



## Sickle cell nephropathy: A review of novel biomarkers and their potential roles in early detection of renal involvement

Osama Y Safdar, Rana M Baghdadi, Sereen A Alahmadi, Bana E Fakieh, Amaal M Algaydi

**ORCID number:** Osama Y Safdar 0000-0002-7773-6687; Rana M Baghdadi 0000-0002-3682-2976; Sereen A Alahmadi 0000-0002-6869-1026; Bana E Fakieh 0000-0001-9274-7926; Amaal M Algaydi 0000-0002-5640-9505.

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**Osama Y Safdar**, Department of Pediatric, King Abdulaziz University, JEDDAH 21414, Saudi Arabia

**Rana M Baghdadi, Sereen A Alahmadi, Bana E Fakieh, Amaal M Algaydi**, College of Medicine, King Abdulaziz University, JEDDAH 21422, Saudi Arabia

**Corresponding author:** Osama Y Safdar, MD, Associate Professor, Pediatric Nephrology Center of Excellence, Department of Pediatric, King Abdulaziz University, 15 Althalia, Jeddah, JEDDAH 21414, Saudi Arabia. [ssafdar@kau.edu.sa](mailto:ssafdar@kau.edu.sa)

### Abstract

Whether the underlying mutations are homozygous, heterozygous, or co-inherited with other hemoglobinopathies, sickle cell disease is known to afflict the kidneys, leading to the clinical entity known as sickle cell nephropathy (SCN). Although common, SCN remains diagnostically elusive. Conventional studies performed in the context of renal disorders often fail to detect early stage SCN. This makes the quest for early diagnosis and treatment more challenging, and it increases the burden of chronic kidney disease-related morbidity among patients. Novel diagnostic tools have been employed to overcome this limitation. In this study, we discuss various biomarkers of SCN, including those employed in clinical practice and others recently identified in experimental settings, such as markers of vascular injury, endothelial dysfunction, tubulo-glomerular damage, and oxidative stress. These include kidney injury molecule-1, monocyte chemoattractant protein-1, N-acetyl-B-D-glucosaminidase, ceruloplasmin, orosomucoid, nephrin, and cation channels, among others. Furthermore, we explore the potential of novel biomarkers for refining diagnostic and therapeutic approaches and describe some obstacles that still need to be overcome. We highlight the importance of a collaborative approach to standardize the use of promising new biomarkers. Finally, we outline the limitations of conventional markers of renal damage as extensions of the pathogenic process occurring at the level of the organ and its functional subunits, with a discussion of the expected pattern of clinical and biochemical progression among patients with SCN.

**Key Words:** Sickle cell disease; Sickle cell nephropathy; Chronic kidney disease; Kidney injury molecule-1; Monocyte chemoattractant protein-1; N-acetyl-B-D-glucosaminidase

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**Core Tip:** This study discusses the expected clinical and biochemical progression among patients with sickle cell nephropathy, the utility of various biomarkers, and the limitations of conventional biomarkers. Novel biomarkers used in combination have been demonstrated to have a higher diagnostic yield as compared to that of individual markers, necessitating a collaborative approach in the standardization and utilization of promising biomarkers such as kidney injury molecule-1, monocyte chemoattractant protein-1, N-acetyl-B-D-glucosaminidase, ceruloplasmin, orosomucoid, nephrin, cation channels, and endothelial dysfunction.

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## INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy with a global burden of more than 30000 newborns per year. SCD is a broad term used to describe a variety of recognized mutations, including homozygous mutations, heterozygous mutations, and mutations co-inherited with other hemoglobinopathies. The resultant erythrocyte abnormalities instigate a host of sequelae with multi-organ repercussions. The pathogenesis involves vaso-occlusive events, ischemic end-organ damage, reperfusion injury, endothelial dysfunction, vasculopathies, and oxidative stress, among other contributing factors[1]. The disease process is further complicated by an increased predisposition to infections. This is linked to impaired splenic function, micronutrient deficiencies, and sluggish circulation combined with regions of infarction, which act as favorable foci for infections. In addition, therapeutic interventions such as blood transfusions and lines for vascular access predispose patients to blood-borne infections, siderophilic organisms, and catheter-related infections[2]. Notably, chronic transfusion programs are linked to iron overload and endocrine dysfunction with a profound effect on growth and sexual maturation, which is particularly relevant to the pediatric population.

SCD can affect the kidneys through multiple pathways outlined below. The resultant entity, known as sickle cell nephropathy (SCN), typically presents during early childhood. Unfortunately, prompt diagnosis of early SCN is difficult. Therefore, it is necessary to discover new diagnostic biomarkers to facilitate the diagnosis of early stage SCN, enabling timely treatment and reducing related morbidity and mortality.

In this review, we discuss biomarkers of SCD, explore the applications of novel biomarkers for diagnostic and therapeutic approaches, and outline the limitations of conventional markers of renal damage.

## PATHOPHYSIOLOGY

The pathogenesis of SCN is multifaceted and involves the effects of different components on different regions of the kidney. The extent of these effects depends on the disease chronicity and severity.

Altered hemodynamics at the level of the glomerulus and the resulting hyperfiltration have been attributed to various biochemical properties of sickling, including local factors such as the release of vasorelaxants and global factors such as increased cardiac output in chronic anemia, leading to increased renal blood flow. Consistent with Brenner's hyperfiltration theory, these changes have been described as precursors to structural changes ranging from endothelial hyperplasia and mesangial proliferation to glomerular sclerosis[3]. These glomerular changes lead to the onset of proteinuria[4].

