Advances in Biomarker Sciences and Technology 7 (2025) 65–75

Contents lists available at ScienceDirect

Advances in Biomarker Sciences and Technology

journal homepage: www.keaipublishing.com/ABST

A mini review: Role of novel biomarker for kidney disease of future study

Palash Mitra [a,b], Sahadeb Jana [a,b], Suchismita Roy [a,*]

[a] Nutrition Research Laboratory, Department of Paramedical Allied Health Sciences, Midnapore City College, Kuturiya, Bhadutala, Midnapore, 721129, India

[b] Biodiversity and Environmental Studies Research Center, Midnapore City College, Kuturiya, Bhadutala, Paschim Medinipur, Midnapore, 721129, West Bengal, India

ARTICLE INFO

Keywords:
kidney disease
Biomarker
Genomic
End-stage renal disease

ABSTRACT

In the world, kidney disease is most common cause of death. Primary care physicians must conduct appropriate diagnosis, and management in order to avoid detrimental consequences linked to death as well as end-stage kidney disease. In this scenario biomarkers can detect renal pathology more accurately and early than currently known biomarkers, including serum creatinine, estimated glomerular filtration rate and urine albumin, they hold out hope for bettering the care of individuals with kidney illnesses. Nowadays, nephrology is concentrating extensively on finding novel indicators of acute stage of kidney disease in order to prevent further complications from chronic kidney disease as well as end-stage renal disease. The best treatment targets for a particular patient or illness context may also be determined with the use of proteomic and genomic biomarkers. Therefore, current advancements in the study of important biomarkers including tumor necrosis factor, transforming growth factor, interleukin −1, interleukin-18, nephrin, uromodulin, collagen, osteopontin, NGAL and Dickkopf-3 are linked to different aspects of renal injury. Prognosis and risk classification can be enhanced by a variety of proteome and genome biomarkers that are linked to different pathophysiological processes that follow renal damage.

1. Introduction

Renal failure and a number of clinical symptoms are common outcomes of acute kidney injury and chronic renal disease. One major factor contributing to the rise in mortality rates globally is the rising occurrence of chronic illnesses that has a substantial impact on the patient and their immediate environment. It also places a heavy load on the healthcare system. Globally, about 850 million people suffer with chronic renal disease. It is crucial to identify these patients early on in order to improve prognoses and intervene promptly.[1,2] A variety of illnesses and potentially harmful substances contribute to the development of chronic renal disease. However, chronic renal disease pathogenesis results in irreversible glomerular and tubular damage, which can be anticipated utilizing a number of biochemical indicators. Therefore, it is now more crucial than ever to identify those who are at risk of developing end-stage renal

Peer review under the responsibility of KeAi Communications Co., Ltd.

* Corresponding author. Nutrition Research Laboratory, Department of Paramedical and Allied Health Sciences, Midnapore City College, Kuturiya, Bhadutala, Midnapore, 721129, India.

E-mail addresses: pmitra664@gmail.com (P. Mitra), janasahadeb71@gmail.com (S. Jana), suchismitaroy2011@yahoo.in (S. Roy).

https://doi.org/10.1016/j.abst.2025.02.002
Received 11 January 2025; Received in revised form 1 February 2025; Accepted 11 February 2025
Available online 11 February 2025

disease early. This categorisation is aided by current metrics like proteinuria and estimated glomerular filtration rate. As a biomarker of kidney disease progression and response to treatments, proteinuria is limited. For the advancement of kidney disease, additional validated biomarkers are therefore needed. Data about possible biomarkers in kidney disease will be provided by proteomic studies, but these need to be contextualised in a clinical setting[3,4] Numerous studies demonstrate that there is a lack of public awareness regarding kidney illness/injury, despite the fact that early detection is a crucial approach for preventing kidney disease and inflammation, its progression, and associated problems. Thus, public health goals include expanding knowledge and putting sustainable solutions for kidney disease early detection into practice. With the ability to identify kidney injury before the widely used indicators of renal diseases, new possible biomarkers have emerged. This review's aim is to provide an overview of the most proficient recent research on the majority of kidney disease biomarkers and their clinical practice implications for future direction.

2. Method

This review article was detected on the practical therapeutic implications of kidney diseases nowadays. Kidney function, the limits of the present various kidney diseases recommendations, and biomarker discovery and development have all been taken into

Table 1
Role of biomarker in various type of kidney diseases.

Biomarker	Kidney disease	Reference
TNFα	Against folic-acid-induced acute kidney injury, renal IRI, diabetic kidney disease, acute interstitial nephritis, chronic kidney disease for hemodialysis patients, IgA nephropathy, unilateral ureteral obstruction (UUO) model	5 6 7 8 9 10
TGF-β	Glomerulonephritis, UUO and ischemic/reperfusion kidney injury, diabetic kidney disease renal tubular epithelial cell apoptosis and inflammation	11,12 13 14
Interleukin (IL)-1	Diabetes renal disease, cisplatin induced kidney injury, obesity induced kidney injury unilateral ureteral obstruction renal injury	15 16,1718–20
IL-18	UUO, cisplatin-induced kidney injury, acute kidney injury, hemodialyzed patients, Inflammatory Kidney Disease, diabetes renal disease, polycystic renal diseases	4 21 22 23 24 25 26
Nephrin	Diabetic nephropathy, hypertensive nephropathy, steroid-resistant nephropathy, focal segmental glomerulosclerosis, crescentic glomerulonephritis, collapsing glomerulopathy, lupus nephritis	27 28 29
Uromodulin	Diabetic renal disease, hypertension renal failure ischemic injury, tubulointerstitial kidney diseases, chronic kidney disease	30 31 32 33 34
Collagen	Renal fibrosis, IgA nephropathy, nephritis, diabetic renal disease, chronic kidney disease, chronic inflammatory or autoimmune disease, hypertension, unilateral ureteral obstruction	35 36 37 38 39
Osteopontin	Kidney cancer diabetic kidney disease, lupus Nephritis, immunoglobulin A nephropathy, membranous glomerulonephritis, chronic kidney disease aldosterone-induced kidney damage, hypercholesteremic kidney disease	40 41 42 43 44
NGAL	IgA nephropathy, drug induced tubular injury, diabetic kidney disease, acute kidney injury	45 46 4 47
Dickkopf-3	Contrast-induced AKI fibrosis in kidney disease, IgA nephropathy, membranous glomerulopathy, diabetic renal disease, nephritis,	48 39, 13 49

consideration. A wide variety of databases pertaining to healthcare were used in the search. Medline, Google Scholar and PubMed were used for multi-field database searches (Table 1).

