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Chapter 8

Biomarkers of Common Childhood Renal Diseases

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http://dx.doi.org/10.5772/intechopen.74016

Abstract

Novel biomarkers are now used in the diagnostic and prognostic evaluation of common kidney diseases in children. The increased scientific interest in these biomarkers is partly due to the remarkable progress in their discovery techniques, and their validation in clinical subjects. However, the wide variation in their sensitivity and specificity is still a major concern. In the identification of biomarkers of kidney injury, an ideal biomarker should be produced after organ injury in concentrations which directly correlates with the degree of injury; should be easily measured in body fluids; and should serve as a potential tool to monitor therapeutic response which is predicated upon a post-injury decrease in its concentration. This book chapter aims to highlight and discuss the novel biomarkers used in the diagnostic and prognostic evaluation of common acute diseases of the kidney in children, such as urinary tract infection (UTI) and acute kidney injury (AKI), as well as chronic kidney disease (CKD) secondary to idiopathic nephrotic syndrome (INS) and diabetic nephropathy (DN).

Keywords: acute diseases, chronic diseases, kidney, children, biomarkers

1. Introduction

Novel biomarkers are now utilized in the diagnostic and prognostic evaluation of common kidney diseases in children [1–3]. Unlike in developing countries where they are scarcely used in medical diagnostics, they are currently used as site-of-care and laboratory tools for disease evaluation in developed settings although some of them have not been fully validated for routine clinical use. The increased scientific interest in novel biomarkers is nevertheless due to the remarkable progress in their discovery techniques, their validation in clinical populations and their utility as diagnostic tests. Despite the reliability of the conventional diagnostic methods for some of these diseases, their limitations as diagnostic tools have underscored the

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need for a paradigm shift to biomarkers. The attraction of these novel biomarkers lies in the non-invasive nature of their use in disease evaluation. However, the wide variation in their sensitivity and specificity is still a major challenge.

According to the definition by the *National Institute of Health Biomarkers Definitions Working Group*, a biomarker refers to 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention' [4, 5]. In other words, it is a measurable indicator of a biological state or condition. Although there are diverse perspectives to the definition of a biomarker, for the purpose of the current topic, a biomarker can be defined as a substance whose detection indicates a particular disease-state, or a change in expression/state of a protein which correlates with the risk/progression of a disease, or with disease susceptibility to a given therapy. In fact, the most actively studied biomarkers presently are the biological macromolecules. For instance, proteins are most easily measured by immunoassays or by mass spectrometry combined with high-resolution separation techniques, while nucleic acids can be amplified by the polymerase chain reaction (PCR) and related techniques.

In the identification of biomarkers of kidney injury, an ideal biomarker should be produced after organ injury in concentrations which directly correlate with the degree of injury; should be easily measured in body fluids; and should serve as a potential tool to monitor therapeutic response, predicated upon a post-injury decrease in its concentration [6].

In this book chapter, novel biomarkers which essentially meet these requirements with respect to evaluating common kidney diseases in children are highlighted and discussed.

2. Acute diseases of the kidney and biomarkers

Biomarkers have been identified for the following acute diseases of the kidney: acute pyelonephritis or upper urinary tract infection (UTI) and acute cystitis/urethritis or lower UTI, as well as acute kidney injury (AKI). UTI ranks third in the hierarchy of common childhood infections in developing countries [7], and remains one of the commonest causes of febrile illness in the pediatric age group [8, 9].

2.1. Biomarkers of UTI

Serum procalcitonin (PCT), urine/serum interleukin 6 (IL-6) and 8 (IL-8), and urine neutrophil gelatinase-associated lipocalin (NGAL) are currently the major biomarkers identified in the evaluation of the disease. Other novel biomarkers include urine interleukin 1-beta (IL-1β), urine 8-hydroxy-2-deoxyguanosine (8-oxodG), and urine total anti-oxidant capacity (TAC) (**Figure 1**).