At the level of the medullary nephron, the same conditions that contribute to normal physiology pertaining to the exchange of solutes and the control of urinary concentrations have deleterious effects on red blood cells that are prone to sickling.

The concentration gradient created by the “countercurrent” system is paramount to the unique ability of mammalian kidneys to concentrate urine. The countercurrent system is jeopardized by fast transit states; therefore, low renal blood flow in the medulla contributes to the osmolarity gradient. Combined, these factors create a climate of relative hypoxia and hyperosmolarity within the medulla[5]. Among susceptible individuals, these conditions promote red blood cell (RBC) sickling.

Wang *et al*[6] examined this phenomenon on a molecular level using SCD-mice and non-SCD mice to further study the medullary changes and their link to concentration defects. The SCD-mice exhibited elevated urinary vasopressin levels and increased abundance of aquaporin 2, urea transporter A1, and epithelial Na channels-beta subunit. The mice were shown to concentrate urine under water-replete conditions in a vasopressin-dependent compensatory mechanism. However, under water-restricted conditions, the medullary concentration ability among SCD-mice was significantly compromised as compared to the non-SCD population, with changes in urinary osmolarity equal to 28% and 104%, respectively.

Dehydrated RBCs lose solutes through a K-Cl cotransporter, a  $\text{Ca}^{2+}$ -activated  $\text{K}^{+}$  channel (Gardos channel), and uniquely through the nonselective “ $\text{P}_{\text{sickle}}$ ” channel that is activated by conditions of low oxygen tension[7]. Widespread RBC adhesion and inflammation within the vasa recta ensure that hemolysis causes the release of free hemoglobin, which sequesters nitric oxide and causes an overall increase in vascular tone[5]. Consequently, juxtamedullary nephrons are impaired, and defective countercurrent exchange mechanisms fail to reabsorb free water. This produces the early findings of SCN, including nocturia, polyuria, and an increased susceptibility to volume depletion. Additionally, these features are particularly problematic among this patient population because volume loss can precipitate vaso-occlusive crises as well as prerenal acute kidney infection (AKI), complicating the original renal insult.

Long-term tubular compromise is accompanied by concentration defects, impaired distal tubular function with renal tubular acidosis, and compensatory increases in proximal convoluted tubule function. The cascade of damage and the factors leading to its acceleration are shown in Figure 1.

In addition to the events described above and their consequences, pathogenesis may be aggravated by the presence of renal cysts, which have been reported to occur more frequently in patients with SCD and in younger patient groups than in the general population[8]. Other pathological changes, such as renal amyloidosis, have been described in case reports and have been shown to be resistant to interventions such as hydroxyurea and angiotensin converting enzyme inhibitors[9].

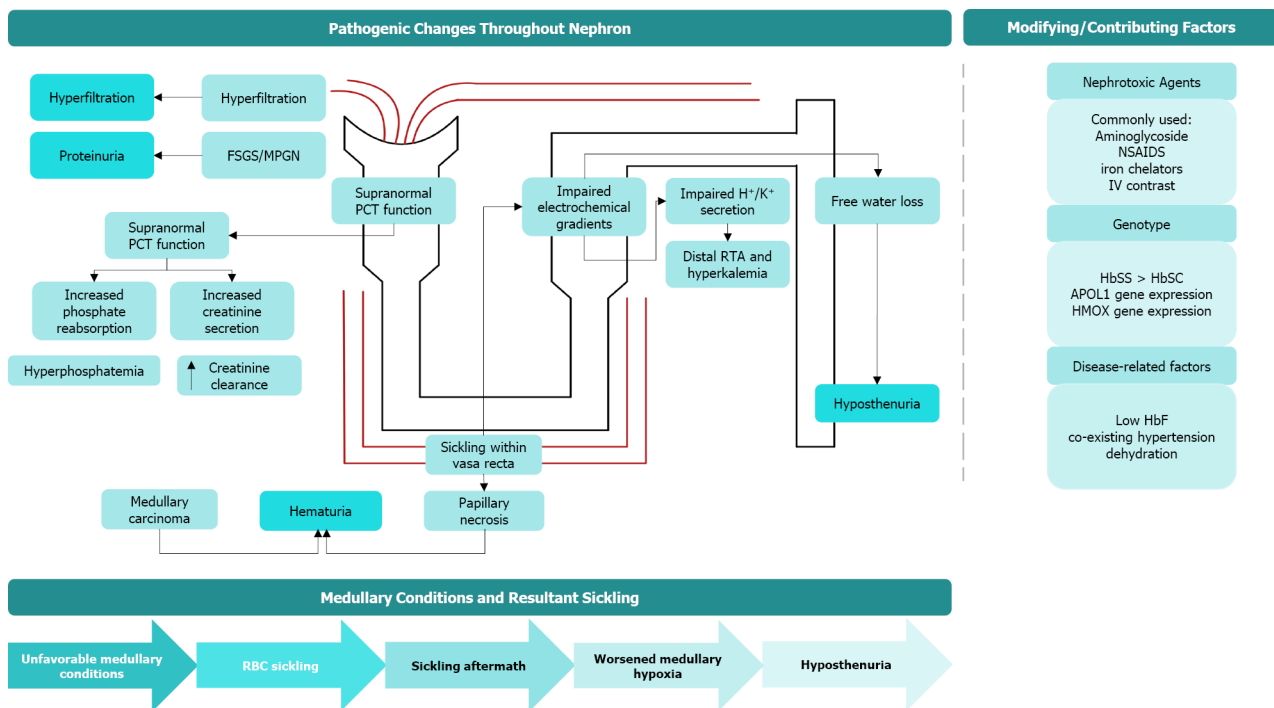
A summary of pathogenic changes and modifying factors were shown in Figure 1.

