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Kidney Injuries in Sickle Cell Disease

Samit Ghosh

Abstract

Sickle cell disease (SCD), characterized by the presence of unstable sickle hemoglobin in the homozygous state (HbSS), results in progressive organ damage and early mortality with the median age of death in the 40s. The kidney is one of the most severely affected organs in SCD. Kidney diseases gradually develop in individuals with SCD. Microalbuminuria is evident in childhood, progressing to apparent proteinuria, deteriorating glomerular filtration rate (GFR) in early adulthood. While CKD becomes prevalent in adults. Moreover, among SCD patients, exacerbation of anemia is an independent risk factor for acute kidney injury (AKI) which is a predisposing factor for CKD and End Stage Renal Diseases (ESRD), altogether contributing to 16–18% mortality among this patients' population. The pathogenesis of renal diseases in SCD is not completely understood. While epidemiological studies have shown a strong association between rate of hemolysis, severity of anemia and CKD, intrinsic inflammatory, oxidative and hypercoagulative stress that contribute to the characteristic endothelial dysfunction also promotes development of renal diseases in SCD. This chapter will elaborately discuss current research on the pathogenesis of AKI, AKI-to-CKD transition and future research perspectives for development of novel therapeutic strategies.

Keywords: sickle cell disease, hemolysis, endothelium, AKI, CKD

1. Introduction

Kidney diseases are a major clinical concern in sickle cell disorders (SCD). Acute kidney injury (AKI) as well as chronic kidney disease (CKD) is associated with higher risk of inpatient mortality, prolonged hospital stay and expensive hospitalizations [1, 2]. While an estimated 100,000 people are affected by SCD in the United States (US) [3–5], about 20–25 million people are living with SCD worldwide and the number is expected to increase by about 30% globally by 2050 [6]. In the US, the majority of healthcare for SCD is attributed to in-patient hospitalization for acute complications with an estimated annual cost of \$953,640 per patient per year [7]. Progressive kidney disease leads to significant morbidity and mortality in both pediatric and adult patients with SCD. Sickle cell nephropathy (SCN) comprehends a spectrum of renal abnormalities that begins in childhood and may progress to advanced renal disorders in adulthood. In contrast to mild renal manifestations of sickle cell nephropathy includes decreased urinary concentrating ability, impaired

renal acidification and potassium secretion, hematuria and proteinuria, progressive kidney disease leads to significant morbidity and mortality in both pediatric and adult patients with SCD. Acute Kidney Injury (AKI) causes sudden drop in kidney function and promotes chronic kidney disease (CKD) and end stage renal disease (ESRD) [8–10]. In SCD, incidences of AKI are common among hospitalized SCD patients [11–13] and it is associated with increased mortality in those admitted to intensive care unit [14]. It is also an independent risk factor for increase morbidity, longer hospitalizations, and increased costs [15] as well as with risk for CKD progression in SCD [16]. Approximately 30% of SCD individuals develop CKD by adulthood and a large proportion of this sub-population develops ESRD [17]. The annual rate of incidence of AKI and reported CKD is 2–3-fold higher among SCD patients compared to non-sickle individuals [2]. Although newborn screening along with early intervention decreased early childhood mortality in SCD, accumulation of kidney diseases and age dependent renal deterioration of renal health poses increased risk of mortality in this population.

