Review Article

Biomarkers and kidney diseases: a brief narrative review

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Background and Objective: Current biomolecular identification techniques expose new aspects in the biological universe of the human body. Omics strategies through genomics, metabolomics, lipidomics and proteomics generate thousands of information that demand math resources to integrate the meanings of multiple molecular patterns in the construction of modern biochemical knowledge of the interior environment. Biomarkers are endogenous molecules, detected qualitatively and/or quantitatively, which provide peculiar data for the identification of physiological or pathophysiological processes, as well as for the control of pharmacological responses. This narrative literature review aims to provide an update on biomarkers of kidney diseases.

Methods: We searched the PubMed database for clinical trial articles published in English, in the timeline from January 1990 to December 2021, with the following search terms: "AKI Biomarkers", "Podocytopathy Biomarkers", "Lupus Kidney Biomarkers", "Diabetic Glomerulopathy Biomarkers", "Diabetic Nephropathy Biomarkers", "Tubular Renal Biomarkers" and "Renal Biomarkers".

Key Content and Findings: Excluding 9 cross-responses and 1 veterinary study, 224 publications were selected, 77% of which have been published since 2010. We designed this narrative review primarily on the basis of this set of manuscripts.

Conclusions: Kidney biomarkers can be classified according to the morphophysiological characteristics of the nephron, regarding both the renal function (glomerular and tubular) and tissue integrity of its endothelial or epithelial cells. The development of these biomarkers is not focused on the identification of a specific disease, but on the detection of a renal pathophysiological phenomenon, with variable complexities and etiologies. This new molecular panel could be very useful for nephrologists in helping to make clinical decisions.

Keywords: Biomarkers; kidney; metabolomics

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Introduction

Current biomolecular identification techniques expose new aspects in the biological universe of the human body (1). Omics strategies through genomics, metabolomics, lipidomics and proteomics generate thousands of information that demand math resources to integrate and translate the meanings of multiple molecular patterns in the construction of modern biochemical knowledge of the

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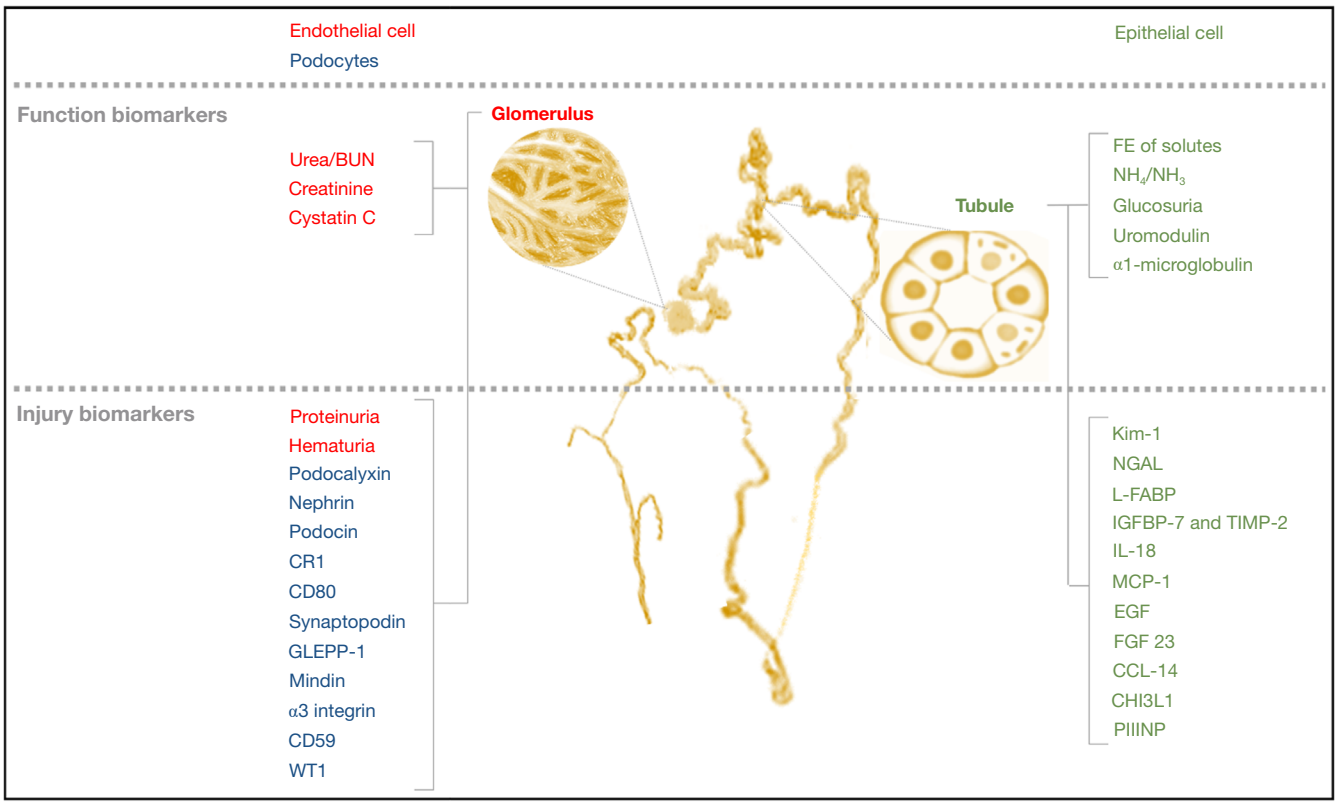