## CLINICAL FEATURES AND PROGRESSION

As previously described, hyposthenuria is an early constituent of the temporal continuum of the SCN. Its presence is reflective of chronic complications and the cause of acute decline from baseline function. Previously, a negative correlation between the degree of hyposthenuria and fetal hemoglobin has been reported, and a positive correlation with age has been observed. Similar to the general population, patients with SCD in the pediatric age group may experience nocturnal enuresis, which may be partly due to delayed maturation. Unlike in patients without SCD, this otherwise nonalarming presentation is compounded by nocturnal polyuria owing to hyposthenuria as well as the potential effects of cerebral vasculopathy on bladder control. Although most patients outgrow this phenomenon, up to 10% of individuals may continue to experience this phenomenon as high school students, resulting in severe effects on psychosocial well-being[10].

Glomerular hyperfiltration is another relatively early finding. Hyperfiltration occurs with glomerular filtration rates (GFRs) of 1.50-2.34 mL/s/1.73 m<sup>2</sup> or more and is commonly observed early in infancy or in children with SCD[11]. Moreover, hyperfiltration can be followed by progressive declines in the estimated GFR (eGFR), as demonstrated in approximately one-third of adult patients with SCD[12]. Two widely cited clinical trials, BABYHUG and HUTSLE, confirmed this pattern with high GFR values among entrants from ages 9 to 12 mo and showed a progressive increase in short-term follow-up. The latter study further demonstrated that high GFR values persisted into early adulthood. By the fourth decade of life, however, renal clearance deteriorates and GFR exhibits a declining pattern[11].

Hyperfiltration with eGFR values greater than 2.17-2.34 mL/s/1.73 m<sup>2</sup> is linked to microalbuminuria (3.39-33.90 mg/mmol)[11]. Microalbuminuria is estimated to affect



**Figure 1 Summary of pathogenic changes and modifying factors.** FSGS: Focal segmental glomerulosclerosis; MPGN: Membranoproliferative glomerulonephritis; PCT: Proximal convoluted tubule; RTA: Renal tubular acidosis; NSAIDs: Nonsteroidal anti-inflammatory drugs; IV: Intravenous; HbSS: Classic sickle cell; HbSC: Hemoglobin C sickle cell; APOL1: Apolipoprotein L1 gene; HMOX: Heme oxygenase 1 gene; HbF: Fetal hemoglobin; RBC: Red blood cell.

20%-35% of patients during adolescence, and progressive glomerular changes in response to a hemodynamic environment persist with age, eventually leading to macroalbuminuria ( $> 33.90$  mg/mmol) in 60% of adult patients[13]. Glomerular changes that result in increased permeability to proteins have been described as products of chronic glomerular capillary hypertension. Furthermore, Roy *et al*[14] demonstrated that angiotensin II signaling contributes to glomerulopathy, independent of hemodynamic changes and hyperfiltration, thereby acting as a biomarker of glomerular damage in SCD, with or without hyperfiltration[12]. Another study proposed that inflammatory processes are responsible for the development of proteinuria, demonstrating a correlation between the levels of inflammatory mediators and albumin/creatinine ratios (ACR) in urine[15].

Niss *et al*[12] recognized that although the association between SCN and albuminuria is well established, there is a gap in our understanding of the progression of albuminuria with age. Their longitudinal study of 303 patients with SCD estimated that the progression of albuminuria occurs at a rate of 0.4 mg/mmol per year and suggested an ACR of 11.3 mg/mmol as a surrogate of persistent proteinuria among affected patients.

### Hematuria

Hematuria, either microscopic or macroscopic, is reported in 13%-30% of patients with SCD, correlating positively with increased age and male sex[11,16]. Additionally, hematuria can be attributed to vaso-occlusive events and micro-infarctions, resulting in ischemic parenchymal injury and papillary necrosis. Capillary congestion in the medulla also contributes to the process by causing RBC leakage into the renal tubules [13]. Although normally asymptomatic, this process can produce abdominal colic and back pain when extensive. A less common yet more worrisome etiology to consider in the setting of hematuria among patients with SCD is medullary cell carcinoma, which may present during early childhood or adulthood[17].

### Hypertension

Generally, blood pressure values among patients with SCD appear to be lower than those in the medically free population. This is attributed to unbalanced fluid losses and possibly to a reduction in systemic vascular resistance[13]. Paradoxically, when present, hypertension has been shown to be predictive of poorer outcomes with increased incidences of both AKI and chronic kidney disease (CKD)[18]. The term



“relative systemic hypertension” has been employed to describe relative elevations in blood pressure among patients with SCD. Relative systemic hypertension is observed in 45% of patients and is defined as a systolic blood pressure of 16.0-18.5 kPa and diastolic blood pressure of 9.3-11.9 kPa.

Novelli *et al*[19] demonstrated through a large cohort of 661 patients that pulse pressure has a higher yield than systolic and diastolic blood pressures in predicting long-term outcomes related to SCD vasculopathy. Thus, pulse pressure is also independently associated with proteinuria and elevated serum creatinine levels.