PCT is one of the inflammatory markers recognized as a biomarker of severe bacterial infection [10]. It is essentially a peptide precursor of the hormone- calcitonin - produced by the thyroid parafollicular cells, as well as the neuroendocrine cells of the lungs and intestines. Its serum level in healthy subjects is below the limit of detection (0.01 μg/L) of laboratory assays [11]. Notably, serum PCT level is not elevated significantly with viral or non-infectious inflammatory process, but may rise up to 100 μg/L in systemic inflammatory response from severe bacterial infection. In fact, estimation of PCT can be used as a marker of severe bacterial

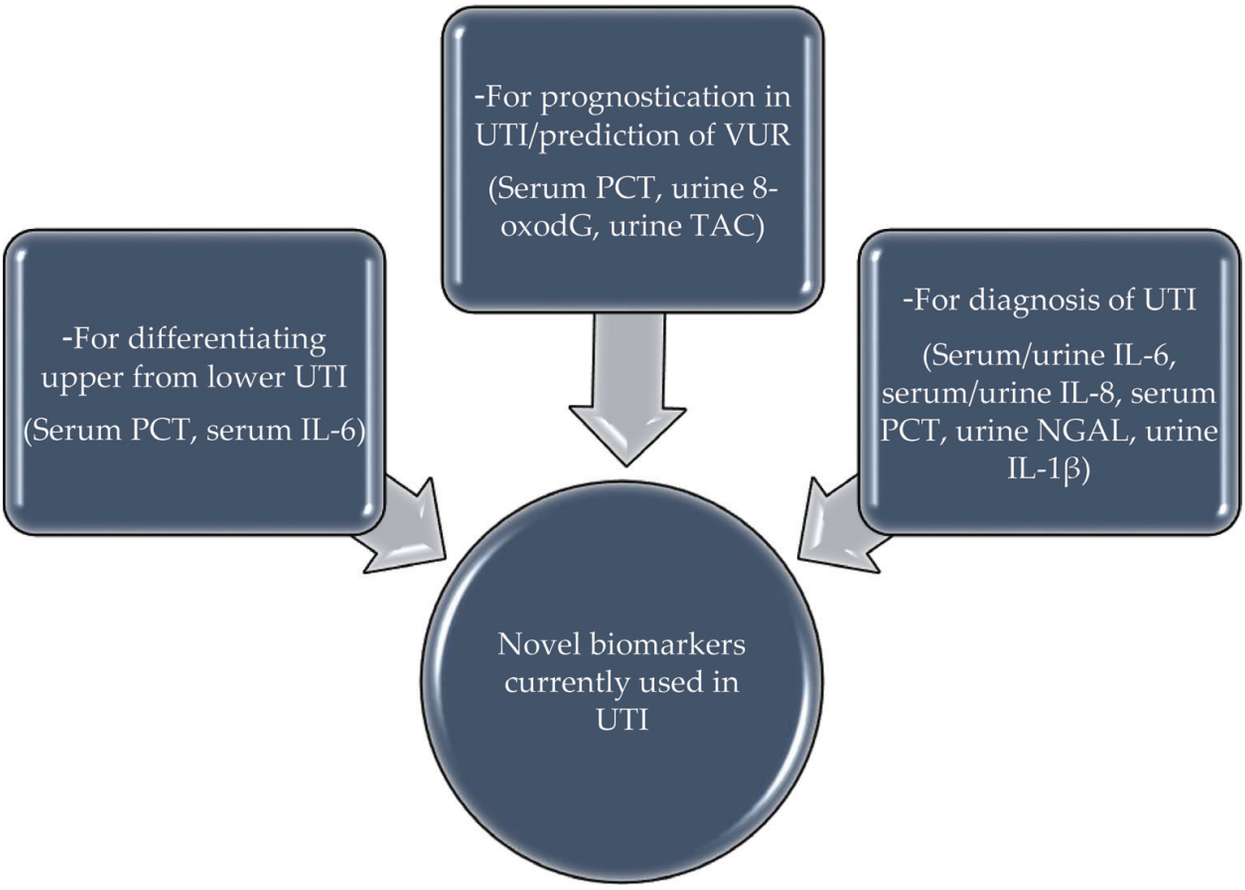


Figure 1. Schematic representation of the list of biomarkers used in the three-fold evaluation of urinary tract infection (UTI).

