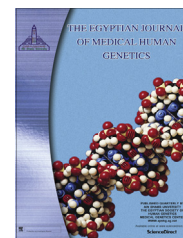




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REVIEW

# The scope of clinical morbidity in sickle cell trait



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**KEYWORDS**

Sickle cell trait;  
Morbidity;  
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Rhabdomyolysis;  
Thrombosis

**Abstract** Sickle cell trait (SCT), the heterozygous state of the sickle hemoglobin beta globin gene (HbAS) is carried by as many as 100 million individuals including up to 25% of the population in some regions of the World. Sickle cell trait is the best-characterized genetic polymorphism known to protect against falciparum malaria. Although SCT was initially considered as a benign condition, data are accumulating of serious morbidities in SCT individuals including increased incidence of hematuria, renal papillary necrosis, renal failure and malignancy, thromboembolic disorders, splenic infarction as a high altitude complication, and exercise-related rhabdomyolysis and sudden death. Despite these associations, the average life span of individuals with sickle cell trait is similar to that of the general population. Nonetheless, given the large number of people with sickle cell trait, it is important that physicians be aware of these associations. The aim of this article is to review publications reporting and discussing morbidities in SCT individuals.

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## 1. Introduction

Sickle hemoglobin (HbS) is a structural variant of normal adult hemoglobin. Adult hemoglobin (HbA) is made up of two alpha and two beta globin chains. HbS is the result of a single point mutation (Glu → Val) on the sixth codon of the beta globin gene [1]. Homozygotes for hemoglobin S (HbSS) with two affected beta chains develop sickle cell disease, in which polymerized hemoglobin causes red blood cells to sickle and occlude blood vessels. Vaso-occlusion affects many organs and tissues, and results in high morbidity and mortality [1,2].

Individuals who are heterozygous for HbS are carriers of the sickle cell trait (SCT). Heterozygous individuals are not anemic and have normal red cell indices with hemoglobin S percentages typically near 40% [3]. They generally enjoy normal life spans without serious health consequences related to their sickle cell status, but under extreme conditions such as severe dehydration and high-intensity physical activity, complications such as exertional rhabdomyolysis, splenic infarction, and papillary necrosis can occur [4].

**Table 1** Adverse events associated with sickle cell trait [6–9].

<b>Exertional rhabdomyolysis, exercise-related sudden death</b>
<b>Spleen</b>
<i>Splenic infarction</i>
<b>Renal</b>
<i>Hyposthenuria</i>
<i>Hematuria</i>
<i>Papillary necrosis</i>
<i>Renal medullary carcinoma</i>
<i>Asymptomatic bacteriuria in pregnancy</i>
<b>Venous thromboembolic events</b>
<b>Pregnancy/perinatal outcome</b>
<i>Fetal loss</i>
<i>Low birth weight</i>
<i>Preeclampsia</i>
<i>Premature delivery</i>
<b>Complicated hyphema</b>

Sickle cell trait occurs in approximately 300 million people worldwide, with the highest prevalence of approximately 30–40% in sub-Saharan Africa [1].

In regions of the world where malaria is endemic, SCT confers a survival advantage in childhood malaria; this is thought to be a major selective pressure for persistence of the HbS mutation (Glu6Val). [5]

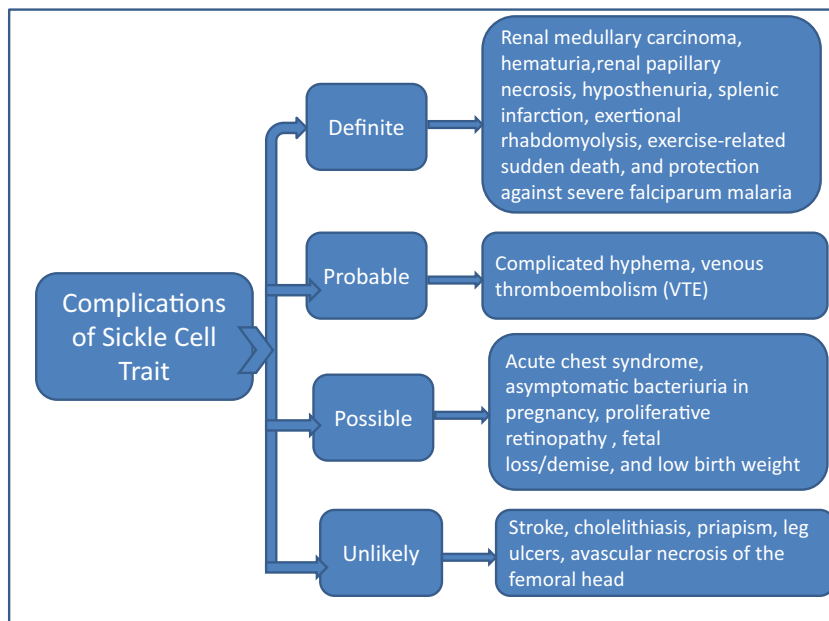
## 2. Morbid complications in sickle cell trait individuals

Early publications linked SCT to a wide variety of medical conditions, but many of these studies were small case series or uncontrolled observational studies [6,7].