### **CKD and end-stage renal disease**

The aforementioned pathogenic components accumulate over time and culminate in end-stage renal disease (ESRD). Some modifying factors, also described in Figure 1, increase the likelihood of patients succumbing to CKD. ESRD has been linked to risk factors such as older age, hypertension, proteinuria, hematuria, and deteriorating anemic state[16]. Notably, Yeruva *et al*[18] reported a 2-3-fold increase in the incidence of CKD in patients with SCD when compared with patients without SCD, based on a study performed over a 6-year period. Statistical variations between different studies have been noted and have been linked to discrepancies in the definition of renal failure as well as the different equations used to estimate GFR. These differences may lead to underestimation of the reported incidence and prevalence of renal impairment.

Compared with patients with non-SCD CKDs, patients in this category may experience rapid deterioration of kidney function, posing unique challenges in the area of renal replacement therapy. One issue is vascular access for hemodialysis in patients with frequent hospital admissions and compromised peripheral access[16]. More major issues revolve around the higher rates of mortality due to dialysis-related complications. Finally, although renal transplantation is the optimal therapeutic approach for patients with ESRD, patients with SCD perform poorly on transplant waiting lists[20]. If successful in obtaining a kidney, however, prognostic outcomes post-transplant are similar to those with ESRD due to other etiologies[21].

Furthermore, patients with SCD and renal failure display higher propensities for developing chronic restrictive pulmonary disease, leg ulcers, and stroke than those with intact kidney function.

### **Conventional renal studies and their limitations in SCN**

Routine follow-up protocols currently implemented in SCD follow-up utilize conventional renal studies to diagnose SCN. These include blood pressure assessments, urinalyses, metabolic panels featuring creatinine, and selective imaging based on these findings. The eGFR values are often extrapolated from creatinine-based equations. Creatinine levels, under the influence of muscle mass and hydration status, have limitations in the general population. Among patients with SCD, such limitations are compounded by the effects of hyperfiltration and hypersecretion into the renal tubules. Thus, the rate of creatinine clearance may be misleading in the early stages of the disease. This is exemplified in numerous studies. For example, Asnani *et al*[22] reported that serum creatinine only started rising after the GFR level decreased below 0.84 mL/s. A similar conclusion was made by Guasch *et al*[23], who showed that serum creatinine levels started to rise once the GFR fell below 0.5 mL/s.

The discrepancy between estimated and measured GFRs among patients with SCD is one of the factors hindering our understanding and management of SCN[24]. Current estimating equations vary in the SCN setting[25]. The CKD epidemiology equation produced estimates that were comparable to the measured GFR values, according to Arlet *et al*[26] and Asnani *et al*[27]. Additionally, a study by Asnani *et al* [25] compared eGFR values among 98 patients against values measured using 99m-Tcnetium diethylenetriamine pentaacetic acid nuclear renal scans and showed that the creatinine-based modification of diet in renal disease formula overestimated GFR values by a mean of 1.18 mL/s. The creatinine-based EPI formula yielded improved concordance rates between measured and estimated values, with a mean overestimation of 0.69 mL/s.

Another formula used to estimate GFR, specifically among the pediatric population, is the Schwartz formula, which considers the height and enzymatically measured serum creatinine levels of the patients. In a study of the effects of hydroxyurea on infant renal capacity, a double-blinded randomized controlled trial, BABYHUG, compared the estimated GFR as per the Schwartz formula with quantitative GFR measurements in 176 infants. The age of the infants ranged from 9 to 19 mo. The results showed that this formula markedly overestimated GFR and was found to be useful only in children with low GFRs. Considering the natural history of the disease and the late decrease in GFR, CKD may need to be redefined in SCN using criteria for

a decline in estimated GFR from baseline. This would require a consistent method of routine GFR measurements, starting from a predetermined baseline age[24].

Another limitation pertaining to GFR measurements among patients with SCD is its influence on poor nutritional status, which could lead to eGFR underestimation and hence, premature CKD determination[28].

### **Cystatin C-based GFR**

Cystatin C is a non-glycosylated low-molecular-weight protein produced by all nucleated cells. Its production rate increases during inflammatory events, and the protein undergoes renal metabolism, which is characterized by free filtration at the glomerulus followed by reabsorption by tubular epithelial cells[29]. Relative to creatinine clearance, cystatin C is described as a superior marker for GFR because it is not affected by height, sex, diet, and muscle bulk[30]. Its renal handling is also advantageous in that unlike creatinine, it is not secreted by tubules.

Asnani *et al*[31] corroborated this finding in a study examining 98 subjects with SCD, which presented a significant correlation between serum cystatin C and measured GFR, serum creatinine, urine ACR ( $r = 0.79$ ), and systolic blood pressure.

Tantawy *et al*[32] reported the sensitivity and specificity of serum cystatin C at 91% and 90%, respectively. These values were superior to those of serum creatinine, with a sensitivity of 79% and a specificity of 85%. Another study conducted by Economou *et al*[33] concluded that 36% of patients with chronic hemolytic anemia showed high serum cystatin C levels.

The implications of these findings have been explored in the domain of management and monitoring of patient responses to hydroxyurea because patients managed with hydroxyurea have been shown to have relatively low cystatin C levels [32]. Additionally, the utility of cystatin C in SCD has been shown to extend to extrarenal complications as well as SCN, with a positive correlation between cystatin C levels and carotid intima-media thickness[32].

Alternatives to both creatinine and cystatin have also been explored. For example, beta-trace protein (BTP) is a low-molecular-weight glycoprotein that is easily filtered by the glomerulus with very little or no tubular reabsorption. In 1997, Hoffmann *et al* [34] discovered increased levels of serum BTP among hemodialysis patients and suggested that BTP is a potential diagnostic marker for renal disease.