3. Novel biomarker for kidney diseases

3.1. Tumor necrosis factor

Tumor Necrosis Factor (TNF)-α is a proinflammatory cytokine that is produced by immune cells such as lymphocytes and macrophages, but subsequent research has shown that endothelial and epithelial cells also produce it. TNF-α is expressed as a 26-kDa plasma membrane protein that is secreted into the extracellular space by the metalloproteinase TNF-α-converting enzyme; in solution, this 17-kDa protein forms homotrimers and activates two different receptors; transmembrane TNF-α also forms trimers and can activate TNF receptors. TNF-α is produced in the kidney by invading inflammatory cells, podocytes, mesangial cells, and epithelial cells from thick ascending limbs, collecting ducts, and proximal tubules. Hypertension, renal injury, diabetic nephropathy,[6,50] IgA nephropathy (**Li** et al., 2018) glomerulonephritis, endotoxemia, calcium-sensing receptor activation, lipopolysaccharide, angiotensin II, and interstitial tubular nephritis all cause an elevation in TNF-α.[50,5] Research indicates that TNF-α levels rise in diabetic patients than in healthy individuals, and that these levels increase as diabetic nephropathy worsens. Increased soluble TNFRs were also linked to diabetic renal disease, the circulating TNFR levels also showed progression to ESRD and a reduction in eGFR. According to a mouse study, TNF-α inhibition in diabetic kidney disease protects the kidneys by lowering serum creatinine, albuminuria, histopathologic alterations, and the recruitment of macrophages to the kidneys.[51–53] According to Moledina et al. reported that acute interstitial nephritis is caused by oxidative stress, IL-9–mediated activation of mast cells, which subsequently release TNF-α which involved pathogenesis of acute interstitial nephritis.[7] Conversely, the Unilateral Ureteral Obstruction model, the most popular vivo model of kidney fibrosis, has been used in a number of prior studies to clarify the pathophysiology of the TNF-α pathway in the development of kidney fibrosis by accumulation EMT. These studies have shown that the TNF-α pathway is a promising therapeutic target for kidney fibrosis, as evidenced by the successful anti-fibrotic effects of TNF-α inhibition via the pegylated form of soluble TNF receptor type 1.[10] A clinical study reported that a series of protein kinases are produced upon activation of TLRs, including TRL-4, which triggers the production of IL-6, IL-8, IFN-γ, and TNF-α (Fig. 1).[8]

3.2. Transforming growth factor

Transforming growth factor (TGF)-β has long been thought to be a master cytokine in the pathophysiology of renal fibrosis and inflammation. TGF-βs, activins, inhibins, growth and differentiation factors, bone morphogenetic proteins, and glial-derived

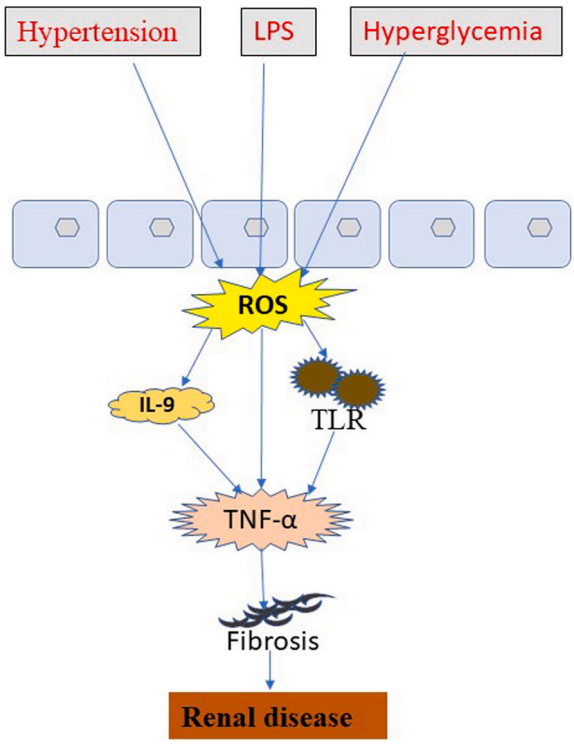

Fig. 1. Role of TNF-α for development of renal disease.

neurotrophic factors are all members of the TGF-β superfamily. Mammals have three known isoforms of TGF-β, and TGF-β1 has been implicated as a profibrotic mediator in a number of kidney disorders.[54] In a mouse model of crescentic glomerulonephritis, TGF-β1 protects the damaged kidney by preventing the release of inflammatory cytokines and the infiltration of $CD3^+$ T cells and macrophages. TGF-β1 can facilitate the transition of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. Short-term stimulation, however, would speed up the process of renal healing, while prolonged activation would result in renal fibrosis. Remarkably, TGF-β1 has anti-inflammatory effects by modulating c-Jun N-terminal kinase signalling, interacting with the β-catenin/Foxo complex, or blocking the NF-κB pathway via Smad7. TGF-β1 also stimulates the β-catenin/TCF relationship in mice with UUO and ischemic/reperfusion models. This boosts β-catenin binding to Foxo and TCF, respectively, which drives pro-fibrotic and anti-inflammatory responses at the same time. Furthermore, a number of investigations further illustrated how TGF-β1 signalling mediates the Akt/ERKs, P38/MAPK, and ERK1/2 pathways, hence contributing to fibrosis[11,12] and non-canonical pathways include the MAPK, PI3K/Akt/mTOR, TGF-β1/p38 MAPK, ILK, EGFR, and Wnt/β-catenin signalling pathways, which are all directly activated by TGF-β1. The pathophysiology of renal fibrosis is primarily influenced by these non-canonical pathways, which include matrix formation, proximal tubular cell dedifferentiation, migration, cell proliferation, and apoptosis cell death (Fig. 2).[12] TGF-β1 signalling is the primary mechanism of extracellular matrix formation, causing the production of myofibroblasts from a variety of sources, such as pericytes, resident, fibroblasts, epithelial cellsendothelial cells, and. Epithelial cells change into mesenchymal phenotypes in the well-known pathological process of renal fibrosis known as the Epithelial to Mesenchymal Transition (EMT). The loss of epithelial adhesion, de novo α-SMA expression, and cell migration are important events of EMT that are driven by TGF-β1 signalling both in vivo and in vitro on diabetic kidney disease. After the transition, epithelial adhesion and E-cadherin protein were lost, but migratory capacity and mesenchymal markers, fibronectin, and α-smooth muscle actin (α-SMA) were acquired during EMT.[12,13] Possible outcomes include tube dysfunction, interstitial fibroblast proliferation, inflammation, and increased extracellular matrix deposition due to hyperactivation of TGF-β1/Smad3 signaling. To stop the renal tubular epithelial cell apoptosis, inflammation, restoring the balance of TGF-β1 signaling provides a strong antifibrotic approach.[14]

3.3. *Interleukin-1*

One important upstream pro-inflammatory cytokine, Interleukin (IL)-1, is involved in the inflammation, host defence, acute phase responses, inflammatory cell infiltration, and adhesion molecule expression increase.[55] Research indicates that the IL-1R1 receptor has a complex involvement in kidney damage, particularly when its function is examined in a cell-specific way. Many investigations have demonstrated that IL-1R1 plays a generally harmful role in kidney injury since worldwide genetic deletion of IL-1R1 lowers unilateral ureteral obstruction, cyst development, cisplatin kidney injury and renal fibrosis.[18,19] After kidney damage, the NLRP3 inflammasome causes a number of cytosolic proteins to come together, activating caspase-1, which in turn encourages the activation of enzyme and release of mature IL-1β. IL-1β triggers the production of many pro-inflammatory mediators by activating widely distributed IL-1 receptors.[20] Numerous investigations have shown that renal parenchymal cells in experimental and human diabetes renal disease exhibit elevated expression of NLRP3 inflammasome components, leading to conjecture regarding a potential function of IL-1β in the course of kidney disease.[16,17] A study reported that by increasing TNF production and enhancing inflammatory signals between renal parenchymal cells and invading myeloid cells, IL-1R1 activation worsens cisplatin-induced acute kidney injury.[15]