sepsis, as its levels correlate with the severity of sepsis [12]. In comparison with other acute phase reactants such as IL-2, IL-6, IL-8, C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α), PCT has a high sensitivity (85%) and specificity (91%) for discriminating between patients with systemic inflammatory response syndrome (SIRS) and those with sepsis [13]. It is now well established that serum PCT has a good diagnostic accuracy for the diagnosis of acute pyelonephritis than for lower UTI, with reported high sensitivity and specificity values [14–16]. For instance, sensitivity and specificity values of 94.1 and 89.7% respectively, and sensitivity and specificity values of 83.3 and 93.7% respectively, have been documented [15, 16]. PCT also has a good predictive ability for vesico-ureteric reflux (VUR), as high levels of this biomarker are significantly related to high-grade VUR [17–19]. Again, children with VUR reportedly presented with significantly higher median PCT levels than those without VUR; sensitivity and negative predictive values of 94.3 and 95.4% respectively for predicting high-grade VUR (using the biomarker alone), as well as 97.1 and 97.8% respectively (using a combination of the biomarker and ultrasound studies) have been recorded [18]. Finally, PCT can also serve as an early predictor of renal parenchymal damage in children with UTI [20]. The implication is that the prognostic utility of PCT may in future preclude the need for dimercaptosuccinic acid (DMSA) scan, or better still, may serve as an adjunct to this imaging study.

Similarly, other biomarkers such as urine 8-hydroxy-2′-deoxyguanosine (8-oxodG) and total antioxidant capacity (TAC) are useful in the prediction of renal parenchymal injury in children with UTI [21]. Interestingly, those patients with positive DMSA scan had higher levels of

urine 8-oxodG and higher urine TAC than the patients with normal DMSA scan: showing that urine levels of 8-oxodG may directly correlate with renal parenchymal injury.

Urine NGAL is another biomarker for the diagnostic evaluation of UTI. NGAL (also called lipocalin-2) is a protein involved in innate immunity as it is involved in the sequestration of iron which ultimately blocks bacterial growth [22]. It is expressed mainly in neutrophils and in low concentrations in the kidney, prostrate, as well as respiratory and gastrointestinal epithelia [23]. NGAL is currently employed as a biomarker of renal injury [24], given that it is secreted in high concentrations into the blood and urine within 2 hours of AKI [25]. In addition, the biomarker is easily excreted and detected in the urine because it is protease-resistant. Thus, urine NGAL appears to be a specific and sensitive biomarker for the diagnosis of UTI and for the prediction of renal parenchymal injury in the disease [26, 27].

Finally, some interleukins also play a role in disease diagnosis and in differentiating upper from lower UTI. Generally, the infection stimulates both local and systemic cytokine responses [28, 29]. For instance, *Escherichia coli* is known to activate a cytokine response in the uroepithelial cell lines to produce IL-6 and IL-8, and in peripheral blood monocytes to produce interleukin 1-alpha (IL-1α), IL-1β, IL-8, IL-6, and TNF-α [28]. Adherence of this bacterium on the mucosal sites of the urinary tract triggers inflammation, including a mucosal cytokine-response which results in the secretion of IL-6 and IL-8 by activated uroepithelial cells [29, 30]. Thus, since IL-6 and IL-8 are expressed early after a UTI episode and are secreted by uroepithelial cells, these cytokines have clearly fulfilled some of the five characteristics of an ideal biomarker outlined in the introductory section. Reports indeed suggest that urine IL-6 and IL-8 are proven biomarkers for UTI in children [31]. The serum and urine levels of IL-6 were more sensitive and specific for upper UTI than levels of IL-8 [32]. Sensitivity and specificity values for serum IL-6 were noted to be 88 and 83% respectively, while for urine IL-6, sensitivity and specificity values were 86 and 81%, respectively [32]. Furthermore, serum IL-6 was able to differentiate upper from lower UTI with a sensitivity of 88% and specificity of 74%, while serum IL-1β was known to have a sensitivity of 97% and a specificity of 59% for detecting upper UTI [14].