Figure 1 Biomarkers of kidney diseases. Glomerular function biomarkers: urea/BUN, creatinine and cystatin C. Glomerular injury biomarkers for endothelial cells: proteinuria and hematuria; and for podocytes: podocalyxin, nephrin, podocin, complement receptor-1 (CR1), CD80, synaptopodin, GLEPP-1, mindin, α3 integrin, CD59, WT1. Tubular function biomarkers: FE of solutes, NH_4/NH_3, glucosuria, uromodulin, α1-microglobulin. Tubular injury biomarkers: Kim-1, NGAL, L-FABP, IGFBP-7 and TIMP-2, IL-18, MCP-1, EGF, FGF-23, CCL-14, CHI3L1, PIIINP. Abbreviations: BUN, blood urea nitrogen; CCL-14, C-C motif chemokine ligand 14; CHI3L1, chitinase 3 like-1; EGF, epidermal growth factor; FE, fractional excretion; FGF-23, fibroblast growth factor 23; GLEPP-1, glomerular epithelial protein-1; IGFBP-7, insulin-like growth factor binding protein-7; IL-18, interleukin-18; Kim-1, kidney injury molecule-1; L-FABP, liver fatty acid binding protein; MCP-1, monocyte chemotactic peptide-1; NGAL, neutrophil gelatinase-associated lipocalin; NH_3, ammonia; NH_4, ammonium; PIIINP, type III aminoterminal propeptide procollagen; TIMP-2, tissue inhibitor of metalloproteinase 2; WT1, Wilms tumor protein-1.

interior environment.

The molecular scenarios designed with these tools contain biomarkers that, together or in isolation, are potentially capable of predicting or confirming diagnoses, guiding therapeutic strategies and predicting clinical outcomes. Biomarkers are endogenous molecules, detected qualitatively and/or quantitatively, which provide peculiar data for the identification of physiological or pathophysiological processes, as well as for the control of pharmacological responses. After more than a century restricted to the first biomarkers for the detection of kidney dysfunction—urea and creatinine (Cr), and kidney damage—proteinuria, nephrology now has a series of new molecular information and submits them to repeated validation so that they can be properly incorporated into clinical practice (2).

Kidney biomarkers can be classified according to the morphophysiological characteristics of the nephron, related both to the renal function (glomerular and tubular) and to the integrity of its endothelial or epithelial cells (*Figure 1*). The development of these biomarkers is not focused on the identification of a specific disease, but on the detection of a renal pathophysiological phenomenon, with variable complexities and etiologies. The absence or normal levels

of certain biomarkers can also be clinically useful to define negative predictive values for various pathologies.

In this brief review, we describe old and new molecules, proposed as biomarkers and whose clinical insights have been demonstrated in the literature for various kidney diseases, with the aim of providing an update on the topic. We present the manuscript according to the Narrative Review reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-22-1/rc). The main glomerular and tubular biomarkers described in the literature so far are presented below.

Methods

We searched the PubMed database for clinical trial articles in English, published between January 1990 and December 2021, with the following terms: "AKI Biomarkers", "Podocytopathy Biomarkers", "Lupus Kidney Biomarkers", "Diabetic Glomerulopathy Biomarkers", "Diabetic Nephropathy Biomarkers", "Tubular Renal Biomarkers", "Renal Biomarkers" (*Table 1*).

Glomerular function biomarkers

The quantification, in plasma and/or in urine, of endogenous low molecular weight molecules, which are freely filtrated by capillary endothelium, can be employed clinically for estimating glomerular filtration rate (GFR). Elevated serum levels of these biomarkers may indicate: (I) glomerulopenia, constitutional or acquired, as occur in chronic kidney disease (CKD), or (II) abrupt, intrinsic or reflex loss of glomerular function, which occurs in acute kidney injury (AKI). With its quantitative data, these molecules are part of the classic metabolomics of kidney failure, the metabolic signature from different past biological phenomena that compromised the functioning of the kidneys. As small molecules, these biomarkers are dialyzable and can be used as adequacy parameters for extrarenal clearance achieved by dialysis methods.

Urea/blood urea nitrogen (BUN)

Urea was isolated from human urine in 1797 (3) and was the first biomarker related to renal dysfunction. For over a century, the term uremia, meaning "urine in the blood", has been used as a synonym for kidney failure. This 60-Da molecule is a nitrogenous product of protein metabolism, contains 2 nitrogen atoms, is freely filtered by the kidneys and between 40% to 70% of the filtered urea returns to the plasma through the tubular epithelium (4). Serum urea levels depend on: (I) hepatic urea generation rate; (II) protein intake; (III) urea tubular reabsorption intensity; (IV) use of some medications and (V) presence of gastrointestinal bleeding. Simple to dose and easy to interpret, urea has high sensitivity but low specificity for the diagnosis of kidney disease and is not used to quantify GFR.