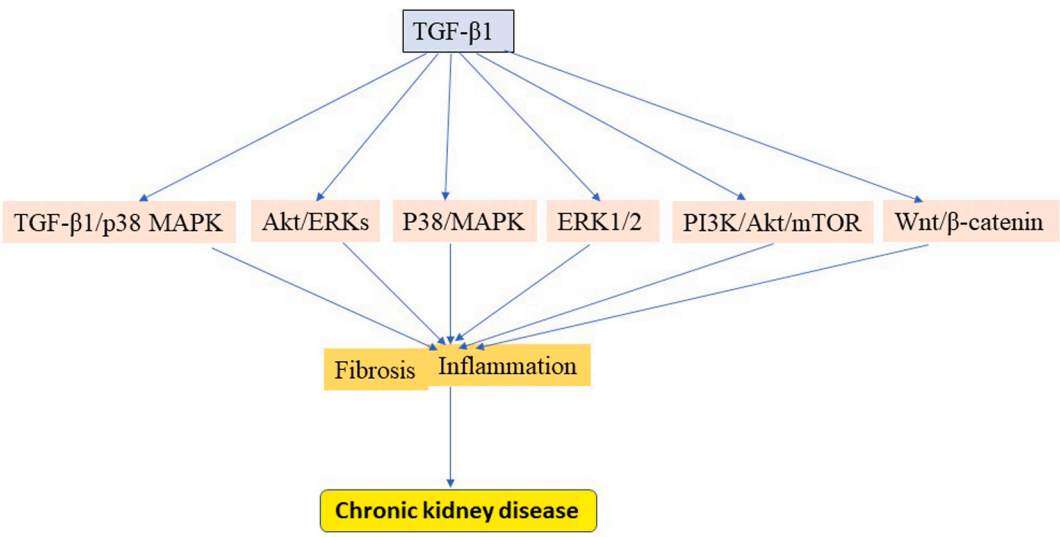

Fig. 2. Mechanism of Renal fibrosis and inflammation via upregulation of TGF-β1 signaling pathway.

3.4. Interleukin-18

The pro-inflammatory cytokine Interleukin (IL)-18 shares structural similarities with IL-1β. IL-18 significantly triggers a Th1 response and increases the synthesis of interferon gamma (IFN-γ)[24] that is produced when oxidative stress triggers inflammation, a redox-sensitive mechanism that stimulates the transcription factor NF-κB, which predominantly controls the expression of genes involved in inflammation.[56] Researchers have recently examined the biological and pathological functions of IL-18 in a variety of illnesses, such as sepsis, autoimmune diseases, metabolic syndrome, emphysema, and ischaemic heart disease.[22] First, research on kidney injury demonstrated that in animal model at risk for ischaemia, IL-18 promotes tubular injury, while IL-18 deficiency prevents tubular damage. Afterwards, human data showed that patients with kidney injury had greater urine IL-18 levels than either patients with temporary acute renal failure or controlled subjects.[22,23,57]. According to a recent study, mice with unilateral ureteric obstruction and cisplatin-induced kidney injury treatment showed considerably higher levels of IL-18 expression. Following, there was a considerable rise in the mRNA expression of IL-18, which is thought to be a crucial indicator for assessing renal tubular injury.[4]

It has been proposed that urine IL-18 is a novel biomarker for kidney injury based on pathophysiological plausibility. Following kidney transplantation, patients with acute tubular necrosis have been shown to have elevated urinary IL-18 levels. Numerous clinical investigations have been carried out, and the urine level of IL-18 is anticipated to be an early diagnostic marker of acute kidney damage.[58] The urinary level of IL-18 in patients with acute tubular necrosis has been shown to be significantly elevated compared to patients with urinary tract infections, acute renal failure, kidney disease.[57] Following lipopolysaccharide and cisplatin injection, IL-18 and IL-18Rα mRNA expressions in $CD4^{+}$ T cells generated from splenocytes were markedly elevated. In comparison to wild-type mice, the IL-18Rα-deficient mice exhibited decreased levels of pro-inflammatory cytokines including IL18 and IFN-γ, a greater survival rate, and reduced blood urea nitrogen levels.[24,21] A significant part of the onset and advancement of diabetic renal disease is played by inflammatory cytokines. Elevated levels of IL-18 in the plasma and urine was linked to diabetic renal disease in clinical investigations. So, IL-18 was also found to be an indicators for the onset of diabetic renal disease in diabetic patients and to be linked to the advancement of renal injury and or impairment[25,59–61] Recently, studies reported that necroptosis play due to expression of IL-18 that vital roles in cisplatin treated kidney injury and polycystic renal diseases.[26] It implied that IL-18 deletion's early renal protective function might be mediated by lowering early tubular damage (Fig. 3).

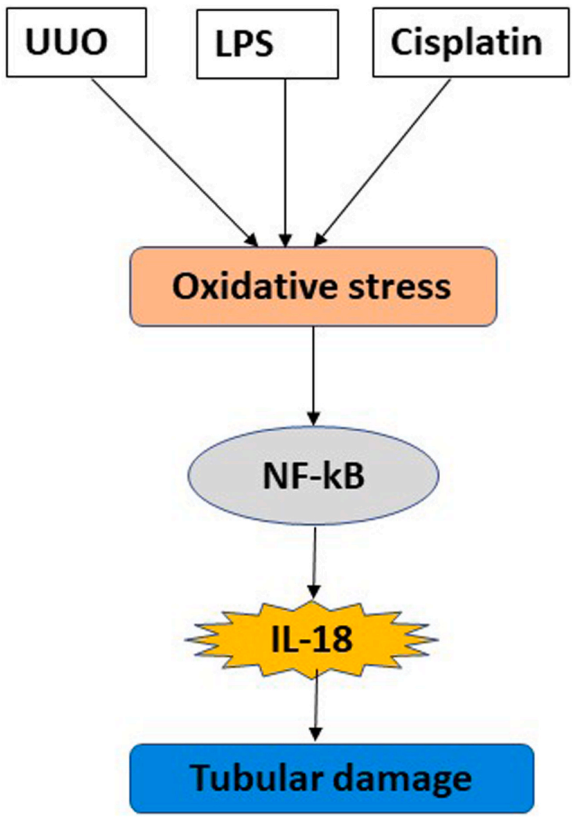

Fig. 3. Pathophysiology of tubular damage through IL-18 signal.

3.5. Nephrin

Glomerular podocytes express the 180 KD transmembrane protein known as nephrin. It was initially discovered in children with finnish-type congenital nephrotic syndrome. Nephrin plays a crucial role in podocyte formation, which forms the glomerular filtration barrier along with endothelial cells and the basement.[62] Additionally, nephrin has been found in the brain, spinal cord, pancreas, and lymphoid tissues. Nephrin is a crucial component of podocytes, which combined with the basement and endothelial cells make up the glomerular filtration barrier and leading causes of various renal disease including diabetic nephropathy, hypertensive and drug induced nephropathy. On the urinary side, the filtration barrier is made up of a podocyte monolayer, glomerular endothelial cell monolayer, and basement membrane. The four primary roles of podocytes are all dependent on their distinct and specialised architecture. These include the following: endocytosis of filtered proteins, remodelling of the glomerular basement membrane, structural support for the glomerular capillary, and control of glomerular permeability selectivity[27,63,64] It is now known that podocyte destruction and dysfunction are a common hallmark of minimal change disease, membranous, crescentic glomerulonephritis, collapsing glomerulopathy, focal segmental glomerulosclerosis and lupus nephritis.[28] Glomerular nephrin expression in the STZ rats four weeks following diabetes induction. Four to six weeks after the STZ-rats were given diabetes, nephrin was discovered in their urine. Nephrin expression, however, appears to be decreased in advanced diabetic renal injury. An in vivo RNA interference technique to create transgenic mice with doxycycline-inducible shRNA-mediated Nphs1 knockdown. Our in vivo research shows that glomerular shape and function were unaffected by short-term, nephrin knockdown, which began after kidney development was completed. Conversely, mice who received a 20-week chronic nephrin knockdown showed signs of podocyte death, glomerular basement membrane thickening, mesangial hypercellularity and sclerosis, filtration slit narrowing, foot process effacement, mild proteinuria, and subendothelial zone expansion.[29,65]