Beta-2-microglobulin, a constituent of class I major histocompatibility molecules, has also been explored as a surrogate for GFR estimation. This protein was found to be strongly correlated with measured GFR values. However, its values may fluctuate in response to inflammatory processes and lymphoproliferative diseases. Moreover, to date, only Inker *et al*[35] reported a GFR equation based on a combination of BTP and Beta-2-microglobulin. Unfortunately, this equation did not show any advantages over equations combining creatinine and cystatin C in a variety of populations.

Estimated GFR formulas employed in sickle cell nephropathy were shown in Table 1.

## **NOVEL BIOMARKERS**

As previously discussed, findings from conventional renal studies, otherwise referred to as first-generation biomarkers, have numerous shortcomings. Owing to the kidney's functional reserve, elevations in blood urea nitrogen and creatinine are not appropriately reflective of early renal damage or impending AKI. The limitations of this well-recognized hindrance expand beyond the scope of SCN. The collaborative InnoMedPredTox project, for example, explores biochemical alternatives to conventional renal studies in the interest of detecting nephrotoxicity to determine pharmaceutical safety[36]. Fortunately, the demand for novel biomarkers is coupled with great strides in biomedical capabilities and high-throughput omics.

Validating new diagnostic biomarkers requires the fulfillment of certain criteria and the consideration of a variety of logistics, including diagnostic yield *vs* cost effectiveness. The following criteria were established by the Predictive Safety Testing Consortium Nephrology Working Group in their quest to identify novel biomarkers that could be employed in the early detection of nephrotoxicity. The principles of their criteria, listed in Table 1, may be extrapolated to satisfy the context of SCN[37]. An exception to this may be the point labeled "2," which is less applicable to nonpharmacological settings. Applying these principles to the context of SCD, the ideal biomarker for SCN should predate clinically apparent findings, creatinine elevation, microalbuminuria, and compromised GFR. This is key in the process of early intervention to halt

**Table 1** Estimated glomerular filtration rate formulas employed in sickle cell nephropathy

Formula	Equation
CKD-EPI (Cr)	F with Cr $\leq 62 \mu\text{mol/L}$ ( $\leq 0.7 \text{ mg/dL}$ ): $144 \times (\text{creatinine}/0.7) - 0.329 \times 0.993 \text{ age} (\times 1.159 \text{ if Black})$ ; F with Cr $> 62 \mu\text{mol/L}$ ( $> 0.7 \text{ mg/dL}$ ): $144 \times (\text{creatinine}/0.7) - 1.209 \times 0.993 \text{ age} (\times 1.159 \text{ if Black})$ M with Cr $\leq 80 \mu\text{mol/L}$ ( $\leq 0.9 \text{ mg/dL}$ ): $141 \times (\text{creatinine}/0.9) - 0.411 \times 0.993 \text{ age} (\times 1.159 \text{ if Black})$ ; M with Cr $> 80 \mu\text{mol/L}$ ( $> 0.9 \text{ mg/dL}$ ): $141 \times (\text{creatinine}/0.9) - 1.209 \times 0.993 \text{ age} (\times 1.159 \text{ if Black})$
MDRD	$175 \times \text{creatinine} - 1.154 \times \text{age} - 0.203 \times 0.742$ (if female)
Schwartz	$0.413 \times [\text{height (cm)}/\text{creatinine}]$
CKD-EPI (Cystatin C)	Cystatin C $\leq 0.8 \text{ mg/L}$ : $133 \times (\text{cystatin C}/0.8) - 0.499 \times 0.996 \text{ age} (\times 0.932 \text{ if female})$ ; Cystatin C $> 0.8 \text{ mg/L}$ : $133 \times (\text{cystatin C}/0.8) - 1.328 \times 0.996 \text{ age} (\times 0.932 \text{ if female})$

CKD-EPI: Chronic kidney disease epidemiology; Cr: Creatinine; F: Female, M: Male; MDRD: Modification of diet in renal disease.

the progression of CKD. Furthermore, oscillations in values in response to injury and recovery may be ideal for monitoring disease progression and response to therapy. Noninvasive accessibility to biomarkers in urine or plasma samples is another point that must be fulfilled for increased convenience in clinical settings. Localization of kidney injury may shed light on the pathogenic process and aid in a targeted treatment approach. However, some markers discussed below are indicative of global changes, as opposed to localized insults.

Ideal features of biomarkers used to detect drug-induced kidney toxicity were listed in [Table 2](#).

Jerebtsova *et al*[38] recognized that despite considerable efforts being dedicated to the discovery and validation of novel biomarkers of renal damage there have yet to be groundbreaking discoveries that are clinically applicable. The authors also cited shortcomings in proteomic technology over the past decade as a reason for this and discussed logistic issues in the domain of sample collection, result reproducibility, and validation tools, leading to a proposal of the roles of new proteomic technology in bypassing previous limitations. The authors also suggested that, although urine samples are readily available, one must consider the impact of concentration defects on the urinary concentrations of the studied biomarkers.

A summary of studies of novel biomarkers were listed in [Table 3](#).