2. SCD pathophysiology and susceptibility to acute kidney injury

The genetic basis of SCD includes a single point mutation in the beta-globin chain of hemoglobin resulting in a morphologically and functionally different red blood cells (RBC). The modified hemoglobin (HbS) polymerizes under hypoxic condition causing RBC sickling [18, 19]. This characteristic feature of SCD leads to two major pathophysiological consequences, namely, vasoocclusion and hemolysis [20]. Moreover renal medullary hypoxia, acidosis, hyperosmolarity and reduced blood flow contribute to elevated endothelial adhesion and recurrent ischemia–reperfusion (IR) injury [13]. Earlier studies implicated several aspects of SCD including volume depletion, rhabdomyolysis, infections and the use of non-steroidal analgesics (NSAIDs) as predisposing factors for AKI [13, 21–25]. A cascade of these events individually or in combination possibly generates a constellation of sterile inflammation and oxidative stress, which overwhelm the normal physiology and trigger several chronic and acute multiorgan damage including kidney injury in SCD. Recurrent episodes of IR injury trigger vasoocclusive pain crisis (VOC), one of the major causes for intensive care unit (ICU) admission for patients with SCD. This medically vulnerable population is at higher risk of developing AKI due to co-morbid conditions of kidney and other organs including heart and lung. Patients with SCD frequently develop cardiopulmonary events like pulmonary hypertension (PH) and acute chest syndrome (ACS) which often lead to premature death [26]. AKI is emerging as a major clinical concern among SCD patients hospitalized for VOC and acute chest syndrome (ACS). It has been reported in ~14% of adults [12] and 8% children [27] with ACS, and in 17% of children with VOC [28]. Additionally, while hyperfiltration and microalbuminuria are common in SCD [13], chronic kidney disease (CKD) occurs in up to 60% of these patients [17]. Recent epidemiological evidences increasingly indicate that CKD and AKI are linked and probably promote one another [29, 30]. Underlying CKD is now recognized as a clear risk factor for AKI, as both decreased glomerular filtration rate (GFR) and increased proteinuria.

2.1 Hemolysis and acute kidney injury in SCD

Acute exacerbation of anemia that potentially generate excess extracellular heme is an independent risk factor for AKI in SCD [27, 28, 31]. Earlier studies implicated

several aspects of SCD including volume depletion, rhabdomyolysis, infections and the use of non-steroidal analgesics (NSAIDs) as predisposing factors for AKI [13, 21–25]. Recent clinical studies have concluded that incidences of AKI are associated with rapid decline in hemoglobin (Hb). The link between acute hemolysis and AKI is corroborated with significantly low level of total Hb at the time of hospitalization among SCD patients who develop AKI compared to those who do not [16], and higher risk of developing acute renal insufficiency among ACS patients with rapidly progressive decline in total Hb [32]. Intravascular hemolysis is a cardinal pathophysiological event in SCD that raises cell free plasma Hb and arginase-1 levels to collectively reduce nitric oxide (NO) bioavailability and enhance reactive oxygen species (ROS) formation [33, 34]. Cell-free hemoglobin is primarily scavenged by plasma protein haptoglobin (Hp). The resulting duo (Hb-Hp complex) is internalized by macrophage receptor CD163 for subsequent globin and heme metabolism. Haptoglobin is depleted in SCD resulting high amount of plasma hemoglobin that can easily get exposed to the underlying oxidative environment. Heme is subsequently released following oxidation of Hb to methemoglobin (metHb) with ferric heme. Extracellular circulating heme is rapidly transferred to hemopexin (Hx), the plasma protein with the highest binding affinity for heme. It is well known that heme-hemopexin (heme-Hx) complex is transported to the liver for degradation by heme oxygenase-1 (HO-1) [35, 36]. In SCD, plasma Hx is also intrinsically exhausted due to chronic hemolysis [37, 38]. Lack of haptoglobin and hemopexin along with chronic and acute hemolysis elevate extracellular hemoglobin and heme in plasma of SCD patients [33]. Furthermore, the HbS is a relatively unstable molecule that can easily undergo autooxidation contributing to increase circulating free heme in SCD [39]. Both cell-free circulating hemoglobin and heme are toxic, unless sufficiently metabolized, to the cells and may cause significant damage to organs including kidney.

2.2 Pathogenesis of acute kidney injury in SCD

The primary etiology of AKI involves four major structures of kidney including tubules, glomeruli, interstitium and intrarenal blood vessels. While acute tubular injury is the major pathological manifestation of AKI, rapid decline in renal function identified by reduced glomerular filtration rate (GFR) clinically define AKI [40]. The dimeric form of circulating cell free Hb can filter through glomerular sieve and enters in proximal tubular segment. The endocytosis of Hb molecules is possible through the megalin and cubilin receptors on tubular epithelial cells. The internalized hemoglobin breaks down in to heme that induces caspase-3 mediated apoptosis of the tubular cells leading to AKI development. This idea was supported by the presence of hemoglobin and myoglobin in plasma and urinary space in multiple in vivo models of AKI induced by glycerol, ischemia, sepsis and cisplatin [41–43].