Creatinine

Serum Cr, the most widely used biomarker in nephrology, is an endogenous component constantly released into the circulation from muscle creatine, at a daily rate between 1% and 2% of the body's creatine content. Cr has 113 Da, does not bind to proteins, is freely filtered, not reabsorbed or metabolized in the kidney and was the first biomarker used for clinical quantification of GFR. About 25% of urinary Cr is secreted by renal tubules, influenced by drugs such as probenecid, penicillin, cimetidine and trimethoprim (5). Because Cr is related to muscle mass, its reference values vary between genders and age. Pharmacodynamic analysis estimated that the biological half-life of Cr in a healthy adult is around 4 h and is prolonged to 8 and 80 h with 50 and 5 percent of GFR respectively (6). As there is no linearity between serum Cr levels and GFR, math equations were developed for GFR estimation and this approach allowed clinical standardization of nomenclature for staging of nephropathies (7).

Cystatin C (Cys C)

Cys C is a 13-kDa cysteine proteinase inhibitor protein that has been incorporated as the latest biomarker to quantify and classify the stages of CKD (8). Cys C is synthesized in all nucleated cells, its serum levels do not depend on the musculature and do not suffer from age interference, showing some advantages for clinical use in relation to Cr. In the kidney, Cys C is freely filtered through the glomerular membrane, immediately reabsorbed in the proximal tubule (PT), where it is catabolized and, therefore, Cys C is not normally found in the urine nor returns to the circulation (9). Serum Cys C levels are affected by thyroid function, increase in hyperthyroidism and, unlike Cr, decrease in hypothyroidism. As serum levels of Cys C and Cr have the same hyperbolic relationship with GFR both biomarkers are employed in the same prediction equations for GFR (9). Cys C is a better as an option for patients

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	December 4 to 31, 2021
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	"AKI Biomarkers"; "Podocytopathy Biomarkers"; "Lupus Kidney Biomarkers"; "Diabetic Glomerulopathy Biomarkers"; "Diabetic Nephropathy Biomarkers"; "Tubular Renal Biomarkers"; "Renal Biomarkers"
Timeframe	January 1990–December 2021
Inclusion criteria	English text; human clinical trial
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Both authors selected and had consensus

Table 2 Qualitative and quantitative characteristics of proteinuria

Proteinuria	Daily excretion	Qualitative characteristics
Nephrotic	>3.5 g	Heavy proteinuria
Glomerular	1–20 g	Plasma proteins (albumin mainly)
Tubular	<2 g	LMW proteins (UMOD, RBP, α2 and β2 microglobulin)
Overflow	Up to 20 g	Overexcretion of small proteins (MB, LCP)

LMW, low molecular weight; UMOD, uromodulin; RBP, retinol binding protein; MB, myoglobulin; LCP, light chain protein.

with reduced muscle mass and degenerative muscle disease, where it is clearly a more accurate biomarker (8).

Glomerular injury biomarkers

Glomerular endothelial or podocyte/epithelial injury biomarkers can be detected in urine, qualitatively and quantitatively, and reveal an impairment of the glomerular capillary barrier, without necessarily affecting the GFR.

Proteinuria

Proteinuria can vary in quantity and quality and manifest as a transient or persistent elimination pattern. The urine of healthy individuals may contain a small amount of protein (<150 mg/day) which includes albumin, other plasma proteins (immunoglobulins, beta-2-microglobulin, etc.) and Tamm-Horsfall tubular protein (*Table 2*). Elevated proteinuria for more than 3 months, with or without a reduction in GFR, is sufficient to characterize the existence of CKD. Proteinuria is also a parameter used to assess therapeutic and pharmacological measures. Albuminuria is relevant for screening and prognosis in CKD, but it is also an independent risk factor for cardiovascular disease, end-stage kidney disease, stroke, and death. The nomenclature for the classification of albuminuria (7) is described in *Tables 3*. Classification A2 is associated with an increased risk of progression of kidney disease and cardiovascular events, and A3 is associated with lower renal survival (7).

Hematuria

Blood cells do not cross the glomerular barrier in a significant amount and the presence of red blood cells in urine is always a concern, whether by macroscopic or microscopic detection, intermittently or continuously. Hematuria is defined as >10 erythrocytes per field (400×) (10). Urinary dipsticks are useful for screening and detecting the heme group of hemoglobin. At low density (<1.006), hypotonicity causes lysis of red cells and a test with positive strip for hemoglobin and paradoxically negative hematuria on microscopy can be possible. Glomerular hematuria is sometimes asymptomatic and symptom-rich hematuria usually originates along the urinary tract. Hematic casts make the diagnosis of active

Table 3 Albuminuria classification

Albuminuria classification	Intensity	Daily excretion	Relationship, albumin/creatinine
A1	Normal/light	<30 mg	<30 mg/g
A2	Moderate	30–300 mg	30–300 mg/g
A3	Serious	>300 mg	>300 mg/g

Reagent strip tracking: + (30 mg/dL); ++ (100 mg/dL); +++ (300 mg/dL).

glomerulonephritis, which is usually accompanied by different degrees of proteinuria. Glomerular hematuria has a wide morphological variation and the identification of erythrocyte dysmorphism can be facilitated by phase-contrast microscopy, which allows the identification of acanthocytes and codocytes (11).