3.6. Uromodulin

The glycoprotein known as uromodulin, or the Tamm-Horsfall protein, is mostly expressed by kidney epithelial cells. There is evidence that autosomal dominant tubulo-interstitial kidney disease is caused by uncommon mutations in the UMOD gene, which produces uromodulin. Cysteine-rich domains, zona pellucida domains, epidermal growth factor-like domains, and a leader peptide are some of its structural elements. Insertion is guided to the endoplasmic reticulum by the leader peptide. The maturation of uromodulin depends on its processing in the endoplasmic reticulum because of its complicated structure, which includes several cysteine residues involved in the creation of disulphide bonds. Polarised trafficking mostly accumulates mature uromodulin in the apical membrane, where it is subsequently released into the urine by proteolytic cleavage by the serin protease hepsin.[30,31] Recent discoveries of uromodulin and its connection to renal disorders have altered new knowledge of uncommon hereditary illnesses. Uromodulin increases water channels and sodium transporters in tubular epithelial cells, and improper reabsorption of water and salt causes hypertension. Natriuresis and water diuresis are two ways whereby uromodulin suppression is expected to alter hypertension or volume overload. The idea that uromodulin controls the tubulo-glomerular feedback (TGF) pathway is also plausible. Urinary uromodulin may have an impact on TGF, which could lower intraglomerular pressure since the macula densa regulates TGF and serves as a sensor of the luminal fluid by apical NKCC2. An ischemic injury shifts uromodulin from the apical towards the basolateral domain. According to this theory, uromodulin is an enhanced renal protective agent.[66,32] To develop new treatment strategies, more research is needed to understand the regulatory functions of uromodulin in ion transport, particularly sodium transport. A ground breaking large-scale investigation on two population-based cohorts in Switzerland found numerous important correlations: kidney volume, urine volume, urinary electrolytes, and urinary uromodulin levels were positively connected with an eGFR <90 mL/min/1.73 m^2. On the other hand, Correlated with diabetes mellitus and age and tubulointerstitial kidney diseases.[33,34]

3.7. Collagen

Fibrotic tissue builds up in various organs, including the kidney and heart, as a result of ECM remodelling, which is primarily caused by the proteins collagen type I and III. Two major peptides implicated in ECM remodelling are fibrillar collagen types I and III. They are produced by fibroblasts as promolecules, and two peptidases must be involved in their activation. In the process of collagen type III synthesis, this results in the production of procollagen type III N-terminal peptide (P3NP), which is produced when procollagen type III is broken down by amino-peptidase. In the general population, the typical range is 1.2–4.2 μg/L[35,48,67] However, urine P3NP may be a sign of kidney fibrosis, which could help some people avoid needless kidney biopsies. P3NP levels were noticeably higher in patients who passed away at three years (244.1 ± 172.9 μg/L vs. 240.6 ± 218.1 μg/L)[68,36] P3NP levels were strongly linked to characteristics of kidney and cardiovascular disease in research; this association may be due to age-related impairments in the injury repair process, which are typified by excessive collagen deposition during the formation of extracellular matrix that causes renal fibrosis.[69,37] A renal biopsy showed diffuse chronic fibrosing mononuclear tubule interstitial nephritis and diffuse endoproliferative exudative sclerosing glomerulonephritis with collagen III deposition in the mesangium and capillary walls.[38] In children with a single working kidney, an elevated urine level of PIIINP may be a sign of early renal damage.[70] As in UUO, inflammation is thought to be a key factor and driver of renal fibrogenesis because reducing the recruitment of macrophages and T cells might lessen renal fibrosis. Apart from its ability to chemoattract monocytes and macrophages, which are the primary producers of TGF-β, MCP-1 may also promote collagen production and endogenous up-regulation of TGF-β expression in fibroblasts, which could result in autocrine and/or juxtacrine stimulation of collagen gene expression.[39]

3.8. Osteopontin

The pleiotropic, secreted, multiphosphorylated glycoprotein known as osteopontin was initially identified as secreted phosphoprotein 1 (SPP1). Later studies showed that it is expressed in other tissues, although it was first discovered in bone.[71] Numerous biological processes, including biomineralisation, several physiological processes related to cellular homeostasis, and diseases such chronic inflammation and tumour biology, are mediated by osteopontin. Osteopontin, sometimes referred to as bone sialoprotein 1 and early T-lymphocyte activation 1 protein, has been shown to activate immune cells such as Kupffer cells, T-cells, B-cells, macrophages, and natural killer cells.[72,40] Numerous research conducted over the past ten years have examined the involvement of osteopontin in the pathophysiology of diabetic renal disease as well as various type of renal disease and have found that it is highly expressed in the glomeruli and tubular epithelium of the renal cortex in rat and mouse models of diabetic renal disease[73,41] The release of profibrotic factors (such as cytokines, growth factors, and chemokines), an excessive buildup of fibroblasts and extracellular matrix (ECM) in the interstitial compartment, a phenotypic alteration and irreversible loss of parenchymal cells, and a decrease in kidney microvasculature are the hallmarks of kidney fibrogenesis after kidney injury. This glycoprotein is believed to be linked to the evolution of kidney disease because it promotes fibroblast proliferation, macrophage infiltration and retention in tissues, macrophage activation, cytokine production, and ECM creation.[42,43] According to one of the most recent investigations, a lack of osteopontin shields the kidney against oxidative stress, inflammation, and interstitial fibrosis brought on by aldosterone.[74] In contrast to ApoE−/−HD mice, collagen type IV staining was markedly inhibited in ApoE−/−/osteopontin −/−HD mice. This suggests that osteopontin deficiency leads to less lipid buildup and glomerulosclerosis. This supports earlier study shown osteopontin deficiency decreased aldosterone-induced kidney damage as demonstrated by the inhibition of collagen type IV accumulation.[44]

3.9. Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa lipocalin iron-carrying protein that is expressed by tubular renal epithelial cells after tubulointerstitial injury. NGAL is expressed at low levels in a number of cell types, such as the lung, kidney, and prostate. NGAL has been an established marker for acute kidney injury, but its role in chronic kidney disease (CKD) is less well-studied. Urinary NGAL levels were higher in patients with IgA nephropathy than in controls, and they were also linked to the severity of the disease.[45] Patients with polycystic kidney disease and those with glomerular proteinuria exceeding 1 g/24 h had higher NGAL levels than controls, and these levels were substantially connected with SCr. In children with renal tubular injury caused by non-steroidal anti-inflammatory drugs (NSAIDs), urine NGAL has been demonstrated to identify renal injury in the early stages. Continuous monitoring of NGAL in children utilizing NSAID allows clinicians to detect subclinical AKI and its progression since a rise in NGAL levels would allow treatment to prevent AKI and functional impairment.[46] Although NGAL concentrations in plasma and urine are very low and frequently undetectable, they are elevated after acute kidney injury and chronic kidney disease in humans, and similar elevated NGAL levels were also found in urine and plasma from animal models of kidney disease like cisplatin induced kidney disease.[4,47]