In vivo, excess circulating heme, a byproduct of acute hemolysis, triggers VOC and ACS, the two major SCD complications associated with hospitalization and AKI development in SCD [44, 45]. Our recent study demonstrated that modest elevation of extracellular heme in circulation promotes clinically relevant AKI in an established humanized murine model of SCD containing human HbS. In this study, the researchers have established that a secondary heme scavenger, alpha-1-microglobulin (A1M) is elevated in mice and human with SCD as an adaptive response to decreased hemopexin, the primary heme scavenger responsible for clearance of circulating free heme [46]. Several other studies have shown that heme bound to A1M is transported to renal tubular epithelial cells [47]. Excess deposition of heme causes proximal tubular

Figure 1. Pathogenesis of AKI in SCD. Hemolysis cause release of cell free Hb and heme in circulation. Free dimeric Hb or free heme bound to A1M passes through glomerular filtration and internalized into renal proximal tubular epithelial cells. Excess heme can overwhelm the HO-1 degradation capacity and induce multiple cell death pathways. On the other hand, Hb may cause podocyte injury leading to glomerular dysfunction. Tubular cell death and/or glomerular damage develops AKI.

epithelial cell death and promotes AKI (**Figure 1**). This study identifies that relative concentration of A1M and Hx may serve as prognostic factor of future AKI events in SCD during acute hemolytic events [46, 48].

3. Chronic kidney disease (CKD) in sickle cell disorders

Kidney diseases gradually develop in individuals with SCD. Microalbuminuria is evident in childhood, progressing to apparent proteinuria, deteriorating glomerular filtration rate (GFR) in early adulthood, while CKD becomes prevalent in adults [49]. Development of CKD in SCD is complex, but several studies have invariably demonstrated its association with low hemoglobin level and hemolysis [50–53]. Higher frequency of severe anemia (Hb: 7–9 g/dl) among SCD patients with ESRD (71%) compared to non-SCD patients with ESRD (25%) has also been reported [54]. Moreover, among SCD patients, exacerbation of anemia is an independent risk factor for acute kidney injury (AKI) which is a predisposing factor for CKD and ESRD [27, 28, 31]. Progression of kidney damage is defined as CKD when eGFR is reduced to

<60 mL/min/1.73 m². The reduced GFR is often associated with hematuria, albuminuria and nephrotic syndromes. Intravascular hemolysis is a cardinal pathophysiological event in SCD that raises cell free plasma hemoglobin and arginase 1 to collectively reduce nitric oxide (NO) bioavailability and enhance reactive oxygen species (ROS) formation [33, 34]. Worsening anemia and elevated persistent oxidative stress lead to decline in GFR in association with reduced erythropoietin synthesis. Individuals with SCD develop CKD at a median age of 23.1 years, while 16–27% of pediatric patients have CKD [17].

3.1 Glomerular hyperfiltration, hyper perfusion and progressive kidney damage

Increased renal blood flow and higher GFR are characteristics of kidney function among SCD patients at their younger age. The hyperfiltration subsides to normal GFR that eventually lowers to subnormal level with the progression of age and the development of CKD [13, 55]. Sustained glomerular hyperfiltration causes damage to different parts of the glomerulus including the endothelium and the epithelial layer of the Bowman's capsule. These events predispose the development of focal segmental glomerular sclerosis (FSGS), which is a common feature in SCD. Hyperfiltration occurs due to glomerular hyper perfusion that increases the renal blood flow. Hyper perfusion stems from underlying anemia and decreased vascular resistance, while the reduced blood flow is evident within hypoxic renal medulla due to vasoocclusion of sickle red blood cells. This phenomenon commonly known as “perfusion paradox” generates increased oxidative stress, mesangial proliferation, endothelial barrier disruption, and thickening of the glomerular basement membrane [56].

3.2 Proteinuria and chronic kidney disease in SCD

Hyperfiltration among children with SCD is associated with proteinuria in the form of microalbuminuria (urine albumin 30–300 mg/g creatinine). This condition increases with age and about 68% of these patients experienced macroalbuminuria (urine albumin >300 mg/g creatinine) as they grow older [57, 58]. While about 4% of SCD patients exhibit macroalbuminuria at the nephrotic range (urine albumin >500 mg/g creatinine), a substantial number of patients suffer from irreversible kidney complications. Several studies have indicated association of albuminuria with hemolysis, incidences of vasoocclusive crisis and acute chest syndrome, and pulmonary hypertension. These events also impact blood pressure which in turn can regulate hyperfiltration [13, 17, 21, 53].