Glomerular podocytopathy biomarkers

Podocytes are epithelial cells and their foot processes cover the visceral epithelial layer on the exterior the glomerular basal membrane (GBM) surface. GBM integrity can be verified by non-invasive methods simply by taking a urine sample to identify and quantify podocyte-specific biomarkers. Podocyte urinary biomarkers reveal compromised structural integrity of the glomerulus and constitute clinically relevant information for glomerulopathies (12). Glomerular podocytopathies include minimal change disease (MCD), membranous glomerulopathy (MG), crescentic glomerulonephritis, collapsing glomerulopathy, focal segmental glomerulosclerosis (FSGS), diabetic nephropathy (DN), and lupus nephritis (LN). The following podocyte proteins can be detected in urine: podocalyxin, nephrin, podocin, complement receptor-1 (CR1), CD80, synaptopodin, GLEPP-1, mindin, alpha 3 integrin, CD59, and Wilms tumor protein 1 (WT1).

Podocalyxin

Podocalyxin in urine was related to podocyte injury (13,14) in patients with IgA nephropathy (IgAN) and Henoch-Schonlein purpura nephritis with a high sensitivity (88.4%) and specificity of 100% (15). In these patients, proteinuria levels are not able to reflect the severity of the disease, but urinary podocalyxin level does and represents an excellent non-invasive tool for the clinical management (16). Patients with severe diabetes mellitus albuminuria have more podocalyxin positive in the urine than diabetic patients with low microalbuminuria (17). Patients with FSGS that are excreters of podocalyxin in the urine had a fall of serum Cr in follow-up, indicting recovery (17). The connection between preeclampsia and podocytes has been enlightened by podocalyxin found in urine of women with preeclampsia and it can be used to diagnose this gestational pathology (18).

Nephrin

Nephrin is a 180-kDa transmembrane protein expressed in podocytes that was first identified in children with congenital nephrotic syndrome of the Finnish type (NPHS1) (19). Podocytopathies result in the detection of nephrin in the urine and nephrinuria is an early biomarker that showed positive correlation with proteinuria and severity of podocyte injury (20). Nephrinuria is elevated in DN and may play a role in clinical stratification of these patients (21) been a robust biomarker of preclinical DN (22). In adults with lupus or chronic glomerulonephritis, urine nephrin levels were positively correlated with disease severity and proteinuria (23). In obstetric patients, nephrinuria showed high sensitivity and specificity in pre-eclampsia detection (24).

Podocin

Podocin is a 42-kDa membrane-associated protein expressed by the *NPHS2* gene which is mutated in some patients with steroid-resistant autosomal recessive nephrotic syndrome (25). The name podocin derives from the location of the protein, which is the podocyte membrane, where it plays a role in mediating cell signaling by interacting with nephrin (26). Podocin has greater diagnostic accuracy as a biomarker for preeclampsia podocytopathy compared to podocalyxin and nephrin (27). Urinary podocin and nephrin mRNA presented correlated with the rate of decline in GFR in patients with lupus, ND, IgAN, MCD, and MN (28).

CR1

CR1, also named CD35 or C3bR, is a podocyte membrane

receptor with 200 kDa, expressed in both fetal and mature podocytes. CR1 expression on podocytes may contribute to complement-mediated damage in the kidney and CR1 urine levels have been studied in patients with lupus active glomerulonephritis and nephrotic syndrome (29,30).

CD80

CD80, also named B7-1, CD80 is a 53 kDa membrane podocyte protein that is also expressed in renal tubules, and has an immune role in T-lymphocyte activation. Promising data shows that urinary levels of CD80 in patients with relapsed MCD were significantly greater when compared to those in patients with MCD in remission and other glomerulopathies (31,32). Urinary CD80 is not affected by serum CD80 suggesting that it can also be derived from tubular epithelium, its specificity as a biomarker for podocytopathy remains to be confirmed.

Synaptopodin

Synaptopodin, also called 44 KDa podocyte protein, it is a podocyte actin-binding protein that regulates the cytoskeleton, which is also expressed in the central nervous system (33,34). Synaptopodin is a marker used in *in vitro* cell culture to control podocyte phenotypic differentiation. This protein has a renoprotective effect linked on its property to maintain and restore the podocyte's cytoskeleton after injury. Data from patients with DN (35) showed that urinary synaptopodin mRNA significantly correlated with the number of glomerular podocytes seen on histological examination, suggesting that urinary mRNA could be used to monitor disease progression (36). The same application would be proposed to follow the progression in LN, IgAN, MCD and MN (36), but it does not seem to be a good biomarker for preeclampsia (37).

Glomerular epithelial protein 1 (GLEPP-1)

This was the first protein characterized in podocytes and named GLEPP-1 (38). It is an apical membrane protein also called protein tyrosine phosphatase receptor type-0 (PTPR0) with 132 kDa and a large extracellular domain participating in glomerular barrier integrity. Mutations with phenotypic changes of GLEPP-1 podocytes have been shown in patients with idiopathic nephrotic syndrome, steroid resistant subtype (39). GLEPP-1 is a potential biomarker that has been used in experimental models, but to date there are no relevant data in human glomerulopathy.

Mindin

Mindin or spondin-2 is a secreted extracellular matrix protein expressed in glomerular podocytes that can be detected and quantified in urine. This protein may have a role as a recruiter of inflammatory cells in the pathogenesis of glomerular lesions and functions as an opsonin for the phagocytosis of bacteria (40). One series showed that diabetic patients had increased urinary Mindin in proportion to their respective levels of albuminuria and the amount of urinary Mindin increased with the progression of DN. When compared with the same levels of albuminuria, lower values of urinary Mindin were found in patients with IgAN. Mindin seems to be related to podocyte injury in patients with type 2 diabetes and DN (41).