3.10. Dickkopf-3

Dickkopf-3 (DKK3) is a member of the 38 kDa molecular weight glycoprotein family that is produced by stressed tubular epithelia and is highly expressed in mesenchymal cells and mesenchymal progenitor cells in vitro. These glycoproteins affect the Wnt signaling pathway.[75] DKK proteins are crucial for vertebrate development because they locally suppress Wnt-regulated functions such the creation of eyes and limbs.[76] A stress-induced protein generated from the renal tubular epithelium, urinary dickkopf-3 (DKK3) activates the canonical Wnt/β-catenin signaling pathway, which controls transforming growth factor (TGF) β signaling and causes tubulointerstitial fibrosis. Encourages interstitial fibrosis and tubular atrophy. One biomarker that has been found to predict the course of chronic kidney disease (CKD) is DKK3.[77] uDKK3 levels have been shown to directly correlate with the degree of tubular atrophy and interstitial fibrosis in a variety of human glomerular and tubulointerstitial disorders based on analysis of human kidney biopsy samples. Additionally, DKK3 has been shown to be a prognostic marker for both adult and pediatric short-term declines in kidney function.[78,49] Regardless of the underlying etiology of kidney disease, baseline kidney function, or albuminuria, clinical trials have shown that elevated urine DKK3 levels identify patients at high risk for short-term CKD development. Regardless of whether CI-AKI occurred or not, our data demonstrated elevated DKK3/creatinine concentrations following contrast media administration. Given DKK3's potential for pathogenicity, we hypothesize that subclinical renal damage is mirrored by a high urine DKK3 ratio.[79] however this sudden rise in DKK3 mean that there is a higher chance of kidney damage in the future.

4. Role of omics on kidney disease

Several targeted strategies have been developed to find new early specific biomarkers of kidney diseases, such as acute kidney injury and chronic kidney injury diagnosis, while keeping in mind that standard laboratory measures of declining kidney function are rarely affected in the early stages of kidney disease. Innovative proteomics and genomics biomarkers such as IL-18, NGAL, TNF, osteopontin, and others offer an earlier and more accurate detection of renal pathology than traditional biomarkers like serum creatinine and urine protein. The identification of the most effective therapy targets may benefit from the use of proteomic and genetic indicators. Knowledge of disease processes is expected to be significantly advanced by systems biology, which is founded on proteomics in addition to genomes, transcriptomics, metabolomics, and phenomics.[80] The current status of proteomic and genomic

biomarkers from animal models such as unilateral ureteral obstruction, diabetic nephropathy, and cisplatin-induced kidney injury, as well as human research such as glomerular diseases, transplantation, dialysis, acute and chronic kidney injury, and drug-induced renal injury, in order to assess relevant findings and clinical utility. Among the proteomic and genomic techniques include polymerase chain reaction, surface-enhanced laser desorption/ionization, liquid chromatography-mass spectrometry, capillary electrophoresis-mass spectrometry, and two-dimensional gel electrophoresis. Developments in genomic biomarkers and novel genetic tests can help improve kidney disease management by encouraging early identification and bettering patient care.[81–83] In the diagnosis of primary membranous nephropathy (up to 70 % of cases), proteomics has already been shown to be useful in detecting anti-M-type phospholipase A2 receptor autoantibodies. The genome, epigenome, proteome, transcriptome, and metabolome may all be thoroughly and efficiently explored thanks to omics technologies.[84,85]

5. Discussion

The fact that non-invasive testing is typically used to detect kidney injury is a significant feature of its classification. Since the classification of kidney injury has been linked to outcomes like cardiovascular disease, all-cause mortality, and renal disease progression, it is significant. Additionally, it can enable therapeutic interventions at an earlier stage to delay the progression of the disease, reduce problems associated with a lower estimated GFR (eGFR), lower the risk of cardiovascular disease, and enhance survival and quality of life.[86] The most significant indicator of renal function is GFR. Since most clinical or research situations make it difficult to detect GFR (see below), estimation equations are based on filtration markers such cystatin C and serum creatinine (SCr). Because creatinine is not a reliable indicator of renal function, prediction equations have been utilized extensively to calculate eGFR from endogenous filtration markers without requiring clearance calculations. Stable kidney function is one of the prerequisites for using estimating equations based on SCr. Furthermore, when using creatinine, non-GFR determinats including changes in muscle mass, tubular secretion, extrarenal creatinine excretion, and production variations linked to dietary intake must be taken into consideration.[87] The fact that the international consensus criteria for the diagnostic and staging of kidney injury solely concentrate on changes in sCr, urine output (oliguria), and estimated glomerular filtration rate makes it difficult to diagnose and treat kidney injury early and differentially. There are certain drawbacks including sCr Delayed marker of kidney damage, Insensitive to small changes in GFR, Unchanged despite kidney damage in tubulointerstitial and vascular disease and others to these currently utilized indicators because of their delayed response to renal injury and lack of sensitivity and specificity.

Finding structural indicators of kidney injury in the urine or systemic circulation that are either directly produced by the kidney or accumulate as a result of the malfunction of tubular cells after kidney damage has been the focus of study using innovative technologies in order to overcome these constraints. For renal disease to be diagnosed promptly, its severity and outcome to be predicted, and proximal tubule damage to be monitored in both acute and chronic kidney disease, better biomarkers are desperately needed.[4] These biomarkers such as tumor necrosis factor, transforming growth factor, interleukin −1, interleukin-18, nephrin, uromodulin, collagen, osteopontin, NGAL and Dickkopf-3 ought to be able to identify the kind of injury or the precise location of damage.

6. Conclusion

The demand for new, reliable, non-invasive methods that can identify people at risk of kidney disease and aid in the management of renal disease is reflected in the explosion of research on proteomic and genomic-related biomarkers. Such verified biomarkers including tumor necrosis factor, transforming growth factor, interleukin−1, interleukin-18, nephrin, uromodulin, collagen and osteopontin would be useful in the following areas: monitoring kidney disease, patient stratification, and the identification of undiscovered disease. Numerous potential biomarkers have been found, although they are mostly the result of limited, single-center research. It is necessary to confirm the usefulness of these biomarkers in both distinct populations and bigger cohorts. Further methodological obstacles that genomics biomarkers must overcome before any clinical implementation can be included in guidelines include complexity and cost-effectiveness, the creation of suitable gold standards, standardization of the various technologies, and validation of the biomarkers in clinical trials. The application of many biomarkers at the same time is expected to replace the usage of single biomarker methodologies as the field develops since they offer better accuracy, sensitivity as well as specificity. Longer-term, more extensive research is necessary before using these biomarkers in therapeutic settings.

CRediT authorship contribution statement

Palash Mitra: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Sahadeb Jana:** Writing – original draft, Writing – review & editing. **Suchismita Roy:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The author declare no conflict of interest.

Acknowledgments

The authors grateful to Midnapore City College, a well-organized work environment and laboratory facilities for conducting related research work.

