL	Rapid response gene expressed in neutrophils and tubular cells	In clinical use for AKI	Not specific for CKD, not adequately studied in CKD	AKI	Reviewed in [9]
Urine [TIMP2]* [IGFBP7] (NephroCheck)	Increased gene expression/ excretion in urine during injury	In clinical use for AKI	Not specific for CKD, not adequately studied in CKD	AKI	Reviewed in [8]
Urine CKD273	Panel of 273 urinary peptides. In clinical use in Germany of early diagnosis and risk stratification of CKD	Non-invasive, supported by multiple studies for diverse forms of CKD. Same assay may provide information non other conditions	Only one provider, not shown that its use improves outcomes	CKD	[14]
Potential future biomarkers					
Serum WFDC2	ECM-related protein WAP family suppress multiple proteases activities and inhibit type 1 collagen degradation	Relationship with tubular cell damage and tubulointerstitial fibrosis	Mechanism of upregulation unknown, not shown that its use improves outcomes	NA	[12]
Serum MMP-7	Member of a family of proteolytic zinc-containing enzymes	Association with renal fibrosis and renal decline	Not specific, association with other fibrosis diseases such as lung fibrosis, not shown that its use improves outcomes	NA	[12]
Serum TNFR-1 and/or TNFR-2	Proinflammatory cytokine, activation of TNF pathway	Consistent association with decline in kidney function	Not specific due to relationship with inflammation, not shown that its use improves outcomes	NA	[15–18]
Serum MCP-1	Member of C-C chemokine family, recruitment of monocytes, and transformation to macrophages Endothelial function	Association with kidney function decline in T2DM and macroalbuminuria	Limited investigation of blood concentration and on T2DM population, not shown that its use improves outcomes	NA	[17]
Serum YKL-40	Role in limiting tubular cell apoptosis	Indicator of tubular injury severity	Inconsistent findings of relationship with eGFR decline and DKD progression, not shown that its use improves outcomes	NA	[17]
Serum LAYN	Transmembrane protein	Profibrotic features: kidney interstitial fibrosis and inflammation	Limited literature, not shown that its use improves outcomes	NA	[19]
Serum DLL1	Transmembrane ligand protein, role in CNS	Profibrotic features	Unspecific due to its role in neuronal cells, not shown that its use improves outcomes	NA	[19]
Serum MAPK11	Role in the cascade of cellular responses to inflammation and physical stress	Profibrotic features	Limited information, not shown that its use improves outcomes	NA	[19]
Serum Endostatin	Fragment of collagen XVIII expressed in glomeruli and peritubular capillaries	Related with fibrosis and kidney aging	Not shown that its use improves outcomes	NA	[19]
Serum ESAM	Cell-cell junction assembly expressed in vascular endothelial cells	Adhesion molecule of glomerulus	Discrepant findings, not shown that its use improves outcomes	NA	[19]
Serum TWEAK	Member of TNF superfamily	Related with increased inflammation in renal tubular cells both in vivo and in vitro	Unclear role in the development/ progression of DKD, not shown that its use improves outcomes	NA	[20]
Serum FGF-20	Neurotrophic factor	Strong and independent association with protection against renal decline and progression	Possible genetic predisposition or inherited component, not shown that its use improves outcomes	NA	[20]
Serum ANGPT1	Growth factor involved in angiogenesis and vascular inflammation	Alone is a sufficient predictor of rate of progressive renal decline and risk of ESRD	Highly related with natural antagonist ANGPT2, not shown that its use improves outcomes	NA	[20]
Serum KIM-1, beta-2-microglobulin	Cell surface receptor in epithelial and lymphoid/myeloid cells/ lymphoid cell product	Associated to CKD progression	May reflect decreased clearance or increased production (e.g., lymphoid tumors for beta-2-microglobulin), not shown that its use improves outcomes	NA	[10, 11, 18]

Urinary albumin:creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR), which allow the diagnosis of CKD and stratification of risk for CKD, are not shown. Note that some biomarkers are most informative as part of a panel of biomarkers. NA, not applicable.

support from the FDA in patients with kidney disease [24]. Additionally, the capillary electrophoresis coupled to the mass spectrometry (CE-MS) platform used to calculate CKD273 quantifies multiple other urinary peptides that are informative for other health conditions, including cardiovascular disease [24]. CKD273 comprises 273 urinary peptides that provide information on the pathophysiology of kidney disease, as is characterized by low levels of urinary collagen peptides, likely reflecting the downregulation of ECM degradation leading to ECM deposition and kidney fibrosis (Table 1) [24].

In longitudinal studies, increased CKD273 values precede the development of pathological (A2) albuminuria by 2–5 years, and the onset of A3 albuminuria by up to 3–7 years in patients with diabetes; moreover, treatment with irbesartan improved CKD273 in DKD [24, 25]. CKD273 was a better predictor of rapid CKD progression in patients with normal eGFR than eGFR plus albuminuria [26].