2.2. Biomarkers of AKI

Serum creatinine represents a poor traditional biomarker for AKI due to some limitations. First, its levels are only altered when renal function diminishes by 50% [33]. Second, there are well-known confounders to serum creatinine levels such as muscle size, chronologic age, gender, drugs and state of hydration [34]. Third, a sudden reduction in renal function may not be shown by a rise in serum creatinine until after 24–48 hours. Finally, it provides little information about the underlying cause and nature of kidney injury, and is less accurate for patients with small muscle mass and unusual diets [1]. These draw-backs have resulted in a paradigm shift to novel biomarkers.

Generally, there are two main types of AKI biomarkers: *biomarkers of kidney function* and *biomarkers of kidney injury*. Irrespective of the type of kidney injury and the clinical scenario, an inflammatory response appears to play a significant role in the pathogenesis of AKI [34]. The major triggers of AKI (ischemia, nephrotoxins, and bacterial endotoxins) stimulate the release of inflammatory mediators from renal endothelial and tubular cells. As AKI progresses, a number of causative factors result in the accumulation of biomarkers in plasma and urine, and possibly indicate different pathophysiologic events during the process of kidney

injury and repair [1]. For example, biomarkers like NGAL, interleukin-18 (IL-18), N-acetyl-β-D-glucosaminidase (NAG), kidney injury molecule-1 (KIM-1), accumulate in urine due to an induced tubular epithelial synthesis in different parts of the nephron, or as a consequence of reduced reabsorption of the filtered load in the proximal tubule (NGAL, cystatin C) [34]. Furthermore, production of biomarkers from transmigrated, activated immune cells into the tubular lumen may be contributory (NGAL, IL-18), while increased production of some biomarkers in other tissues (NGAL, IL-18) also occurs, thus raising concerns about their diagnostic value in the disease [35]. Biomarkers of AKI have been classified as follows: *functional markers* (serum cystatin C, urine albumin and NGAL), *up-regulated proteins* (KIM-1, liver-type fatty-acid binding protein [L-FABP], IL-18, β-trace protein and asymmetric dimethyl arginine), *low-molecular weight proteins* (urine cystatin C, NAG, glutathione S-transferase, γ-glutamyl-trans peptidase [γGT]) and *enzymes* (alanine amino-peptidase and lactate dehydrogenase) [36]. Other markers which have shown diagnostic ability include hepatocyte growth factor (HGF), vasoactive endothelial growth factor (VEGF), interferon gamma-induced protein 10 (IP-10) and total protein [37]. Some of the novel biomarkers are highlighted as below.

First, KIM-1 is a transmembrane tubular glycoprotein which is upregulated approximately 50- to 100-fold in the kidney, and is secreted into the urine after proximal tubular injury. KIM-1 is highly expressed in renal tubules, and is typically seen in areas of fibrosis and inflammation. The results of a meta-analysis indicate that urine KIM-1 represents a promising biomarker for early detection of AKI, with a good predictive value, especially in cardiac surgery patients [38]. Furthermore, in comparison to other biomarkers used as indicators of drug toxicity, KIM-1 significantly performed better than serum creatinine and blood urea nitrogen at detecting renal tubular injury in murine models; this makes it a useful marker for determining drug toxicity [39].

Second, NAG (another biomarker of kidney injury) is a large (>130 kDa) lysosomal enzyme which is located in several human cells including the renal tubule [34]. Its size hinders glomerular filtration, and elevated urine levels are thus presumed to emanate from the tubules, indicating tubular injury. In fact, during active renal disease, urine NAG activity is increased [40]. This feature makes it a potential and sensitive biomarker of AKI.

Third, cystatin C is a low-molecular-weight protein produced by all nucleated cells in the body at a constant rate, freely filtered by the glomeruli but completely reabsorbed and catabolized by the renal tubule [41]. Thus, its elevated urine levels are also seen in a tubulopathy because of the reduced re-absorptive capacity of the proximal tubules: making it a non-specific biomarker of AKI [42]. However, urine cystatin C could correctly predict the need for dialysis in intensive care unit (ICU) patients with established AKI [43]; could be an early predictor of AKI in children and in pediatric RIFLE classification, as well as a predictor of reduced estimated GFR (eGFR) after cardiac surgery [44]; while serum cystatin C could be used alone or in combination with serum creatinine and eGFR for early and accurate diagnosis of AKI in patients at emergency settings [45].