References

1. Francis A, Harhay MN, Ong ACM, et al, American Society of Nephrology, International Society of Nephrology. Chronic kidney disease and the global public health agenda: an international consensus. *Nat Rev Nephrol*. 2024;20(7):473–485. https://doi.org/10.1038/s41581-024-00820-6.
2. Xu Y, Xie Y, Shao X, Ni Z, Mou S. L-FABP: a novel biomarker of kidney disease. *Clinica chimica acta; international journal of clinical chemistry*. 2015;445:85–90. https://doi.org/10.1016/j.cca.2015.03.017.
3. Fassett RG, Venuthurupalli SK, Gobe GC, Coombes JS, Cooper MA, Hoy WE. Biomarkers in chronic kidney disease: a review. *Kidney Int*. 2011;80(8):806–821.
4. Jana S, Mitra P, Dutta A, et al. Early diagnostic biomarkers for acute kidney injury using cisplatin-induced nephrotoxicity in rat model. *Current research in toxicology*. 2023;5, 100135. https://doi.org/10.1016/j.crtox.2023.100135.
5. Pefanis A, Ierino FL, Murphy JM, Cowan PJ. Regulated necrosis in kidney ischemia-reperfusion injury. *Kidney Int*. 2019;96(2):291–301. https://doi.org/10.1016/j.kint.2019.02.009.
6. Chen Y, Lee K, Ni Z, He JC. Diabetic kidney disease: challenges, advances, and opportunities. *Kidney Dis*. 2020;6(4):215–225. https://doi.org/10.1159/000506634.
7. Moledina DG, Wilson FP, Pober JS, et al. Urine TNF-α and IL-9 for clinical diagnosis of acute interstitial nephritis. *JCI insight*. 2019;4(10), e127456. https://doi.org/10.1172/jci.insight.127456.
8. Grabulosa CC, Manfredi SR, Canziani ME, et al. Chronic kidney disease induces inflammation by increasing Toll-like receptor-4, cytokine and cathelicidin expression in neutrophils and monocytes. *Exp Cell Res*. 2018;365(2):157–162. https://doi.org/10.1016/j.yexcr.2018.02.022.
9. Li G, Wu W, Zhang X, et al. Serum levels of tumor necrosis factor alpha in patients with IgA nephropathy are closely associated with disease severity. *BMC Nephrol*. 2018;19(1):326. https://doi.org/10.1186/s12882-018-1069-0.
10. Taguchi S, Azushima K, Yamaji T, et al. Effects of tumor necrosis factor-α inhibition on kidney fibrosis and inflammation in a mouse model of aristolochic acid nephropathy. *Sci Rep*. 2021;11(1), 23587. https://doi.org/10.1038/s41598-021-02864-1.
11. Zhao X, Luo G, Fan Y, Ma X, Zhou J, Jiang H. ILEI is an important intermediate participating in the formation of TGF-β1-induced renal tubular EMT. *Cell Biochem Funct*. 2018;36(2):46–55. https://doi.org/10.1002/cbf.3316.
12. Tang PC, Chan AS, Zhang CB, et al. TGF-β1 signaling: immune dynamics of chronic kidney diseases. *Front Med*. 2021;8, 628519. https://doi.org/10.3389/fmed.2021.628519.
13. Mitra P, Jana S, Roy S. Insights into the therapeutic uses of plant derive phytocompounds onDiabetic nephropathy. *Curr Diabetes Rev*. 2024;20(9), e230124225973. https://doi.org/10.2174/0115733998273395231117114600.
14. Li J, Zou Y, Kantapan J, Su H, Wang L, Dechsupa N. TGF-β/Smad signaling in chronic kidney disease: exploring post-translational regulatory perspectives. *Mol Med Rep*. 2024;30(2):143. https://doi.org/10.3892/mmr.2024.13267 (Review).
15. Privratsky JR, Zhang J, Lu X, et al. Interleukin 1 receptor (IL-1R1) activation exacerbates toxin-induced acute kidney injury. *Am J Physiol Ren Physiol*. 2018;315(3):F682–F691. https://doi.org/10.1152/ajprenal.00104.2018.
16. Shahzad K, Bock F, Dong W, et al. Nlrp3-inflammasome activation in non-myeloid-derived cells aggravates diabetic nephropathy. *Kidney Int*. 2015;87(1):74–84. https://doi.org/10.1038/ki.2014.271.
17. Qiu YY, Tang LQ. Roles of the NLRP3 inflammasome in the pathogenesis of diabetic nephropathy. *Pharmacol Res*. 2016;114:251–264. https://doi.org/10.1016/j.phrs.2016.11.004.
18. Chen Y, Lu X, Whitney RL, et al. Novel anti-inflammatory effects of the IL-1 receptor in kidney myeloid cells following ischemic AKI. *Front Mol Biosci*. 2024;11, 1366259. https://doi.org/10.3389/fmolb.2024.1366259.
19. Chen Y, Xu F, Xiao X, et al. Assessment of osteopontin as an early nephrotoxicity indicator in human renal proximal tubule cells and its application in evaluating lanthanum-induced nephrotoxicity. *Ecotoxicol Environ Saf*. 2024;271, 115928. https://doi.org/10.1016/j.ecoenv.2024.115928.
20. Lei Y, Devarapu SK, Motrapu M, et al. Interleukin-1β inhibition for chronic kidney disease in obese mice with type 2 diabetes. *Front Immunol*. 2019;10:1223. https://doi.org/10.3389/fimmu.2019.01223.
21. Faubel S, Lewis EC, Reznikov L, et al. Cisplatin-induced acute renal failure is associated with an increase in the cytokines interleukin (IL)-1beta, IL-18, IL-6, and neutrophil infiltration in the kidney. *J Pharmacol Exp Therapeut*. 2007;322(1):8–15. https://doi.org/10.1124/jpet.107.119792.
22. Nisula S, Yang R, Poukkanen M, et al, FINNAKI Study Group. Predictive value of urine interleukin-18 in the evolution and outcome of acute kidney injury in critically ill adult patients. *Br J Anaesth*. 2015;114(3):460–468. https://doi.org/10.1093/bja/aeu382.
23. Radwan GAE, Yousef AE, Bayomy MF. Serum interleukin 18 level in kidney diseases and age. *Urol Ann*. 2024;16(2):133–139. https://doi.org/10.4103/ua.ua_140_22.
24. Hirooka Y, Nozaki Y. Interleukin-18 in inflammatory kidney disease. *Front Med*. 2021;8, 639103. https://doi.org/10.3389/fmed.2021.639103.
25. Yaribeygi H, Atkin SL, Sahebkar A. Interleukin-18 and diabetic nephropathy: a review. *J Cell Physiol*. 2019;234(5):5674–5682. https://doi.org/10.1002/jcp.27427.
26. Luan J, Fu J, Jiao C, et al. IL-18 deficiency ameliorates the progression from AKI to CKD. *Cell Death Dis*. 2022;13(11):957. https://doi.org/10.1038/s41419-022-05394-4.
27. Martin CE, Jones N. Nephrin signaling in the podocyte: an updated view of signal regulation at the slit diaphragm and beyond. *Front Endocrinol*. 2018;9:302. https://doi.org/10.3389/fendo.2018.00302.
28. Kandasamy Y, Smith R, Lumbers ER, Rudd D. Nephrin - a biomarker of early glomerular injury. *Biomark Res*. 2014;2:21. https://doi.org/10.1186/2050-7771-2-21.
29. Li X, Chuang PY, D'Agati VD, et al. Nephrin preserves podocyte viability and glomerular structure and function in adult kidneys. *J Am Soc Nephrol : JASN (J Am Soc Nephrol)*. 2015;26(10):2361–2377. https://doi.org/10.1681/ASN.2014040405.
30. Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet*. 2019;51(6):957–972. https://doi.org/10.1038/s41588-019-0407-x.
31. Gudbjartsson DF, Holm H, Indridason OS, et al. Association of variants at UMOD with chronic kidney disease and kidney stones-role of age and comorbid diseases. *PLoS Genet*. 2010;6(7), e1001039. https://doi.org/10.1371/journal.pgen.1001039.
32. El-Achkar TM, Wu XR. Uromodulin in kidney injury: an instigator, bystander, or protector? *Am J Kidney Dis : the official journal of the National Kidney Foundation*. 2012;59(3):452–461. https://doi.org/10.1053/j.ajkd.2011.10.054.
33. Pruijm M, Ponte B, Ackermann D, et al. Associations of urinary uromodulin with clinical characteristics and markers of tubular function in the general population. *Clin J Am Soc Nephrol : CJASN*. 2016;11(1):70–80. https://doi.org/10.2215/CJN.04230415.
34. Thielemans R, Speeckaert R, Delrue C, De Bruyne S, Oyaert M, Speeckaert MM. Unveiling the hidden power of uromodulin: a promising potential biomarker for kidney diseases. *Diagnostics*. 2023;13(19):3077. https://doi.org/10.3390/diagnostics13193077.
35. Mavrogeorgis E, Mischak H, Latosinska A, et al. Collagen-derived peptides in CKD: a link to fibrosis. *Toxins*. 2021;14(1):10. https://doi.org/10.3390/toxins14010010.
36. Ureche C, Dodi G, Şerban AM, et al. Predictive value of collagen biomarkers in advanced chronic kidney disease patients. *Biomolecules*. 2023;13(2):389. https://doi.org/10.3390/biom13020389.
37. Santanasto AJ, Cvejkus RK, Wojczynski MK, et al. Circulating procollagen type III N-terminal peptide and physical function in adults from the long life family study. *The journals of gerontology. Series A, Biological sciences and medical sciences*. 2021;76(7):1273–1279. https://doi.org/10.1093/gerona/glaa197.
38. Jakopin E, Bevc S, Ekart R, Hojs R. Collagen type III nephropathy as a systemic disease? - a case report. *Nefrologia*. 2020;40(1):106–108. https://doi.org/10.1016/j.nefro.2019.04.008.
39. Devocelle A, Lecru L, Ferlicot S, et al. IL-15 prevents renal fibrosis by inhibiting collagen synthesis: a new pathway in chronic kidney disease? *Int J Mol Sci*. 2021;22(21), 11698. https://doi.org/10.3390/ijms222111698.