3.3 Genetic variants associated with chronic kidney disease in SCD

Apart from the underlying hemoglobin gene mutation, progression and severity of CKD development are associated with polymorphisms of multiples genes among SCD patients. A major proportion of SCD population has alpha thalassemia. Two polymorphisms in the α -chain of the globin chain including i) a 3.7 Kb deletion and ii) a 4.2 Kb deletion are associated with reduced albuminuria, higher eGFR and hence lower risk of CKD progression [59, 60].

The variants of apolipoprotein L1 gene (*APOL1*) gene associated with risk of CKD development have been studied widely. The G1 (S342G and I384M) as well as G2 (N388 and Y389 deletion) variants found in 11–13% of African Americans account for about 70% CKD risk in this population. Homozygous or compound heterozygous

inheritance of G1/G2 variants within SCD population increase the macroalbuminuria, progression of CKD and development of ESRD [61–63].

Besides the increased risk of AKI with longer GT tandem repeats of HMOX-1 gene promoter, the allele frequency of a variant of *HMOX-1* (rs743811) was found to be associated with worsening CKD [61, 64]. Several other genetic variants including (i) Duffy antigen (Fy rs2814778) of the RBC, (ii) myosin heavy chain 9 (*MYH9*-rs5750248, rs1192763), (iii) *TGF- β /BMP* (BMP1B) have also been implicated with CKD risk among various cohorts of SCD patients [65–67].

3.4 Renal endothelium and pathogenesis of chronic kidney disease in SCD

In SCD, intrinsic hemolytic, inflammatory, oxidative and hypercoagulative stress contribute to the characteristic endothelial dysfunction that alters the systemic vascular biology [68]. Endothelial interaction with multiple blood components, including sickled red blood cells, leukocytes and platelets, injure the endothelium and obstruct the vasculature impacting internal organs [69]. Renal pathology in sickle cell nephropathy includes extensive peritubular microvascular congestions and chronic thrombotic microangiopathy that can lead to CKD by peritubular microvascular rarefaction, interstitial fibrosis and tubular atrophy [70–72].

Several studies including ours have demonstrated that extracellular heme triggers endothelial barrier disruption in various organs in SCD including the kidneys [44, 73–76]. Endothelial dysfunction may occur in the glomerulus affecting the podocytes that maintain the glomerular endothelial integrity. One study has shown that renal endothelial dysfunction is triggered by an increase in soluble fms-like tyrosine kinase 1 (sFLT-1), a splice variant of vascular endothelial growth factor receptor-1 (VEGFR1) in SCD. The sFLT-1 blocks interaction of VEGF with glomerular endothelium leading to endothelial damage associated with increased albuminuria [77]. Moreover, endothelin-1 (ET-1) generated by endothelial cells under inflammation causes endothelial injury by reducing NO bioavailability. Alongside, ET-1 mediates podocyte injury by binding endothelin A (ETA) receptor. In animal studies, antagonists to ETA receptor showed renal protection [78, 79].

Hemolysis and hemoglobinuria, cardinal features of SCD are associated with proteinuria and progression of CKD in SCD patients [51, 53]. Multiple chronic and acute hemolytic events may induce episodes of vasoocclusion leading to vulnerability of the endothelium susceptible to injury. The peritubular capillaries may split leading hematuria through extravasation of RBCs. These events may prompt development of vasoocclusion of vasa recta and papillary necrosis [80].

Endothelial injury in the renal peritubular microvessels is closely linked to rarefaction and interstitial fibrosis that leads to CKD progression [81–83]. Moreover, free heme reflects the function of danger associated molecular pattern in hemolytic diseases activating vital defense response compartments including toll-like receptor-4 signaling, neutrophil extracellular trap formation and inflammasome activation [84–86]. The inflammatory milieu including activated neutrophils regulate endothelial barrier function through adhesion and secretion dependent mechanisms [87].