α3 integrin (Intα3)

Intα3 is a heterodimeric, podocyte basal-membrane surface protein responsible for the attachment of the foot processes maturation to the underlying GBM. Integrins are transmembrane receptors consisting of αβ subunits, which exhibit different binding properties and mediate cell adhesion and migration, cell-to-cell communication, and activation of intracellular signaling; Integrin α3β1 is the most highly expressed integrin in the kidney, is found in both the glomerulus and the tubules and is the major integrin involved in podocyte stability. *In vivo* study showed that the mutation of murine integrin α3 gene caused abnormal kidney and lung development (42). Children carrying deletion or missense homozygote mutations have kidneys with atrophic glomeruli, FSGS, diffuse interstitial fibrosis, tubular atrophy, proteinuria, and loss and immaturity of the tubules (43). The latency associated peptide-transforming growth factor β (TGF-β) and soluble urokinase plasminogen activator receptor (suPAR) was found as the novel ligands of integrins that contribute to renal interstitial fibrosis and FSGS (44). It has been proposed that suPAR binds primarily to β3 integrin on the surface of podocytes via a tripartite complex of suPAR-APOL1-β3 integrin risk variants (45) and more studies will be needed to fully understand the role of Intα3 in the

pathophysiology of human diseases.

CD59

CD59, also called protectin or 20-kDa homologous restriction factor—HRF20, is a glycosylphosphatidylinositol anchored membrane bound protein that regulates the formation of the complement complex in the immune cascade. CD59 would be able to inhibit the complement mediated immune response to subepithelial immune complex deposition (46). CD59 concentration in the urine of patients with MN was higher in comparison to healthy controls and patients with DN. The urinary CD59 levels did not correlate to serum Cr, urinary protein concentration, or duration of disease (47).

WT1

This protein is a pivotal transcription factor exclusively expressed in glomerular podocytes. WT1 has been shown to be required for normal embryonic kidney development as well as the maintenance of the differentiated state of podocytes in adult kidneys (48). Urinary WT1 mRNA is significantly increased in patients with DN and chronic glomerulonephritis but undetectable in normal volunteers (49). WT1 is constitutively expressed in podocytes from healthy adults and is decreased in FSGS biopsies (49). Urinary exosomal WT1 was detected in some patients with active childhood nephrotic syndrome (50). In a mouse model of collapsing glomerulopathy, urinary exosomal WT1 was predicted for disease onset before proteinuria (51). Urinary WT1 represents a promising non-invasive biomarker for detecting podocyte lesions, monitoring disease progression and predicting therapeutic outcomes.

Tubular function biomarkers

Fractional excretion of solutes (FeS)

Fractional excretion (Fe) of any plasma filtered solute is a simple test used to assess tubular function that does not require timed urine collection and uses spot samples of urine and plasma. The Fe consists of calculating the percentage of filtered solute that is excreted in the urine, using respective simultaneous values of solutes and Cr. The results are computed: Fe_S = [(urinary solutes/plasma solutes)/(urinary Cr/plasma Cr)] ×100 (%). Fe is based on physiological principles that involve the reabsorption of different solutes by the tubular epithelium and reveals how much of the filtered solute has been excreted in the urine. The test is useful to assess Fe_{Na} (sodium) and Fe_U (urea) in cases of uremia and hypovolemia. The damaged tubule is incapable of reabsorbing the filtered elements in adequate amounts and Fe_{Na} <1 and Fe_U <35 are indicative of the integrity of the tubular function, pointing to volume depletion and probable pre-renal AKI. Different factors interfere with the excretion fractions, including the use of diuretics that increase Fe_{Na} but not Fe_U, making the latter a more reliable test for the etiological interpretation of AKI (52). Other exceptions with non-pre-renal AKI Fe_{Na} <1 occur when AKI due to acute tubular necrosis overlap in patients with previous perfusion disorder, as occurs in hepatorenal syndromes, heart failure and major burns. Patients with CKD adaptation mechanisms cause Fe_{Na} to increase inversely to the GFR values. Different hereditary and acquired tubulopathies can alter the excretion fractions of different solutes (such as phosphorus, calcium, uric acid, chlorine, bicarbonate, magnesium, etc.) and must be interpreted in light of physiological and pathophysiological circumstances.

Ammonium (NH_4)/ammonia (NH_3)

Physiologically, acidosis or acid load stimulates ammoniagenesis (NH_3) in PT cells, with subsequent protonation in the lumen. Therefore, the low urinary NH_4 may reflect different dysfunction of tubular cells. The main mechanism of urinary acidification is the excretion of NH_4 and different pathological conditions are able to affect this tubular function. CKD causes the inability to adapt urinary ammoniagenesis and NH_4 excretion to acid load. Urine ammonia was associated with clinical and pathological features of chronicity and tubulointerstitial disease activity among patients with LN and is a tool to help define the chronicity index and estimated GFR (eGFR) at biopsy (53). In AKI, low urine NH_4 may reflect tubular decreased ability to generate NH_4, that also can mean low hydrogen secretion and metabolic acidosis. The association of reduced urinary acidification with the progression of diabetic kidney disease in type 2 diabetes has already been demonstrated. Patients who form idiopathic uric acid calculi have an impaired renal excretory NH_4 response when exposed to an acute acid load, and this defective tubular response appears to contribute to the pathogenesis of nephrolithiasis (54).

