REVIEW ARTICLE

# Sickle cell renal disease; clinical signs of renal damage and novel processes involved

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**ABSTRACT**

One of the most frequent side effects of sickle cell illness is kidney issues (SCD). They start early in life and are a major contributor to mortality in these patients. Vaso occlusion and hemolysis are the key pathogenic mechanisms that underlie the disease. The renal medulla's low oxygen partial pressure, high osmolarity, and acidic pH provide excellent circumstances for the sickling of red blood cells. Hyposthenuria is initially brought on by sickle-cell development in the renal medulla's vasa recta. This is common and manifests in childhood. When the infarcts are severe, microscopic and macroscopic haematuria can also happen, which is partly related to renal papillary necrosis. Glomerular filtration rate rises as a result of prostaglandins released by ischaemia in the renal medulla (GFR). Adaptively, the proximal tubule's sodium reabsorption rises, and creatinine output also rises. As a result, the GFR calculated from creatinine can be too high. The most prevalent glomerular disease is focal segmental glomerulosclerosis. Albuminuria is quite frequent, and treatment with ACE inhibitors or ARBs has been observed to reduce it in 72.8% of participants. Recent research reveals that unbound hemoglobin damages podocytes and may play a role in these patients poor kidney function. Since they may offer a treatment alternative for sickle cell nephropathy, their consequences in SCD need to be more thoroughly investigated.

**Keywords:** Sickle cell nephropathy; Sickle cell disease; Haemoglobin; Albuminuria; Glomerular filtration rate

## INTRODUCTION

The term sickle cell nephropathy is used to describe the collection of Sickle Cell Disease (SCD) renal symptoms. One of the most prevalent and dangerous kidney consequences in SCD is kidney disease. One of the main causes of death in adulthood, they are frequently present since childhood [1].

The term "SCD" (or "Sickle Cell Disease") refers to the collection of abnormalities brought on by the interaction of the hemoglobinopathy S-causing mutation in one of the beta globin (HBB) gene alleles with a different mutation in the other allele. Therefore, the homozygous state (S/S), to which "sickle cell anemia" refers, and the combination of a mutation that results in a silent allele (S/°-thalassemia), are the two most dangerous variations [2].

Nearly 40% of Hemoglobin (Hb) with sickle cell trait is Hb S. Changes in the beta globin gene can coexist with mutations that decrease the synthesis of alpha globin (-thalassemias), as Hb is a tetramer made up of 2 alpha globins and 2 beta globins. When deoxygenated, Hb S is poorly soluble and forms rod shaped polymers that give red blood cells their distinctive sickle or crescent shaped shape. The primary pathogenic factors in SCD are hemolysis and vasoocclusion, which cause endothelial dysfunction and vasculopathy, ischemia/reperfusion injury, oxidative stress, hypercoagulability, nitric oxide deficiency (free Hb produced by intravascular hemolysis binds to and sequesters nitric oxide), platelet activation, and increased neutrophil adhesiveness [3].

All of this results in both acute and long term symptoms that may harm any organ. The most common ones are severe bone crises and persistent anemia. Other symptoms include priapism, avascular necrosis of the hip or shoulder, ulcers in the lower extremities, functional asplenia/hypoasplenia, sepsis, silent cerebral infarcts and stroke, retinopathy, pulmonary hypertension, pulmonary fibrosis, acute chest syndrome, functional asplenia/ hypoasplenia, silent cerebral infarcts, and sickle cell nephropathy itself [4].

The partial malaria protection provided by the sickle cell trait explains why SCD primarily affects persons of African descent, while it can also affect people from the Middle East, India, South and Central America, and the Middle East. Sickle cell trait affects between 10% to 30% of people in sub-Saharan Africa, while the condition affects 2% of people in various nations. The rise in the number of patients being monitored in our nation is due to an increase in the migratory flow from endemic areas, the implementation of universal neonatal screening programs in the autonomous communities, and improvements in survival [5].