40. Lamort AS, Giopanou I, Psallidas I, Stathopoulos GT. Osteopontin as a link between inflammation and cancer: the thorax in the spotlight. *Cells*. 2019;8(8):815. https://doi.org/10.3390/cells8080815.
41. Sinha SK, Mellody M, Carpio MB, Damoiseaux R, Nicholas SB. Osteopontin as a biomarker in chronic kidney disease. *Biomedicines*. 2023;11(5):1356. https://doi.org/10.3390/biomedicines11051356.
42. Steinbrenner I, Sekula P, Kotsis F, et al, GCKD investigators. Association of osteopontin with kidney function and kidney failure in chronic kidney disease patients: the GCKD study. *Nephrol Dial Transplant*. 2023;38(6):1430–1438. https://doi.org/10.1093/ndt/gfac173. official publication of the European Dialysis and Transplant Association - European Renal Association.
43. Cheng Y, Li Y, Scherer N, et al, GCKD investigators. Genetics of osteopontin in patients with chronic kidney disease: the German Chronic Kidney Disease study. *PLoS Genet*. 2022;18(4), e1010139. https://doi.org/10.1371/journal.pgen.1010139.
44. Pei Z, Okura T, Nagao T, et al. Osteopontin deficiency reduces kidney damage from hypercholesterolemia in Apolipoprotein E-deficient mice. *Sci Rep*. 2016;6, 28882. https://doi.org/10.1038/srep28882.
45. Zou C, Wang C, Lu L. Advances in the study of subclinical AKI biomarkers. *Front Physiol*. 2022;13, 960059. https://doi.org/10.3389/fphys.2022.960059.
46. Nehus E, Kaddourah A, Bennett M, Pyles O, Devarajan P. Subclinical kidney injury in children receiving nonsteroidal anti-inflammatory drugs after cardiac surgery. *J Pediatr*. 2017;189:175–180. https://doi.org/10.1016/j.jpeds.2017.06.045.
47. Marakala V. Neutrophil gelatinase-associated lipocalin (NGAL) in kidney injury - a systematic review. *Clinica chimica acta; international journal of clinical chemistry*. 2022;536:135–141. https://doi.org/10.1016/j.cca.2022.08.029.
48. De Gregorio V, Barua M, Lennon R. Collagen formation, function and role in kidney disease. *Nat Rev Nephrol*. 2024. https://doi.org/10.1038/s41581-024-00902-5, 10.1038/s41581-024-00902-5. Advance online publication.
49. Dziamałek-Macioszczyk P, Winiarska A, Pawłowska A, Wojtacha P, Stompór T. Patterns of dickkopf-3 serum and urine levels at different stages of chronic kidney disease. *J Clin Med*. 2023;12(14):4705. https://doi.org/10.3390/jcm12144705.
50. Ramseyer VD, Garvin JL. Tumor necrosis factor-α: regulation of renal function and blood pressure. *Am J Physiol Ren Physiol*. 2013;304(10):F1231–F1242. https://doi.org/10.1152/ajprenal.00557.2012.
51. Li X, Wu TT, Chen J, Qiu W. Elevated expression levels of serum insulin-like growth factor-1, tumor necrosis factor-α and vascular endothelial growth factor 165 might exacerbate type 2 diabetic nephropathy. *Journal of diabetes investigation*. 2017;8(1):108–114. https://doi.org/10.1111/jdi.12542.
52. Carlsson AC, Östgren CJ, Nystrom FH, et al. Association of soluble tumor necrosis factor receptors 1 and 2 with nephropathy, cardiovascular events, and total mortality in type 2 diabetes. *Cardiovasc Diabetol*. 2016;15:40. https://doi.org/10.1186/s12933-016-0359-8.
53. Awad AS, You H, Gao T, et al. Macrophage-derived tumor necrosis factor-α mediates diabetic renal injury. *Kidney Int*. 2015;88(4):722–733. https://doi.org/10.1038/ki.2015.162.
54. Gu YY, Liu XS, Huang XR, Yu XQ, Lan HY. Diverse role of TGF-β in kidney disease. *Front Cell Dev Biol*. 2020;8:123. https://doi.org/10.3389/fcell.2020.00123.
55. Bandach I, Segev Y, Landau D. Experimental modulation of Interleukin 1 shows its key role in chronic kidney disease progression and anemia. *Sci Rep*. 2021;11(1):6288. https://doi.org/10.1038/s41598-021-85778-2.
56. Liu YH, Chen YH, Ko CH, et al. SOD3 and IL-18 predict the first kidney disease-related hospitalization or death during the one-year follow-up period in patients with end-stage renal disease. *Antioxidants*. 2022;11(6):1198. https://doi.org/10.3390/antiox11061198.
57. Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. *Am J Kidney Dis: the official journal of the National Kidney Foundation*. 2004;43(3):405–414. https://doi.org/10.1053/j.ajkd.2003.10.040.
58. Liu Y, Guo W, Zhang J, et al. Urinary interleukin 18 for detection of acute kidney injury: a meta-analysis. *Am J Kidney Dis : the official journal of the National Kidney Foundation*. 2013;62(6):1058–1067. https://doi.org/10.1053/j.ajkd.2013.05.014.
59. Nakamura A, Shikata K, Hiramatsu M, et al. Serum interleukin-18 levels are associated with nephropathy and atherosclerosis in Japanese patients with type 2 diabetes. *Diabetes Care*. 2005;28(12):2890–2895. https://doi.org/10.2337/diacare.28.12.2890.
60. Sueud T, Hadi NR, Abdulameer R, Jamil DA, Al-Aubaidy HA. Assessing urinary levels of IL-18, NGAL and albumin creatinine ratio in patients with diabetic nephropathy. *Diabetes Metabol Syndr*. 2019;13(1):564–568. https://doi.org/10.1016/j.dsx.2018.11.022.
61. Yuan Y, Li L, Wang X, Zhang P, Wang J, Xiao Y. Correlation between plasma NLRP3, IL-1β, and IL-18 and diabetic nephropathy in patients with type 2 diabetes. *Alternative Ther Health Med*. 2023;29(4):52–56.
62. Jana S, Mitra P, Roy S. Proficient novel biomarkers guide early detection of acute kidney injury: a review. *Diseases*. 2022;11(1):8. https://doi.org/10.3390/diseases11010008.
63. Welsh GI, Saleem MA. Nephrin-signature molecule of the glomerular podocyte? *J Pathol*. 2010;220(3):328–337. https://doi.org/10.1002/path.2661.
64. Ohmori T, De S, Tanigawa S, et al. Impaired NEPHRIN localization in kidney organoids derived from nephrotic patient iPS cells. *Sci Rep*. 2021;11(1):3982. https://doi.org/10.1038/s41598-021-83501-9.
65. Li X, He JC. An update: the role of Nephrin inside and outside the kidney. *Sci China Life Sci*. 2015;58(7):649–657. https://doi.org/10.1007/s11427-015-4844-1.
66. Takata T, Isomoto H. The versatile role of uromodulin in renal homeostasis and its relevance in chronic kidney disease. *Internal medicine (Tokyo, Japan)*. 2024;63(1):17–23. https://doi.org/10.2169/internalmedicine.1342-22.
67. Khan S, Subedi D, Chowdhury MMU. Use of amino terminal type III procollagen peptide (P3NP) assay in methotrexate therapy for psoriasis. *Postgrad Med J*. 2006;82(967):353–354.
68. Ghoul BE, Squalli T, Servais A, et al. Urinary procollagen III aminoterminal propeptide (PIIINP): a fibrotest for the nephrologist. *Clin J Am Soc Nephrol : CJASN*. 2010;5(2):205–210. https://doi.org/10.2215/CJN.06610909.
69. Agarwal I, Glazer NL, Barasch E, et al. Fibrosis-related biomarkers and risk of total and cause-specific mortality: the cardiovascular health study. *Am J Epidemiol*. 2014;179(11):1331–1339. https://doi.org/10.1093/aje/kwu067.
70. Taranta-Janusz K, Moczulska A, Nosek H, Michaluk-Skutnik J, Klukowski M, Wasilewska A. Urinary procollagen III aminoterminal propeptide and β-catenin - new diagnostic biomarkers in solitary functioning kidney? *Adv Med Sci*. 2019;64(1):189–194. https://doi.org/10.1016/j.advms.2018.10.002.
71. Xie Y, Sakatsume M, Nishi S, Narita I, Arakawa M, Gejyo F. Expression, roles, receptors, and regulation of osteopontin in the kidney. *Kidney Int*. 2001;60(5):1645–1657. https://doi.org/10.1046/j.1523-1755.2001.00032.x.
72. Lin EY, Xi W, Aggarwal N, Shinohara ML. Osteopontin (OPN)/SPP1: from its biochemistry to biological functions in the innate immune system and the central nervous system (CNS). *Int Immunol*. 2023;35(4):171–180. https://doi.org/10.1093/intimm/dxac060.
73. Susztak K, Böttinger E, Novetsky A, et al. Molecular profiling of diabetic mouse kidney reveals novel genes linked to glomerular disease. *Diabetes*. 2004;53(3):784–794. https://doi.org/10.2337/diabetes.53.3.784.
74. Irita J, Okura T, Jotoku M, et al. Osteopontin deficiency protects against aldosterone-induced inflammation, oxidative stress, and interstitial fibrosis in the kidney. *Am J Physiol Ren Physiol*. 2011;301(4):F833–F844. https://doi.org/10.1152/ajprenal.00557.2010.
75. Fang X, Hu J, Chen Y, Shen W, Ke B. Dickkopf-3: current knowledge in kidney diseases. *Front Physiol*. 2020;11, 533344. https://doi.org/10.3389/fphys.2020.533344.
76. Schunk SJ, Speer T, Petrakis I, Fliser D. Dickkopf 3-a novel biomarker of the 'kidney injury continuum'. *Nephrol Dial Transplant*. 2021;36(5):761–767. https://doi.org/10.1093/ndt/gfaa003. *official publication of the European Dialysis and Transplant Association - European Renal Association*.
77. Roscigno G, Quintavalle C, Biondi-Zoccai G, et al. Urinary dickkopf-3 and contrast-associated kidney damage. *J Am Coll Cardiol*. 2021;77(21):2667–2676. https://doi.org/10.1016/j.jacc.2021.03.330.
78. Dahmer-Heath M, Gerß J, Fliser D, et al, NEOCYST Consortium. Urinary dickkopf-3 reflects disease severity and predicts short-term kidney function decline in renal ciliopathies. *Kidney international reports*. 2024;10(1):197–208. https://doi.org/10.1016/j.ekir.2024.09.023.
79. Seibert FS, Heringhaus A, Pagonas N, et al. Dickkopf-3 in the prediction of contrast media induced acute kidney injury. *J Nephrol*. 2021;34(3):821–828. https://doi.org/10.1007/s40620-020-00910-1.
80. Menon MC, Keung KL, Murphy B, O'Connell PJ. The use of genomics and pathway analysis in our understanding and prediction of clinical renal transplant injury. *Transplantation*. 2016;100(7):1405–1414. https://doi.org/10.1097/TP.0000000000000943.

