

Sickle Cell Trait and Renal Disease

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Individuals with sickle cell trait (SCT), the heterozygous state of sickle hemoglobin β -globin gene (HbAS), are generally reassured that their health will not be affected by their carrier status. Renal disease, especially hematuria, is one of the most common and severe complications experienced by patients with sickle cell disease (SCD); but a complete understanding of the relationship between SCT and the development of chronic kidney disease (CKD) is still lacking. In this short review, we present an overview of SCT and renal complications in SCT, and discuss and identify SCT as a risk factor resulting from an interplay between genetic and environmental influences. Although SCT itself may not be a disease in itself, there is evidence suggesting clinical conditions related to SCT. Additionally, we highlight the rationale for further studies into this area, which could affect the global public health recommendations on any associated health risks.

Keywords

Sickle cell trait, renal failure, chronic kidney disease

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Sickle cell disease (SCD) is a common and serious inherited hematological disorders in humans. Globally, the disorder affects approximately 300,000 live births per year,¹ and thus it is among the most important epidemiological genetic disorders in the world. SCD occurs as a result of substitution of valine for glutamic acid at the sixth amino acid position of the β -globin gene on the short arm of chromosome 11; thus, producing an abnormal hemoglobin, called hemoglobin S (HbS), instead of normal hemoglobin, hemoglobin A (HbA). For the full disorder to be established, this mutation must be present on both inherited alleles. During deoxygenation, the red blood cells (RBCs) containing HbS become less deformable and form a "sickle" shape. Therefore, polymerization is governed by local oxygen tension, and promoted by both acidosis and hyperosmolarity.²

Sickle cell trait (SCT) is defined as inheritance of a single copy of the sickle mutation. It is estimated that the disorder affects one in 12 African Americans and nearly 300 million people worldwide. Most recently, Naik et al. showed that among African Americans, the presence of SCT was associated with an increased risk of chronic renal disease (CRD) as compared to normal subjects.³

The complications of SCD are well documented and can affect many organs in the body. Furthermore, studies reported cases of acute complications in SCT individuals such as splenic infarction, heat stroke, acute renal failure, and sudden death.⁴⁻⁷ Renal manifestations are the most frequently reported complications and include impaired urinary concentration, papillary necrosis, and asymptomatic hematuria.⁷⁻¹⁰ A less common cause of hematuria in these cases is renal medullary carcinoma (RMC), which is almost exclusively found in patients with sickle hemoglobin β -globin gene (HbAS).¹¹

Renal complications in sickle cell trait

Regardless of the generally benign nature of SCT, numerous possibly serious complications have been described over the years. Two rare, but important non-renal complications include increased risk of splenic infarction provoked by hypoxia after high altitude experience, and increased risk of sudden death during prolonged physical exercise or training at high altitude.¹² Furthermore, SCT, alone may not be sufficient for the development of CRD; it could contribute to the progression of chronic renal failure (CRF) in the presence of additional factors such as diabetes, hypertension, and autosomal dominant polycystic kidney disease (ADPKD). Furthermore, the pathophysiological pathways induced by SCT could exacerbate the microvascular complications that arise from diabetes mellitus since SCT patients and diabetes mellitus are prone to suffering from hematuria and papillary necrosis.^{13,14}

Hematuria was first reported in SCT patients more than 50 years ago,¹⁵ and is by far most common complication of SCT.¹² Data from a large series of African American patients showed that hematuria accounted for 4% of hospitalization among patients with SCT, about twice the rate among those

with normal hemoglobin.⁹ In normal male subjects, the reference rate admission for hematuria was 2%; these findings suggest that 50% of the time participants with HbAS would have bleeding unrelated to their SCT. Other causes of hematuria, including lower urinary tract neoplasms and stones, should consequently always be considered in these patients. Two main causes of hematuria are papillary necrosis and renal RMC.⁹

Vascular abnormalities that cause hematuria also lead to the impairment of urinary concentration and even isosthenuria. Microradiographs of kidneys of SCT patients performed more than 30 years ago demonstrated disruption and reduction of vasa recta, the intricate vascular system of the kidney responsible for generating an osmolar gradient. These vascular changes likely lead to the observed impairment of urinary concentration in patients with SCT.¹⁰ The loss of urinary concentration with dehydration could be causative factor in the development of rhabdomyolysis and sudden death associated with exercise in SCT patients.^{12,15-17} The degree of urinary concentration impairment is changeable among patients with SCT, and may be related to the percentage of HbS, which in turn is regulated by the co-occurrence of an α -globin gene deletions.^{18,19} Therefore, among patients with SCT, maximal possible concentration of urine after taking of intranasal desmopressin acetate spans between 530 and 845 mOsm/kg, and is inversely related with the number of α -globin gene deletions.²⁰ In the existence of two α -globin gene deletions, urine concentration is only reasonably reduced, whereas in those with no α -globin gene deletions, the capability to concentrate urine is extremely impaired.²⁰

Renal papillary necrosis signifies ischemic impairment to the renal medulla and is typically associated with SCD, analgesic abuse, and urinary tract infections (UTIs), mainly in the situation of diabetes. While the condition is much more common in SCD, papillary necrosis is not uncommon in SCT. Papillary necrosis usually signifies with painless gross hematuria, and possibly complicated by obstruction or UTI.¹² Bleeding presents as microscopic or gross bleeding and may be associated with renal papillary necrosis. Due to its larger size and higher venous pressure that results from compression of the left renal vein by

the aorta and superior mesenteric vein, involvement of left kidney is more common.^{12,21}

Factors such as acidosis, decreased oxygen tension, dehydration, and high osmolarity are the leading triggers of RBC sickling, and renal medulla presents all of the mentioned conditions. While blood crosses the slow-moving circuit of the medullary vasa recta, the hyperosmolar milieu might improve dehydration of erythrocytes, promoting sickling and probable vaso-occlusion and medullary microinfarctions.^{12,21}

RMC is a rare, highly aggressive but serious complication present nearly exclusively in young black individuals with SCT.¹² Davis et al. reported this neoplasm in series of 34 patients, 33 of who had SCT.²² Dimashkieh et al. reviewed 55 cases of RMC, 50 patients had HbAS, two had hemoglobin SCD (HbSCD), and one had homozygous sickle cell disease (HbSS) disease.²³ The study showed that the average age at tumor presentation was 21 years and male to female ratio was 2:1. Also, the right kidney was involved three times more commonly.

Data examining the relationship between SCT and chronic kidney disease (CKD) exists. Derebail et al. demonstrated a 50% higher incidence of SCT among end-stage renal disease in African Americans, compared to that inferred from newborn hemoglobinopathy screening program, proposing that it may be a risk factor for developing CDK.²³

Conclusion

In conclusion, given the high prevalence of SCT, further investigation of the relationship between this common genetic hemoglobinopathy and CDK is warranted. The evidence suggests that SCT may be neither a completely benign disorder nor a true disease entity, but rather a risk factor for certain adverse outcomes that result from interplay between genetic and environmental influences. If SCT is a risk factor for developing CDK later in life, this could significantly influence the recommended care and referral pattern worldwide by providing counseling on any associated health risks. □

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