Glucosuria

Under physiological conditions there is no urinary excretion of glucose. Around 1.5 kg of glucose are filtered daily and the entire amount is reabsorbed by the renal tubules. Virtually all glucose is recovered in the PT by sodium-glucose cotransporters (SGLT). Glycosuria is a biomarker for the following conditions: (I) hyperglycemia with a filtered glucose load greater than the reabsorption capacity; (II) hereditary or acquired tubulopathies (e.g., Fanconi syndrome); (III) use of glucosuric drugs, especially SGLT2 inhibitors (gliflozines) (55).

Uromodulin (UMOD)

UMDO also known as Tamm-Horsfall protein, is a 95-kDa glycoprotein expressed in the thick portion of the ascending loop of Henle (TAL). It is the most abundant protein in urine, excreting about 50 to 150 mg/day, which can also be found in the composition of tubular casts. UMOD is proposed as one of the new biomarkers for AKI, given the negative association between its urinary concentration and the development of AKI, especially in pediatric patients (56). In AKI, UMOD seems to protect the tissue by reducing inflammatory events in the external medullary zone, an effect generated through Toll-like receptor 4 (TLR4) receptors (57). UMOD is a biomarker of tubular function in Fabry nephropathy (58) and is also able to predict tubulointerstitial inflammation in patients with active LN (59). Among deceased donor transplant recipients, those with AKI had lower levels of UMOD within the tubules. The presence of UMOD is closely related to the development and functional maturation of the loop of Henle (60). Fetuses with prenatal renal failure tend to have lower levels of UMOD, and their elevated levels in amniotic fluid or fetal urine are suggestive of preserved renal function in the fetus (61).

α1 microglobulin (α1-M)

α1-M is a 33-kDa protein synthesized in the liver and freely filtered by glomeruli, with immediate reabsorption by PT cells, where it is catabolized. Under normal conditions only a small amount of filtered α1-M appears in the urine. Because it is stable in the pathophysiological range of urine pH, the protein is used as a biomarker to reveal renal tubular dysfunction as occur in sepsis AKI (62), after heart surgery (63) and even detection of kidney damage after neonatal asphyxia (64). Urinary α1-M excretion in CKD is associated with faster disease progression and higher mortality, and urine α1-M levels >15 mg/g Cr may indicate PT damage (62). Urinary measurement of α1-M can be useful as a screening method for tubular proteinuria of different causes. More recently, elevated tubular proteinuria has been performed in patients hospitalized with COVID-19 and the high amount of α1-M excreted in urine has been associated as a biomarker of mortality in adjusted models (65).

Tubular injury biomarkers

Acute kidney injury molecule-1 (Kim-1)

Kim-1 is a 38.7-kDa transmembrane glycoprotein expressed in PT cells that is involved in the phagocytosis of epithelial cells subjected to ischemic or toxic injury (66,67). Quantitative detection of urinary Kim-1 increases linearly with age, even in healthy individuals, with the highest levels seen in men. Urinary and plasma Kim-1 values show that Kim-1 is an early biomarker of PT cell proliferation and regeneration, with significant sensitivity and specificity for AKI, both in human studies and experimental series (68). In cases of post-cardiac surgery AKI, Kim-1 levels significantly increase between 2 and 24 hours postoperatively (68,69). Kim-1 has been used as a biomarker for the study of drug nephrotoxicity (70). In addition to AKI, Kim-1 is a useful tool for detecting CKD progression and for guiding therapeutic interventions in patients at risk for developing CKD. High levels of Kim-1 are related to the stages of severity of CKD and are altered in cases of proteinuria and inflammatory kidney disease (71). For use in clinical practice new tests provide semi-quantitative results that allow the detection of urinary Kim-1 levels in 15 minutes (72).

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a 25-kDa protein first described in neutrophil granules, but also synthesized in various tissues, such as kidney, lung and digestive tract, after epithelial damage. Circulating molecules are filtered by the glomerulus and reabsorbed in the PT (73,74). The physiological production of NGAL increases with age and is greater in women and the main sites of NGAL generation in the kidney are the ascending loop of Henle and the collecting duct. In AKI, the decrease in tubular reabsorption promotes early urinary detection of NGAL, which rises in urine and

plasma between 3 hours and 5 days after the initial injury. Increased NGAL expression can also occur due to bacterial infections, systemic inflammatory response syndrome and chronic and non-infectious systemic diseases. Therefore, inflammation is a confounding factor for the use of NGAL as an AKI biomarker, especially in critically ill patients with sepsis (75). In adult patients with sepsis, urinary NGAL alone was not an adequate predictive parameter to be used for the prevention of AKI, as well as for the need for Renal replacement therapy and for mortality within 90 days. However, NGAL proved to be a good predictive biomarker for AKI after cardiac surgery in adults (76) and vancomycin nephrotoxicity (77).