81. Cañadas-Garre M, Anderson K, McGoldrick J, Maxwell AP, McKnight AJ. Genomic approaches in the search for molecular biomarkers in chronic kidney disease. *J Transl Med*. 2018;16(1):292. https://doi.org/10.1186/s12967-018-1664-7.
82. Chen L, Su W, Chen H, et al. Proteomics for biomarker identification and clinical application in kidney disease. *Adv Clin Chem*. 2018;85:91–113. https://doi.org/10.1016/bs.acc.2018.02.005.
83. Romanova Y, Laikov A, Markelova M, et al. Proteomic analysis of human serum from patients with chronic kidney disease. *Biomolecules*. 2020;10(2):257. https://doi.org/10.3390/biom10020257.
84. Katsumata Y, Okamoto Y, Moriyama T, et al. Clinical usefulness of anti-M-type phospholipase-A-receptor antibodies in patients with membranous nephropathy and the comparison of three quantification methods. *Immunological medicine*. 2020;43(1):47–56.
85. Mizdrak M, Kumrić M, Kurir TT, Božić J. Emerging biomarkers for early detection of chronic kidney disease. *J Personalized Med*. 2022;12(4):548. https://doi.org/10.3390/jpm12040548.
86. Levey AS, Coresh J. Chronic kidney disease. *Lancet (London, England)*. 2012;379(9811):165–180. https://doi.org/10.1016/S0140-6736(11)60178-5.
87. Lopez-Giacoman S, Madero M. Biomarkers in chronic kidney disease, from kidney function to kidney damage. *World J Nephrol*. 2015;4(1):57–73. https://doi.org/10.5527/wjn.v4.i1.57.