### Kidney injury molecule-1

Kidney injury molecule-1 (KIM-1) is a transmembrane protein expressed by renal cells after exposure to injurious stimuli[13]. Its relationship with diabetes, nephrogenic medications, and ischemia has been well established in animal models and cohort studies. Elevated values have been shown to acutely herald inflammation and chronic fibrosis. Moreover, its urinary excretion parallels tissue levels[39]. In one experimental study conducted by InnoMedPredTox, rats were exposed to nephrotoxic agents, and among other biomarkers, urinary KIM-1 was subsequently quantified by polymerase chain reaction, enzyme-linked immunosorbent assay, and immunohistochemistry. KIM-1 expression was found to correlate with histopathological alterations occurring at the level of the outer cortex, even in the setting of normal kidney function. This revealed the potential applications of KIM-1 as an early and sensitive noninvasive marker of renal injury[36]. Currently, KIM-1 is used as a biomarker for predicting chemo-induced nephrotoxicity. In a cross-sectional study examining AKI in adult patients undergoing cardiac surgery, elevated values were predictive of postoperative AKI[40].

The hypoxic, proinflammatory conditions of the kidney in SCN imply the applicability of this utility to the context of SCN. Sundaram *et al*[41] and Niss *et al*[12] demonstrated a positive correlation within their samples with albuminuria and ACR as endpoints, respectively. Although both of these studies confirmed the sensitivity of the biomarker, questions regarding the diagnostic yield of KIM-1 have been raised. For example, KIM-1 is expressed in the liver, spleen, and kidneys and plays roles in immune tolerance and viral uncoating; genetic polymorphisms may affect its expression and therefore the efficacy of intracellular tracking.

### Monocyte chemoattractant protein-1

Monocyte chemoattractant protein-1 (MCP-1) is a powerful chemotactic agent induced by proinflammatory cytokines. This protein is involved in recruiting monocytes/

**Table 2 Ideal features of biomarkers used to detect drug-induced kidney toxicity**

Features
(1) Identifies kidney injury early (before renal reserve is dissipated and levels of serum creatinine increase)
(2) Reflects the degree of toxicity, in order to characterize dose dependence
(3) Displays similar reliability across species, including humans
(4) Localizes to the site of kidney injury
(5) Tracks the progression of injury and recovery from damage
(6) Is well characterized with respect to the limitations of its capacities
(7) Is accessible in readily available body fluids or tissues

macrophages to areas of renal damage. Macrophages are well-established fibrogenic agents in the setting of chronic inflammation. Similarly, renal fibrosis and ESRD-related histopathological changes are expected to be expedited by this chemokine[42]. These findings have been corroborated by animal models and clinical studies examining this agent in the setting of lupus nephritis and diabetic nephropathy[43, 44]. Additionally, MCP-1 is produced by tubules and glomeruli, and its urinary excretion is proportional to its tissue concentration.

The application of MCP-1 to SCN was first reported by Laurentino *et al*[13], and the findings were further confirmed by Belisário *et al*[15] in 2020. Other contributions by Belisario and colleagues showed a positive correlation between MCP-1 levels and ACR as well as between inflammatory mediators and RAS molecules.

### ***N-acetyl-B-D-glucosaminidase***

N-acetyl-B-D-glucosaminidase is a lysosomal enzyme that is synthesized by proximal tubular epithelial cells and liberated into the urine in the context of proximal tubular injury[45]. Other authors have verified its potential in predicting the onset of diabetes among patients with diabetes. Sundaram *et al*[41] obtained similar results when exploring the potential of N-acetyl-B-D-glucosaminidase as an early marker of SCN. Their results demonstrated elevations in N-acetyl-B-D-glucosaminidase activity, even among patients without microalbuminuria, highlighting its possible role in early detection.

### ***Ceruloplasmin and orosomucoid***

To identify potential biomarkers with elevations predating the onset of albuminuria, Jerebtsova *et al*[46-48] employed mass spectrometry in the analysis of 20 non-albuminuric urine samples. The samples were further subdivided according to the presence or absence of urinary hemoglobin. Of the 270 proteins identified, 18 extracellular proteins were shown to be significantly upregulated or downregulated in hemoglobinuric samples. Further analysis of ceruloplasmin showed that this protein was positively correlated with hemoglobinuria. Further associations with proteins linked to iron metabolism were explored because the samples showed increased ceruloplasmin, transferrin, and ferritin to creatinine ratios in urinary samples when compared with healthy controls. As an extension of this study, orosomucoid, a major acute-phase protein, was also studied as a potential biomarker. Its relationship with other kidney disorders, including diabetic nephropathy and lupus nephritis, has already been demonstrated. Moreover, orosomucoid was found to be correlated with urinary ceruloplasmin values and CKD progression.

### ***Nephrin***

Nephrin is a transmembrane protein that exhibits podocyte cytoskeletal structural integrity. Its presence in the urine is indicative of damage localized to the glomerulus. At the molecular level, various factors are associated with functional disruption of nephrin and have been linked to various glomerulopathies, systemic lupus erythematosus, preeclampsia, and hyperglycemia. Its use as a biomarker of early pathological changes has been studied in these disorders with variable results[49]. A study conducted at a tertiary center in Malawi was the first to explore this biomarker among patients with SCD. The results showed that nephrin-to-creatinine urinary ratios were significantly associated with albuminuria. A cutoff value of 622 ng/mg was identified as predictive of albuminuria with a sensitivity of 96% and a specificity of 64%[50]. The