The role of CKD273 in clinical practice was assessed in the PRIORITY randomized clinical trial, which enrolled participants with DM and normoalbuminuria and assessed whether CKD273 could be used to identify patients at high risk of CKD progression in whom randomization to the mineralocorticoid receptor antagonist spironolactone would provide clinical benefit over placebo by slowing CKD progression systems [14]. PRIORITY confirmed that CKD273 identifies patients at a heightened risk of progression to A2 albuminuria. However, spironolactone was not protective. Ideally, the trial should be repeated using a drug with demonstrated kidney protective properties in DKD, such as finerenone [27].

Urinary proteomic analysis is considered high-end technology with higher costs than urine albumin testing and its availability is limited. More evidence on clinical application and cost-effectiveness in association with interventions that delay the development and progression of DKD is needed for its routine implementation in public healthcare systems [14].

Genetic Biomarkers

The field of genomics is evolving rapidly, and more powerful analyses can be performed at accessible costs. In Alport families, genetic studies may diagnose the disease and allow initiation of treatment in infancy. Exome sequencing allows the identification of pathogenic variants of multiple genes in a single test that can be performed at birth or even prenatally. However, these approaches are marred by the high number of genetic variants of unknown significance. Additionally, genome-wide association studies (GWAS) identified genetic variants associated with increased or decreased risk of CKD (e.g., certain *CO4A3* variants are associated with decreased risk of DKD [28]. More recently, GWAS-based polygenic risk scores have been described as capable of identifying at birth with up to 8-fold higher risk of CKD [29]. It is expected that polygenic risk scores based on whole-genome sequencing will be even more potent.

The Future of Biomarkers for DKD

Current biomarkers such as albuminuria and eGFR provide a late diagnosis that is unlikely to lead to paradigm shifts in the management and outcomes of DKD. These paradigm shifts may be provided by a primary prevention approach based on early biomarkers of CKD risk and the treatment of at-risk populations. Thus far, CKD273 is the novel biomarker with the best support from multiple observational studies and clinical trials as a predictor of DKD progression, even in patients without baseline CKD. In the future, this or other biomarker panels may be used to provide an earlier diagnosis of CKD or, alternatively, identification of high risk for CKD, enabling early treatment of persons at risk of developing DKD within a primary prevention framework.

Acknowledgment

The authors thank the European Renal Association DIABESITY CME (Maribor, Slovenia, September 16–17, 2022).

Conflict of Interest Statement

A.O. has received grants from Sanofi and consultancy, speaker fees, or travel support from Adviccene, Alexion, Astellas, AstraZeneca, Amicus, Amgen, Boehringer Ingelheim, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Menarini, Mundipharma, Kyowa Kirin, Lilly, Freeline, Idorsia, Chiesi, Otsuka, Novo-Nordisk, Sysmex, and and Vifor Fresenius Medical Care Renal Pharma; is the Director of the Catedra Mundipharma-UAM of DKD and the Catedra AstraZeneca-UAM of CKD and electrolytes; and has stock in Telara Pharma.

Funding Sources

Funding sources for the study are as follows: FIS/Fondos FEDER (PI20/00744, PI22/00469, PI22/00050, PI23/00627, PI21/00251, ERA-PerMed2022-248 – SIGNAL (AC22/00028) PI23/00627),

Sociedad Española de Nefrología, Sociedad Madrileña de Nefrología (SOMANE), FRIAT, Comunidad de Madrid en Biomedicina P2022/BMD-7223, CIFRA_COR-CM. Instituto de Salud Carlos III (ISCIII) RICORS program to RICORS2040 (RD21/0005/0001) funded by European Union – NextGenerationEU, Mecanismo para la Recuperación y la Resiliencia (MRR) and SPACKDc PMP21/00109, FEDER funds. COST Action PERMEDIK CA21165, supported by COST (European Cooperation in Science and Technology); PREVENTCKD Consortium Project ID: 101101220, Program: EU4H, DG/Agency: HADEA. KitNewCare, Project ID: 101137054, Call: HORIZON-HLTH-2023-CARE-04, Program: HORIZON, DG/Agency: HADEA.

Author Contributions

Priscila Villalvazo made substantial contributions to the design of the work, bibliographic research, interpretation, and drafting of the manuscript; contributed to text and contents of the manuscript including revisions and edits; approved the content of the manuscript; and agree to be held accountable for the work. Carlos Villavicencio made substantial contributions to the design of the work, participated in the bibliographic search, drafted the manuscript, contributed to text and contents of the manuscript including revisions and edits, approved the content of the manuscript, and agree to be held accountable for the work. Marina Gonzalez de Rivera made substantial contributions to the design of the work, contributed to text and contents of the manuscript including revisions and edits, approved the content of the manuscript, and agree to be held accountable for the work. Beatriz Fernandez-Fernandez made substantial contributions to the design of the work and bibliographic search; drafted the manuscript; reviewed the manuscript, interpretation, discussion, and conclusions; contributed to text and contents of the manuscript including revisions and edits; approved the content of the manuscript; and agree to be held accountable for the work. Alberto Ortiz made substantial contributions to the design of the work and bibliographic search; drafted the manuscript; reviewed the manuscript, interpretation, discussion, and conclusions; provided intellectual senior input; contributed to text and contents of the manuscript including revisions and edits; approved the content of the manuscript; and agree to be held accountable for the work.

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