On the actual disease prevalence in Spain, there are still no statistics. Data from the Spanish Registry of Hemoglobinopathies (REHem), a non-population registry funded by the Spanish society of pediatrics (SEHOP) and involving several hospitals, show that 826 people with SCD were registered there as of the start of 2019. The majority of the participants were situated in the Valencian community and, to a lesser measure, in the community of Madrid, Catalonia. The majority of the children (51.4%) were diagnosed by newborn screening and the majority (63.3%) were born in Spain. SCD is present in 0.16 out of every 1,000 babies in Madrid [6].

When hemolytic anemia or other clinical signs of SCD are present, as well as when there is a risk factor such as ethnic origin, SCD should be suspected. Even in their most severe versions, clinical manifestations won't start until a few months after delivery since fetal Hb (Hb F) diminishes throughout the first year of life [7].

It's not necessarily a marker to be ethnic. In some instances, some genotypes may be devoid of anemia and hemolysis features. In the peripheral blood smear, sickle red cells are typically visible, albeit they are uncommon in the Hb S/C type, where dianocytes cells predominate [8]. In the Hb S/C form, as well as in the forms connected to thalassemia (Hb S/0-thalassemia or Hb S/+-thalassemia), or -thalassemia, Mean Corpuscular Volume (MCV) may decrease (microcytosis). A study of Hb variations utilizing capillary electrophoresis and High Performance Liquid Chromatography (HPLC) will typically be used to finalize the diagnosis. A confirmatory genetic investigation will be helpful in some circumstances [9].

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The only curative therapy is Hematopoietic Stem Cell Transplantation (HSCT), an allogenic procedure. The lack of appropriate donors and the attendant morbidity, particularly when it is conducted after puberty, limit its application in our setting. Less than 15% of patients in the US have a family donor that shares their HLA. Gene editing based therapies is being investigated, and the findings are encouraging. The only medication currently approved in Europe to treat the condition is hydroxyurea. This medication increases Hb F synthesis, which prevents Hb S from polymerizing and forming sickles. Hb S continues to be the predominate Hb, however the Hb F levels attained with the maximum tolerated dose are often between 20 and 30%.

Therefore, hydroxyurea has a limited benefit. Furthermore, there is inadequate data to support its use or the avoidance of chronic problems in patients with non-Hb S/S or Hb S/°-thalassemia genotypes. Additionally, it is yet unknown how several medications that have already received FDA approval, including as L-glutamine, crizanlizumab, and voxelotor, will affect the long term side effects of SCD. As a result, patients with SCD still have a 20–30 years shorter life expectancy in wealthy nations. This review seeks to serve as a tool for the treatment of sickle cell nephropathy patients in this context.

## LITERATURE REVIEW

### Clinical signs and symptoms

**Hyposthenuria:** Hyposthenuria is a common observation in SCD and is characterized as the inability to concentrate urine more than 450 mOsm/kg when water is restricted. Symptoms first appear in infancy and become permanent at the age of 15 in people with genotype S/S or S/°-thalassemia. Around the age of 10, hypostenuria is noticed in those with sickle cell trait.

**Tubular acidosis:** Patients with SCD may experience hyposthenuria and incomplete type IV renal tubular acidosis (distal renal tubular acidosis with hyperkalemia), which is caused by a malfunction in the distal secretion of hydrogen ions and potassium. Despite the fact that the precise pathogenic process is unknown, it may be caused by a decrease in the electrochemical gradient in the collecting ducts as a result of reduced medullary blood flow, which causes hypoxia. It is quite rare to have a severe deficiency of urine acidification, and as a result, the acidosis is incomplete because the majority of the damage occurs in the deepest portion of the loop of Henle. Unless there are additional factors that alter the renal compensatory processes, hyperkalemia is uncommon and mild, Angiotensin Converting Enzyme Inhibitors (ACEI) or Antagonists of Angiotensin II (ARA-II), potassium saving diuretics, beta-blockers, high potassium consumption, rhabdomyolysis, or renal failure are a few examples of medications that block the renin angiotensin aldosterone system.