4. Current management and therapies

Medications and timely management are critical in protecting the kidney. Chronic RBC transfusion therapy is offered to enhance the osmolality and concentrating

ability in children with SCD. Hydroxyurea therapy has been shown to reduce the hyperfiltration in children [88]. Hypotonic fluid is recommended for renal papillary necrosis thiazide or loop diuretics are used to maintain urine flow rate [80]. The angiotensin converting enzyme inhibitors (ACE-inhibitors) can dilate efferent arterioles and help decrease glomerular pressure. ACE-inhibitors are used widely to control albuminuria [89].

5. Future research perspectives

Free heme is considered as an eDAMP (erythroid danger-associated molecular pattern) that induces sterile inflammation in SCD. Heme has been shown to activate toll-like receptor 4 (TLR4) on endothelial cell surface to promote TNF α stimulating innate immune signaling in SCD [45]. Moreover, heme activates NLRP3 inflammasome pathway and releases caspase-1 induced IL-1 β from macrophages. The resulting inflammation is associated with hemolysis induced lethality in SCD mice and heme induced cell death in macrophages [85]. Heme-mediated toxicity is particularly relevant to renal tubular epithelial cells as these cells presumably confront the majority of heme that passes through the glomeruli during acute hemolysis. Inflammasomes potentially activate caspase-1 that mediates cell death leading to release of IL-1 β and IL-18. These are pro-inflammatory cytokines that are induced and cleaved in the proximal tubule, and subsequently easily detected in the urine of SCD patients and their concentrations were associated with hemolysis [90]. In a cross-sectional study, urine IL-18 levels were markedly elevated in patients with established AKI [91]. An in vitro study using immortalized human proximal tubular epithelial cells (HK-2) suggests that activation of inflammasomes mediates contrast-induced AKI [92]. Whether acute hemolytic events followed by exposure of excess heme on proximal tubular epithelial cell surface induces AKI facilitated by stimulation of inflammasome machinery has not yet been established.

The role of the rate limiting heme catabolizing enzyme, HO-1 may be of significant importance. HO-1 degrades heme into iron (Fe), carbon monoxide (CO) and biliverdin, and thereby protects against adverse effects of heme. Multiple studies featured rapid induction of HO-1 under oxidative stress accounts for its beneficial effect against kidney injury [93–95]. Moreover, longer [GT] $_n$ repeats in HO-1 gene (*HMOX1*) promoter, responsible for reduced HO-1 expression, is associated with increased risk of AKI in sickle cell disease patients [16]. The mechanism of cellular regulation of HO-1 induction during AKI events in SCD has yet to be elucidated.

Besides tubular damage, etiology of AKI also includes impaired glomerular structure. Podocytes, the highly differentiated visceral epithelial cells, is a major constituent of glomerular structure and function. One in vitro study has shown that human and murine podocytes exposed to Hb develops increased oxidative stress and undergo apoptosis resulting podocyte dysfunction [96]. In SCD, the cell free HbS may serve as an oxidant to cause podocyte injury that may contributes to AKI, whereas, multiple AKI events may induce focal segmental glomerulosclerosis (FSGS), a characteristic CKD feature in SCD.

The intracellular signaling within the podocyte regulating glomerular endothelial integrity has not been explained.

Despite clinical association, mechanistic studies linking hemolysis to renal peritubular endothelial impairment leading to progressive kidney diseases in SCD have not yet been described. The underlying chronic inflammation in SCD leads to activation

Figure 2.
Overview of sickle cell disease nephropathy. Figure prepared with biorender.com.

of blood cells including neutrophils and platelets. During AKI and CKD, neutrophil and platelet accumulation are evident within renal vasculature. The cellular and molecular mechanism depicting the interactions of activated blood cells and the endothelium leading to progression of CKD is an important area of future research.

Kidney injuries in SCD is multifactorial and may involve multiple unique and overlapping cell biological events in several renal compartments (**Figure 2**). Incidences of AKI are generally considered as independent risk factor for CKD progression not only in general population but also in SCD. Multiple AKI events attributed to acute intravascular hemolytic events in SCD may be responsible for progressive CKD and end stage renal disease among SCD patients. Future studies elucidating mechanisms of AKI to CKD transition along with identification of specific risk factors are warranted for development of potential therapeutics to protect individuals with SCD from broad spectrum of renal complications.

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