Table 3 Summary of studies of novel biomarkers

Ref.	Study design	Sample size	Endpoints	Finding(s)	Criteria fulfillment
KIM-1					
Sundaram <i>et al</i> [41]	Cross-sectional (United States)	116 (ages 5-65 yr, mean age: 18 yr)	MiA: UACR 3.39-33.90 mg/mmol MaA: UACR > 33.90 mg/mmol	KIM-1 detectable in all SCD samples, increased with MiA ( $P = 0.005$ ), further increased with MaA ( $P = 0.0015$ )	Early detection (MiA); reflects severity; localized damage to PCT; detected in urine
Niss <i>et al</i> [12]	Prospective longitudinal, mean FU 23 mo (United States)	303 (2-64 yr, mean age: 21 yr)	Albuminuria: Urine albumin $\geq 11.3$ mg/mmol	KIM-1 linked to baseline and persistent albuminuria with $P < 0.001$	Applicable to larger samples
MCP-1					
Laurentino <i>et al</i> [13]	Prospective cohort (Brazil)	50 (33.2 $\pm$ 10.2 yr)	ELISA, urine sample	Increased urinary MCP-1 in SCD (SSHU: 168.2 $\pm$ 90.1 and SS: 231.4 $\pm$ 123.7) $P < 0.0001$ relative to the control group (42.1 $\pm$ 27.6)	Reflects oxidative stress; localized damage to PCT + glomerulus; detected in urine
Belisário <i>et al</i> [15]	Prospective longitudinal, mean FU 1.1 yr	213 (1.6-19yr)	ELISA	Increased urinary MCP-1 positively related to ACR with $P < 0.0001$	Positively correlated with other biomarkers; detected in urine
Ceruloplasmin					
Jerebtsova <i>et al</i> [46]	Cross-sectional cohort	54	Hemoglobinuria: Hgb/CRE > 0.8 ng/mL CKD stage: Stage 0: eGFR > 1 mL/s/1.73 m <sup>2</sup> ; Stage 1: eGFR > 1.5 mL/s/1.73 m <sup>2</sup> ; Stage 2: eGFR 1-1.49 mL/s/1.73 m <sup>2</sup> ; Stage 3: eGFR 0.5-0.99 mL/s/1.73 m <sup>2</sup> ; Stage 5: eGFR < 0.25 mL/s/1.73 m <sup>2</sup>	CP significantly (31 $\times$ ) higher among samples with hemoglobinuria with $P = 1.8 \times 10^{-5}$ ; Urinary CP/CRE, TF/CRE, and Ftn/CRE were all significantly higher than in non-SCD controls; CP/CRE (only) positively correlated with CKD stage ( $n = 34$ , $P = 0.0008$ ); ROC analysis: Sensitivity, 68.75%; specificity, 95.65%	Reflects iron handling defects in SCN; high sensitivity/specificity; detected in urine
Orosomucoid					
Jerebtsova <i>et al</i> [47]	Cross-sectional cohort	54	Hemoglobinuria: Hgb/CRE > 0.8 ng/mL and CKD stage	ORM significantly higher among samples with hemoglobinuria with $P = 8.4 \times 10^{-3}$ ; ORM positively correlated with CKD stage ( $n = 34$ , $r = 0.51$ , $P = 0.0014$ ); ROC analysis: Sensitivity, 87.1%; specificity, 86.6%	Acute-phase protein; high sensitivity/specificity; detected in urine
Jerebtsova <i>et al</i> [48]	Cross-sectional cohort	51 HbSS and 15 HbSC	Hemoglobinuria: Hgb/CRE > 0.8 ng/mL and CKD stage	PORM significantly higher among HbSS population with UORM/CRE; positively correlated with CKD progression ( $P = 0.0013$ ); ROC analysis: Sensitivity, 60%; specificity, 78.26%	Acute-phase protein; high sensitivity/specificity; detected in urine
Nephryn					
Heimlich <i>et al</i> [50]	Prospective cohort	101 [median age: 9 yr (IQR: 4-11 yr)]	Urine albumin: Creatinine $\geq 3.39$ mg/mmol	Urinary NCR higher in HbSS than in HbAA; NCR significantly associated with albuminuria (odds ratio = 1.002, 95% confidence interval: 1.001-1.003, $P = 0.0003$ ); at an NCR cut-off value of 622 ng/mg: R (albuminuria $\times$ 45.9); at NCR $\geq 622$ ng/mg: Sensitivity, 96%; specificity, 64%	Reflects glomerular injury; localized damage to glomerulus; detected in urine; modest specificity, PPV; high sensitivity and negative predictive value
Cation Channels					
Brewin <i>et al</i> [51]	Prospective cohort (Brazil)	112 (10.7 $\pm$ 4.1 yr; 4-19 yr)	Hyperfiltration: GFR > 2.34 mL/s/1.73 m <sup>2</sup> ; microalbuminuria: > 3 mg/mmol	eGFR, modestly positively correlated with Gardos channel and Psickle ( $r = 0.234$ , $P = 0.002$ ) and ( $r = 0.326$ , $P = 0.005$ ), respectively; ACR, positively correlated with Gardos channel ( $r = 0.246$ , $P = 0.013$ ) and Psickle ( $r = 0.207$ , $P = 0.033$ ) activity; KCC activity, negatively associated with ACR ( $r = 0.334$ , $P = 0.007$ ),	Reflects RBC permeability; detected in RBC samples; strong predictor of microalbuminuria

				suggesting renoprotection	
Endothelial Injury					
Youssry <i>et al</i> [53]	Prospective cross-sectional (Egypt)	47	PCR, blood samples	Urinary NCR higher in HbSS than in HbAA NCR significantly associated with albuminuria (odds ratio = 1.002, 95% confidence interval: 1.001-1.003, <i>P</i> = 0.0003); at NCR cut-off value of 622 ng/mg; R (albuminuria × 45.9); at NCR ≥ 622 ng/mg; Sensitivity, 96%; specificity, 64%	Reflects glomerular injury; localized damage to glomerulus; detected in urine; modest specificity, PPV; high sensitivity and negative predictive value