Liver fatty acid binding protein (L-FABP)

Liver-type fatty acid (FA) binding protein is a 14-kDa intracellular protein expressed in various tissues under physiological and pathophysiological conditions, including the PT and *pars recta* cells of the human nephron. L-FABP plays a relevant role in tissue injury and repair mechanisms and urinary L-FABP levels can identify the occurrence and severity of various kidney diseases. Physiologically, L-FABP is critical for FA homeostasis and is a promising biomarker to be used in different nephropathies (78). The protein binds to FA in the cytoplasm and transports them to the mitochondria or peroxisomes, where they are metabolized and provide energy for the work of the tubular epithelial cells. Urinary L-FABP is an early biomarker for detection and prognosis of acute stress-generating events and tubulointerstitial damage such as ischemia, post-cardiac surgery, post-renal transplantation, radiocontrast nephropathies, nephrotoxicity and sepsis. Urinary L-FABP may also reveal tubular lesions in CKD, such as nephrotic syndrome, DN, and glomerulopathies. These situations lead to excess FA within the tubular cells due to glomerular losses of FA-binding albumin. Under these conditions, it is believed that the increased expression of the *L-FABP* gene in the kidney is a protective response to facilitate the metabolism of FA and inhibit inflammatory phenomena. The greatest technical difficulty for the use of urinary L-FABP in clinical decisions is due to the long time required for its quantification, a barrier that has been overcome by the development of rapid quantitative tests (79) by chemiluminescence, and reagent kits of semiquantitative results (80). Urinary L-FABP is a diagnostic and predictive biomarker of AKI in critically ill patients.

Insulin-like growth factor binding protein-7 (IGFBP7) and tissue inhibitor of metalloproteinase 2 (TIMP-2)

In response to ischemic or septic AKI, the renal epithelial cells suffer from blockage of their cell cycles in the G1 phase. The two biomarkers IGFBP7 with 29 kDa and TIMP-2 with 21 kDa are involved in this stage of the cell cycle and have been studied together through the product of their respective urinary concentrations. In healthy individuals, the product of the values of these biomarkers did not differ significantly between men and women. The data suffer interference from diabetes, hyperbilirubinemia and anemia, which can induce false positive results (81). Therefore, these tests are complementary exams and the interpretations must be associated with the clinical picture that generated the suspicion of renal impairment. Among more than 300 biomarker candidates studied in critically ill patients, the product (IGFBP7) × (TIMP-2) proved to be the best predictive data for AKI 12 hours after the insult, and the simultaneous use of these urinary biomarkers may be useful in the intensive care unit (ICU) in patients at risk of developing AKI (82). One of the limitations for interpretation is not predicting the evolution of the already established AKI, as the duration and evolutionary kinetics of these two urinary biomarkers are not yet known.

Interleukin-18 (IL-18)

IL-18 is a 24-kDa proinflammatory cytokine, originally identified as an interferon-γ-inducing proinflammatory factor that regulates innate and adaptive immunity. The inactive precursor of IL-18 is synthesized in several organs, including the epithelial cells of the PT and renal collecting ducts (83). Inflammatory processes produce caspase 1 which activates IL-18 which is eliminated in the urine. Urinary IL-18 has been investigated as a biomarker of AKI (84). Detected 6 hours after ischemic injury, it can reach 25 times the normal value in 12 hours and IL-18 anticipates the diagnosis of AKI based on Cr in 24 to 48 hours. The best predictive evidence with IL-18 was observed in series of pediatric cardiac surgeries in which urinary levels increased early and significantly in patients who developed AKI (85). Urinary IL-18 is also increased in kidney transplant patients who have delayed graft function (86).

Monocyte chemotactic peptide-1 (MCP-1)

MCP-1, also known as C-C motif chemokine ligand 2 (CCL2), is produced by several different cells and is responsible for the migration of monocytes and macrophages to tissues, as part of the inflammatory reaction. Urinary MCP-1 has been studied as a biomarker of inflammatory processes that occur after AKI resulting from ischemia or toxicity. The use of MCP-1 blockers in experimental models of kidney disease has produced beneficial effects and MCP-1 inhibition is a proposed therapeutic strategy for patients with inflammatory kidney disease (87). Urinary MCP-1 and epidermal growth factor (EGF) have also been studied in the context of diabetic kidney disease, and both have been significantly associated with disease progression (88). In addition to the importance of the isolated values, the lower EGF/MCP-1 ratio was predictive of renal function decline in diabetes mellitus, IgAN, and several other glomerular diseases (89). These biomarkers appear to be useful in detecting the incidence or progression of CKD in patients undergoing cardiac surgery and help to stratify the long-term risk of CKD in other recognized clinical settings of kidney injury (89).

EGF

EGF is a 6-kDa mediator that regulates and stimulates the proliferation, migration and differentiation of mesenchymal cells, especially in the epithelia. EGF expression occurs mainly in PT cells, where it is transiently decreased after an ischemic insult and has been investigated as a biomarker of renal pathophysiological events (90). Clinical evidence shows that urinary EGF levels are reduced in patients with AKI (90). Experimentally, activation of EGF receptors (EGFR) in renal tissue is detected 5 to 30 minutes after ischemia/reperfusion, followed by the generation of free radicals and a reduction in the level of urinary EGF (91). The EGFR stimulates the dedifferentiation and proliferation of cells that survive injuries. Functional studies have shown that conditioned EGFR deletion accelerates renal tissue repair (92). Activation of the EGF/EGFR signaling pathway appears to be a promising strategy for the treatment of AKI and for recovery after AKI. As EGFR activation is associated with cell cycle arrest in the G2/M phase and may stimulate renal fibrogenesis, the therapeutic use of exogenous EGF may not be an adequate strategy for long-term treatment as EGFR may have ambiguous effect regulating both repair and fibrosis. Elevated urinary EGF was associated with greater recovery of renal function within 7 days and lower mortality within 3 months. Lower urinary EGF levels are associated with greater interstitial fibrosis and tubular atrophy (93). Higher EGF levels are associated with a better therapeutic response and remission in several glomerular diseases (94).