**Hematuria and renal papillary necrosis:** Patients with SCD frequently experience hematuria, and individuals with sickle cell trait may experience this condition twice as frequently. At any age, it might happen. It can be tiny, but macroscopic and self-contained is more typical. It results from micro infarctions and vasoocclusive events that affect the renal papillae. The left renal vein is longer and squeezed between the aorta and the superior mesenteric artery (nutcracker phenomenon), increasing relative hypoxia in the renal medulla and favoring sickling. This is probably why it is commonly unilateral emanating from the left kidney.

These infarctions can occasionally be severe, leading to Renal Papillary Necrosis (RPN), which is estimated to affect 30–40% of homozygous patients (Hb S/S). Even with hydronephrosis, it can appear clinically with abrupt discomfort, fever, and acute obstructive renal failure in addition to asymptomatic (but not necessarily present) hematuria.

**Hyper filtration:** In SCD patients, hyper filtration or an elevated GFR (>130 ml/min/1.73 $m^2$ in women and >140 ml/min/1.73 $m^2$ in men) frequently occurs before albuminuria and may start as early as childhood. About half of the people under 40 in a study of homozygous adult patients showed hyper filtration, and in half of them, it was linked to albuminuria.

Patients with SCD have lower filtration fractions than healthy individuals due to increased renal plasma flow, which is even greater than GFR. This phenomenon might be due to juxtamedullary nephron loss, which is selective since they have a greater filtration fraction than cortical nephrons. Since renal hyper perfusion is not reversed by repeated red blood cell transfusions, the increase in cardiac flow caused by anemia cannot account for renal hyper perfusion.

**Increased proximal tubular function:** The adaptive improvement in proximal tubular function as well as the rise in sodium reabsorption is related to the rise in GFR. Additionally, there have been reports of increased uric acid and creatinine secretion, increased reabsorption of 2-microglobulin and phosphate (hyperphosphataemia may exist, particularly if phosphate overload occurs, as in hemolysis patients), and increased maximal transport of para-amino hippuric acid. Due to increased oxidative stress, higher salt reabsorption necessitates oxygen consumption and favors tubular damage. Additionally, increasing oxygen demand will worsen hypoxia, encourage illness, and exacerbate renal injury.

**Proteinuria:** The glomerular endothelium and podocytes may be harmed by the previously mentioned hemodynamic alterations, leading to proteinuria, which then results in tubulointerstitial injury. Focal adhesions to the parietal epithelium result from podocyte damage. The most prevalent glomerulopathy in SCD, localized and segmental glomerulosclerosis, is brought on by these adhesions and has been seen in up to 39% of kidney biopsies taken from individuals with SCD who also have proteinuria and/or kidney failure. Less often seen histological patterns include thrombotic microangiopathy and membranoproliferative glomerulonephritis. Hemosiderin deposits in the tubular cells and hypertrophy of the glomeruli are virtually always observed observations.

**Blood pressure reduction:** Those with the Hb S/S genotype have considerably lower diastolic, systolic, and mean blood pressure than healthy controls of the same age and sex (8.37 mmHg, 2.32 mmHg, and 8 mmHg, 41 mmHg, respectively) according to a meta analysis published in 2014. This fact might be connected to the urine concentration problem. Renal failure and albuminuria below 300 mg/g creatinine appear to be linked to a decreased risk of developing hypertension in sickle cell anemia patients (HTN). According to a study involving 163 patients, Pulmonary Hypertension (PH) and renal dysfunction are more likely to occur in SCD patients who had a Systolic Blood Pressure (SBP) between 120 and 139 mmHg or a Diastolic Blood Pressure (DBP) between 70 mmHg and 89 mmHg [10].

**Acute kidney failure:** Between 4 and 10% of SCD patients are admitted with acute renal failure, which affects them more frequently than patients with acute bouts of bone pain (2.3%) and acute chest syndrome (13.6% if it is severe and accompanied by pulmonary hypertension, which signals venous congestion). A 15% drop in the reversible creatinine clearance has been seen during episodes of pain related vasoocclusive crises. 34 acute renal failures are predisposed by volume depletion, rhabdomyolysis, infections, or the use of non-steroidal analgesics. Similar to iron overload, SCD frequently occurs and requires chelating therapy; deferasirox is the most popular medication. This medication may cause a dose dependent, reversible rise in blood creatinine, hence, a dose reduction should be taken into account in the event of slight increases in creatinine.