ACR: Albumin/creatinine ratio; CP: Ceruloplasmin; CP/CRE: Ceruloplasmin/creatinine ratio; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; ELISA: Enzyme-linked immunosorbent assay; Ftn/CRE: Ferritin/creatinine ratio; FU: Follow-up; Hgb/CRE: Hemoglobin/creatinine ratio; Hgb/CRE: Hemoglobin/creatinine ratio; IQR: Inter-quartile range; KIM-1: Kidney injury molecule-1; KCC: KCl co-transporter; MaA: Macroalbuminuria; MiA: Microalbuminuria; MCP-1: Monocyte chemoattractant protein-1; NCR: Nephron/creatinine ratio; ORM: Orosomucoid; PCR: Polymerase chain reaction; PCT: Proximal convoluted tubules; PORM: Plasma ORM; PPV: Positive predictive value; ROC: Receiver operating characteristic; RBC: Red blood cell; SCD: Sickle cell disease; SS: Sickle cell disease patients not taking hydroxyurea; SSHU: Sickle cell disease patients taking hydroxyurea; TF/CRE: Transferrin/creatinine ratio; UACR: Urine albumin/creatinine ratio; UORM: Urinary orosomucoid.

authors concluded that nephrin may have applications in predicting glomerulopathy and its progression.

### Cation channels

The pathophysiology of SCN has been widely described with reference to the microenvironment of the kidney and its promotion of sickling. However, the molecular pathogenesis of cellular damage has not been thoroughly evaluated. One of the more novel approaches for understanding SCD pathology involves examination of the cation transport system and its role in promoting solute loss, subsequent dehydration, and sickling[7]. Brewin *et al*[51] investigated the potential application of this principle to the early detection of SCN. Radioactive rubidium ( $^{86}\text{Rb}^+$ ) was used to measure the activity of the K-Cl cotransporter,  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channel (Gardos channel), and  $\text{P}_{\text{sickle}}$  channel among patients with SCD. According to their findings, the Gardos channel and  $\text{P}_{\text{sickle}}$  channel were both positively correlated with eGFR and ACR. Although these findings have not yet been confirmed in larger cohorts, detecting changes at the level of altered cellular permeability may prove valuable in determining the prognosis prior to the onset of renal damage. Furthermore, pharmacological interventions targeting these channels offer a potential focus for targeted treatment in the future.

### Endothelial dysfunction

Endothelial dysfunction is thought to be related to SCN. Mediators such as endothelin-1 (ET-1) and soluble fms-like tyrosine kinase-1 have been studied as contributors to pathogenesis, possible diagnostic markers, and even targets for therapeutics. In an experimental animal study, Heimlich *et al*[50] studied ET-1, an established strong vasoconstrictor, proliferative, and proinflammatory molecule that elicits the production of reactive oxygen species in the pathway, leading up to SCN and oxidative damage. These results confirmed the role of ET-1 in humanized sickle cell mice, demonstrating elevated mRNA expression of ET-1 and its receptor ETA.

Furthermore, Saleh *et al*[52] confirmed the increased binding to the aforementioned receptor within the renal vasculature and showed that antagonism of this receptor is linked to decreased urinary protein and nephrin excretion. This has already been established in animal models dedicated to the study of diabetic nephropathy. Closely related to this principle, an Egyptian study explored the effects of SCD on the production of soluble fms-like tyrosine kinase-1, an anti-angiogenic vascular endothelial growth factor receptor and found that its overexpression was linked to vascular dysfunction[53].

### Further studies

Future studies extrapolated from animal-based findings can pave the way for future biomarkers to be explored. For example, a study by Ofori-Acquah *et al*[54] that was targeting SCD mice exhibited that SCD mice had marked deficiency of the protein hemopexin. This biological event in turn leads to a compensatory response, which is an increase in the protein a-1-microglobulin, as discussed above.

The results found a strong correlation between hemopexin deficiency and the induction of AKI in SCD mice under hemolytic stress. Human studies that explore this protein as a biomarker, among others should also be contemplated in the future[54].

## CONCLUSION

Because of its devastating effects on patient mortality, morbidity, and quality of life, SCN has become a major research target. Approaches to both management and diagnosis have not yet been optimized, despite rigorous efforts from investigators in the field. Multiple authors have cited a lack of longitudinal studies as the primary limitation in the standardization and validation of their findings. Most of our current understanding of SCN stems from cross-sectional studies as opposed to large-sample cohorts with prospective follow-up of long-term renal performance. However, according to electronic databases of clinical trials, studies assessing novel parameters and their responses to interventions are underway.

Furthermore, several authors have demonstrated that the diagnostic yield of combinations of novel biomarkers may exceed that of individual markers, necessitating a collaborative approach in the standardization and utilization of promising biomarkers. As highlighted earlier, the lack of efficient renal studies is not a problem exclusive to SCN. Rather, first-generation renal studies should be supplemented with newer investigations detecting impending, rather than irreversible, losses of renal reserve. This highlights the importance of follow-up studies documenting the performance of the abovementioned biomarkers in larger populations, for extended durations, and their fluctuations in response to interventions and crises.

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