Finally, NGAL (which plays a role in the evaluation of UTI as previously mentioned) is a universal iron-transporter protein expressed in the tubular epithelium of the distal nephron and released into the blood and urine following tubular injury. This biomarker was first identified as a 25 kDa protein in the secondary granules of human neutrophils which is released into the bloodstream in response to bacterial infection. Interestingly, its elevated level in the urine may be diagnostic of AKI using the Acute Kidney Injury Network (AKIN) criteria: although

with a moderate predictive value [46, 47]. In addition, its combination with another urine biomarker such as L-FABP resulted in early detection of AKI after cardiac surgery in a sample of adult patients before a rise in serum creatinine was noted [48]. Similarly, in murine models of ischemic and toxic AKI, NGAL was identified as one of the most speedily-induced proteins; its level was elevated by several folds in both serum and urine within hours of the insult [49].

3. Chronic kidney disease (CKD) and biomarkers

Several novel biomarkers have also been identified in the evaluation of childhood CKD: especially CKD secondary to idiopathic nephrotic syndrome and diabetic nephropathy (DN) [2, 50]. Remarkably, an overlap exists between some of the biomarkers of CKD and those of AKI and acute pyelonephritis. For instance, urine NAG, NGAL, cystatin C and L-FABP all play a role in the evaluation of both CKD and these acute kidney diseases. Similar to the grouping of biomarkers of AKI, biomarkers of CKD can be broadly classified into *biomarkers of kidney function* and *biomarkers of kidney damage*.

GFR is the most important marker of kidney function in CKD, although it is poorly estimated in most clinical and research settings. Thus, equations for its estimation are predicated upon filtration biomarkers such as serum creatinine and serum cystatin C [51]. However, equations for eGFR based on cystatin C appear more reliable because this biomarker is not affected by muscle mass and gives a better representation of GFR, in addition to having a more stable rate of production compared to creatinine [52].

Although albuminuria represents the traditional biomarker of kidney damage, it may only be present after significant damage has occurred, or may be absent in other types of kidney damage such as tubulointerstitial disease and hypertensive kidney disease. Therefore, there is now a paradigm shift to novel biomarkers which could identify patients with CKD early enough so that prompt interventions could slow down the progression of the disease.

3.1. Biomarkers of diabetic nephropathy (DN) and other causes of CKD

The major pathogenic components of DN consist of renal fibrosis, mesangial expansion, glomerular hypertrophy, oxidative stress and tubular inflammation [53]. Myriad novel biomarkers of DN have now been identified. An attempt to categorize them has also been made [50]. *Glomerular biomarkers* include transferrin, immunoglobulin G (IgG), ceruloplasmin, type IV collagen, laminin, glycosaminoglycans (GAGs), lipocalin-type prostaglandin D synthase (L-PGDS), fibronectin, podocytes-podocalyxin, and VEGF. *Tubular biomarkers* include NGAL, α-1-microglobulin, KIM-1, NAG, cystatin C, and L-FABP. *Biomarkers of inflammation* comprise TNF-α, IL-1β, IL-18, IP-10, monocyte chemoattractant protein 1 (MCP-1), granulocyte colony-stimulating factor (G-CSF), eotaxins, RANTES (regulated on activation, normal T cell expressed and secreted) or CCL-5, and orosomucoid. A typical example of *biomarkers of oxidative stress* is 8oHdG, while *miscellaneous biomarkers* include some tubular markers such as urine heart fatty acid-binding protein and urine retinol-binding protein 4 (RBP4), and podocyte biomarkers such as podocalyxin, nephrin, and VEGF, and urine advanced glycation end products (AGEs). Notably, these podocyte biomarkers are also regarded as glomerular markers. Some of the biomarkers of DN are shown in **Table 1**, and will be briefly discussed below.