**Chronic kidney disease:** In a study of 410 SCD patients between the ages of 2 and 21, 26.5% had stage 1 CKD, 14.5% had stage 2, and 11.6% had stage 2.35 In another investigation, CKD was found to be the cause of 10.5% of fatalities in adult SCD patients. In 43% of cases involving homozygous patients older than 60 years, CKD was the primary cause of mortality.

The only medication for SCD in our nation, hydroxyurea, is processed in the kidney; therefore, the dosage must be altered in accordance with renal function. It must be administered after the hemodialysis session because hemodialysis removes it.

**Genetic modifiers of sickle cell kidney disease:** Similar to other SCD manifestations, genetics has a significant role in determining the frequency and severity of sickle cell nephropathy. As a result, sickle cell nephropathy is more severe in the Hb S/S and Hb S/0-thalassemia forms, which have higher levels of Hb S and hemolysis, whereas it is milder in the heterozygous compound Hb S/C and Hb S/+-thalassemia forms. Lower Hb S levels and protection from hyposthenuria are linked to the coexistence of

deletions affecting the -globin genes (thalassemic characteristic), and the prevalence of macroalbuminuria in sickle cell anemia is decreased.

**Kidney abnormalities in sickle cell trait:** One allele of the hemoglobinopathy S mutation is present in sickle cell trait carriers, while the other allele is normal. They exhibit deformation and degeneration of the vasa rectus, as seen by renal microangiography, though much less so than those with SCD. However, hematuria is 2 times more common than in SCD, according to a meta analysis that was published in 2018. The higher prevalence of sickle cell trait and the high hematocrit of carriers may be to blame for this observation. In the same study, carriers were found to have a greater risk of proteinuria and CKD than the general population.

## DISCUSSION

### New mechanisms involved in kidney damage

Massive amounts of Hb and heme group are released during hemolysis in SCD patients, and these substances can pass through the glomerular filtration barrier to deposit mostly in proximal tubular cells. Both Hb and the heme group encourage a number of harmful effects in these cells, including mitochondrial damage, inflammation, fibrosis, oxidative stress, and apoptosis. Reactive oxygen species are produced by the heme group and Hb and are responsible for lipid peroxidation, DNA damage, and inflammation. It has been established that the heme group can directly trigger an inflammatory response in mice with SCD by binding to the toll type receptor 4, which is found on endothelial, mesangial, tubular, and podocyte cells. This interaction causes the transcription factor NF-kB to be activated.

Haptoglobin and hemopexin, respectively, carry the Hb and heme group to the liver, where heme oxygenase-1 breaks them down. Chronic hemolysis causes an acquired haptoglobin and hemopexin deficiency in SCD. However, the glomerular barrier connected to -1 microglobulin also eliminates the heme group (A1M). Recent research has shown that markers of hemolysis and tubular damage are related with an up to 10 fold compensatory increase in A1M and the A1M-hemopexin ratio in both humans and mice with SCD (KIM-1, Kidney Injury Molecule-1 and NGAL, neutrophil gelatinase associated lipocalin). In experimental models of SCD, the administration of hemopexin and haptoglobin lessens kidney injury.

## CONCLUSION

Greater awareness is needed among healthcare workers due to the rising incidence of SCD in our nation. In sickle cell disease and the sickle cell trait, renal symptoms are among the most prevalent and severe. In order to create tailored therapy choices that are adapted to the variability of renal involvement and the interactions between the various coexisting processes, it is vital to further our understanding of its pathophysiology. In order to stratify patients based on their risk of developing CKD and to carry out earlier and more efficient treatment measures, biomarkers are required.

Although new medications have been created recently to treat the illness systemically, it is still important to consider how kidney disease is affected.

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