Fibroblast growth factor-23 (FGF-23)

FGF-23, also called phosphatonin, is a hormone that regulates the renal excretion of phosphorus that has been shown to be an early biomarker for AKI and the prognosis of adverse outcomes in patients with established AKI (95). FGF-23, with 28 kDa, is significantly increased in the urine and blood of patients with AKI and in different experimental models, such as ischemia/renal reperfusion and folic acid-induced AKI and rhabdomyolysis. Clinical evidence confirms that circulating levels of FGF-23 significantly increase in infants, children, adults and the elderly with AKI (96). Decreased clearance of FGF-23 in patients with AKI also contributes to increased circulating levels of FGF-23. Several studies have revealed mechanisms underlying the upregulation of FGF-23 in AKI, whose quantitative changes make it a robust candidate for a new predictive and prognostic biomarker to be used in patients with AKI (96,97).

C-C motif chemokine ligand 14 (CCL14)

Recently, the RUBY study (98) described urinary CCL-14 as the best performing cytokine among biomarkers predictive of AKI severity and persistence. Elevated urinary CCL14 levels are correlated with the risk of non-recovery of renal function. The mechanisms by which CCL1 interferes in the persistence of kidney damage are not yet known. CCL14 is a member of the family of small molecule chemokines that were initially linked to leukocyte chemotaxis and are implicated in tissue damage and repair processes (99). The level of urinary CCL14 seems to reflect the extent of the renal parenchymal damage. CCL14 is an important chemokine for monocyte/macrophage recruitment and is associated with pro-inflammatory chemotaxis in a variety of diseases including rheumatoid arthritis, multiple sclerosis and lupus. CCL14 is not expressed in mice and rats and little is known about the role and nature of CCL14 in AKI. CCL14 has a potential role as an inflammatory biomarker in identifying the risk of end-stage CKD in diabetic patients.

Chitinase 3 like-1 (CHI3L1)

CHI3L1, also known as YKL-40, is a 40-kDa glycoprotein secreted by several different cells. Urinary proteomics of experimental models revealed that CHI3L1 protects tubular cells from apoptosis and improves the survival of animals submitted to the ischemia/reperfusion AKI model (98). The molecule began to be investigated in patients at risk for AKI undergoing cardiac surgery and kidney transplantation. The combination of serum and urinary CHI3L1 was a good predictor of AKI associated with elective cardiac surgery at Kidney Disease: Improving Global Outcomes (KDIGO) stage ≥2 12 hours postoperatively and urinary CHI3L1 was associated with staging and death from AKI during hospitalization (100). CHI3L1 represents an AKI stage predictive biomarker ≥ KDIGO 2 in critically ill adult patients (101) and elevated urinary CHI3L1 is considered a promising biomarker for human septic AKI diagnostic (102). Specifically in malaria-associated AKI, CHI3L1 has been shown to be a robust new AKI biomarker with independent risk for mortality (103). In CKD, in baseline eGFR-adjusted models and albuminuria urinary CHI3L1 is associated with increased risk progression and was related to renal fibrosis and activation of myofibroblasts. In interstitial cystitis, serum and urine CHI3L1 levels are suggested as non-invasive biomarkers for the assessment of bladder fibrogenesis. Elevated serum concentrations of CHI3L1 have been reported in patients with type 2 diabetes, with certain solid tumors, other inflammatory conditions and in liver fibrosis (104,105).

Type III aminoterminal propeptide procollagen (PIIINP)

Renal fibrosis results from the deposition of various components of the extracellular matrix, including type III collagen. The degree of tubulointerstitial fibrosis present in renal biopsies is strongly associated with the progressive loss of GFR in CKD of different etiologies. Series of renal biopsies revealed that urinary PIIINP concentrations, with 44 kDa, correlated with the histological severity of tubulointerstitial fibrosis (106,107). As it is a small molecule, capable of glomerular filtration, the quantitative assessment of PIIINP in blood and urine and the PIIINP/Cr ratio in urine aim to validate this biomarker as an assessment tool for parenchymal fibrosis and renal function decline. Unlike blood measurements, urine PIIINP concentrations are associated with progression of CKD in the adult population, independently of baseline GFR conditions, albumin/Cr ratio and diagnosis of CKD (108). Urine PIIINP has the advantage of being a non-invasive method that presents itself as an independent factor associated with all-cause mortality in the elderly and emerges as a promising biomarker to assess the intensity of renal fibrosis and to monitor the evolution of renal grafts (109). Unlike other biomarkers, PIIINP does not reveal acute lesions of tubular cells and provides a predictive characteristic for the progression of nephropathies in the long term.

Conclusions

In summary, advances in biotechnology have made available a variety of biomarker molecules for kidney events. These molecules are of potential application in clinical practice, both for function evaluation and for the detection of pathophysiological processes present in different parts of the nephron. The development of these biomarkers is not focused on the identification of a specific disease, but on the detection of a kidney pathophysiological phenomenon, with variable complexities and etiologies.

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Footnote

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