Biomarkers	Clinical significance	Comments
• Kidney injury molecule-1	• Diabetic nephropathy‡	• Predicts CKD progression to ESKD
• Neutrophil gelatinase-associated lipocalin	• Ig A nephropathy • Polycystic kidney disease	• Predicts CKD progression from early stages to ESKD
• N-acetyl-β-D-glucosaminidase	• Diabetic nephropathy‡,† • Idiopathic glomerulonephritis (MN, FSGS, and MCN)	• Predicts early and late stages of CKD in type 1 diabetics, and early CKD in type 2 diabetics • Predicts proteinuria-induced tubular damage in early stage of disease
• Liver fatty acid-binding protein	• Diabetic nephropathy†,‡	• Predicts early CKD and progression to ESKD in type 1 diabetics and early CKD in type 2 diabetics
• Cystatin C	• Diabetic nephropathy†	• Predicts early CKD in type 2 diabetics
• α-1-microglobulin	• Diabetic nephropathy†	• Predicts early CKD in type 2 diabetics
• Monocyte chemoattractant protein-1 (MCP-1)	• Diabetic nephropathy†	• Predicts CKD and cardiovascular disease risk in type 2 diabetics
• Interleukin-18	• Lupus nephritis • Diabetic nephropathy†	• Elevated urine levels • Same as in MCP-1
• Retinol-binding protein 4	• Tubulointerstitial diseases	• Elevated urine levels

MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MCN, minimal change nephropathy.
‡Among type 1 diabetics.
†Among type 2 diabetics.

Table 1. Novel biomarkers of chronic kidney diseases.

NAG has the ability to predict the onset and progression of CKD in diabetes mellitus. For instance, baseline urine levels of this tubular biomarker can independently predict microalbuminuria and macroalbuminuria in type 1 diabetes mellitus [54]. Furthermore, it is a sensitive biomarker for the detection of early renal damage in type 2 diabetes mellitus [55], while elevated urine levels can precede microalbuminuria in type 1 diabetes mellitus [56].

Furthermore, high levels of KIM-1 have been observed in DN: a disease characterized by renal fibrosis and tubular inflammation, among other components that have been previously

mentioned. For instance, majority of type 1 diabetic subjects with DN (stage 1 to 3 CKD) who had higher plasma KIM-1 levels reportedly ended up with end-stage kidney disease (ESKD); only a few of their counterparts who had lower plasma KIM-1 levels developed ESKD [57]. Baseline plasma KIM-1 levels also correlated with the rate of eGFR decline after adjusting for baseline urine albumin-to-creatinine ratio, eGFR, and glycated hemoglobin (Hb1Ac).

Another biomarker of DN is L-FABP, whose baseline urine levels in newly-diagnosed type 1 diabetics not only predicted the development of microalbuminuria but also the progression of microalbuminuria to macroalbuminuria [58]. In type 2 diabetes mellitus, elevated urine level of this biomarker also plays a role in predicting early CKD [59], and also serves as an independent predictor of CKD progression in type 1 diabetics [60]. Thus, L-FABP has the advantage of predicting kidney injury before albuminuria, especially in type 1 diabetics. Serum and urine cystatin C levels are useful biomarkers for early prediction of nephropathy in type 2 diabetes mellitus [61], and for progression of diabetic kidney disease [62]. Furthermore, α-1-microglobulin has been identified as an inexpensive biomarker for the early prediction of DN [63]. Elevated urine levels occur in patients with normoalbuminuric type 2 diabetes mellitus: preceding the onset of microalbuminuria and confirming this tubular biomarker as a more sensitive urine biomarker of CKD [64].

Expression of MCP-1 is upregulated in kidney diseases which present with a continued inflammatory response, such as in DN and lupus nephritis. Some reports indeed indicate that elevated levels of urine MCP-1 were observed in DN [65], as well as in active lupus nephritis [66]. Serum and urine levels of IL-18 were positively correlated with albumin excretion rate, whereas its serum levels were positively correlated with the development of carotid intima-media thickness in type 2 diabetics, and may therefore be a predictor of DN progression and cardiovascular diseases [67].

Finally, urine RBP4 is elevated in patients with tubulointerstitial disease, and may constitute a risk factor for long-term allograft loss, independent of the histology of renal biopsy, as well as for albuminuria [68].

3.2. Biomarkers of idiopathic nephrotic syndrome

The use of biomarkers in childhood idiopathic nephrotic syndrome has been well documented [2]. It represents a non-invasive approach in diagnostic nephrology, as these markers can be used in the prediction and prognostic evaluation of the disease, as well as in differentiating steroid-resistant nephrotic syndrome (SRNS) from steroid-sensitive nephrotic syndrome (SSNS). **Table 2** summarizes the list of identified biomarkers reported for childhood idiopathic nephrotic syndrome. Adiponectin (ADPN) – one of the adipokines, neopterin, β2-microglobulin, and NAG were reported to be diagnostic markers [69–71]. In addition to neopterin and NAG, urine vitamin D-binding protein (u VDBP) and α1β-glycoprotein were able to differentiate SRNS from SSNS [72, 73] while NAG and β2-microglobulin could also predict steroid responsiveness and renal outcome in SRNS [74]. Some of these biomarkers are further discussed as follows. First, elevated serum ADPN levels were documented in SRNS patients in relapse compared to those in remission [69]. Specifically, strong positive correlations were observed between serum ADPN levels and lipid parameters/proteinuria, whereas negative correlations were noted between ADPN levels and serum protein/albumin levels. Second, serum neopterin levels were found to be significantly elevated among SSNS and

Novel biomarkers (body fluids)	Reported role of biomarkers (references)
• Adiponectin (serum)	• Diagnostic* (Bakkalŏglu et al. [69])
• Neopterin (serum)	• Diagnostic** (Bakr et al. [70]) • Discriminatory† (Bakr et al. [70])
• Vitamin D binding protein (urine)	• Discriminatory† (Bennett et al. [72])
• N-acetyl-beta-D glucosaminidase (urine)	• Discriminatory† (Calişkan et al. [71]) • Prognostic‡ (Fede et al. [74])
• α 1-β glycoprotein (13.8 kDa fragment) (urine)	• Discriminatory† (Piyaphanee et al. [73])
• beta2-microglobulin (urine) • N-acetyl-beta-D glucosaminidase (urine)	• Prognostic*** (Fede et al. [74])
• beta2-microglobulin (urine) • N-acetyl-beta-D glucosaminidase (urine)	• Diagnostic¥ (Calişkan et al. [71])

*Raised serum levels in steroid-resistant nephrotic syndrome (SRNS) relapse.
**Raised serum levels in primary active nephrotic syndrome.
†Differentiates SRNS from steroid-sensitive nephrotic syndrome (SSNS).
‡Predicts steroid-responsiveness.
***Predicts tubular injury and dysfunction in SRNS.
¥Elevated levels in SRNS and SSNS.

Table 2. Role of some novel biomarkers in childhood idiopathic nephrotic syndrome.

SRNS patients with the active disease when compared to those in remission and the controls [70]. The diagnostic utility of neopterin for active idiopathic nephrotic syndrome was thus highlighted, but its poor discriminatory ability for SSNS and SRNS were also noted in the report. Third, uVDBP was reported to have a high discriminatory ability in distinguishing SRNS from SSNS [72]. For instance, levels of uVDBP were significantly higher in patients with SRNS than in patients with SSNS and in the controls. Despite the direct correlation between microalbuminuria and uVDBP, the latter exhibited a higher discriminatory ability for differentiating SRNS from SSNS than the former.

4. Conclusion

Many biomarkers have now been identified for the diagnostic and prognostic evaluation of acute and chronic diseases of the kidney in children. However, more evidence-based studies are still required to validate some of the novel biomarkers. Remarkably, a biomarker-panel comprising several of the markers potentially improves their sensitivity and specificity in disease evaluation. Inequities in the availability and accessibility of the laboratory tools between the developed and developing world still remain a challenge. Biotechnology firms should urgently prioritize the mass production of tools for identifying these biomarkers in order to bridge this gap.

Acknowledgements

The author acknowledges the invaluable information obtained from his previous published works in Refs. [1–3], during the preparation of this book chapter.

Conflict of interest

The author declares no conflict of interest in this work.

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