Recently the current understanding of the complications of SCT [8,9] has been revisited, listing them as: (i) “definite”; (ii) “probable”; (iii) “possible”; and (iv) “unlikely” when there is insufficient evidence to suggest an independent association (Table 1 and Fig. 1). However, it should be noted that the assignment of complications into these categories was not based on a systematic review of the literature, and thus the importance of some of the conditions may have been overrated while others might have been underrated [4]. Despite these associations, the average life span of individuals with sickle cell trait is similar to that of the general population. Nonetheless, given the large number of people with sickle cell trait, it is important that physicians be aware of these associations.

## 3. Sickle cell trait and malaria

Sickle cell trait (SCT) is the best-characterized genetic polymorphism known to protect against falciparum malaria [8]. In a large follow up study including 800 children and adults in Kenya the results revealed that SCT had no impact on the prevalence of asymptomatic parasitemia, it was 50% protective against mild clinical malaria, 75% protective against hospital admission for malaria, and 90% protective against severe or complicated malaria [12].



**Figure 1** Classification of complications of sickle cell trait according to strength of reported associations [9–11].

Although the protective effect of SCT against malaria is well known, the mechanism(s) of protection remain unclear [1]. A number of biochemical and immune-mediated mechanisms have been proposed, and it is likely that multiple complex mechanisms are responsible for the observed protection [5]. Increased evidence for an immune component of protection involving the enhancement of both innate and acquired immunity to the parasite as well as novel mechanisms, such as enhanced tolerance to disease mediated by HO-1 [Hemeoxygenase-1] and reduced parasitic growth due to translocation of host micro-RNA into the parasite, have recently been described [13,14].

#### 4. Exercise, exertional rhabdomyolysis and sickle cell trait

SCT is an established risk factor for exercise-related rhabdomyolysis and sudden death. Exertional rhabdomyolysis (ER) can cause death in the general population [4]. The absolute risk in the general population and, more specifically, in persons with SCT, is not known [15].

##### 4.1. Pathophysiology and clinical manifestations of exertional rhabdomyolysis

ER is an acute clinical syndrome caused by the breakdown of striated skeletal muscle due to metabolic derangement or physical injury. Excessive muscular activity results in a state in which adenosine triphosphate (ATP) production cannot keep up with the demand, subsequently exhausting cellular energy supplies leading to a disruption of muscle cell membranes [16]. Clinical manifestations include severe pain, muscle tenderness or swelling, dark urine (myoglobinuria), and serum creatine kinase (CK) elevations; however, only 50% of patients have these classic findings at presentation [4,17].

The more strenuous or prolonged the exercise, the more damage is incurred in SCT individuals. Factors that increase the risk of exertional rhabdomyolysis are hypokalemia (often

resulting from excessive sweating), high altitude, extreme heat and humidity, exercise-induced asthma, or pre-exertion fatigue [16]. Noteworthy, rhabdomyolysis cases associated with low-intensity exercise have also been reported. In these cases the mechanism remains unknown [4,16].

Rhabdomyolysis (exertional and non-exertional) can have multisystem consequences or complications such as acute kidney injury, disseminated intravascular coagulopathy, hyperkalemia, and cardiac dysrhythmias [16,17].

##### 4.2. Other genetic factors predisposing to exertional rhabdomyolysis

Apart from SCT, other genetic factors, are likely to influence this diverse clinical spectrum of disease and response to exercise. Genetic mutations causative for McArdle disease, carnitine palmitoyl transferase deficiency 2, myoadenylate deaminase deficiency, and malignant hyperthermia have all been associated with ER [18]. Polymorphic variations in the myosin light chain kinase,  $\alpha$ -actin 3, creatine kinase-muscle isoform, angiotensin I-converting enzyme, heat shock protein, and interleukin-6 genes have also been associated with ER and increased risk of ER in SCT patients [19].

##### 4.3. Prevention and management of SCT related exertional rhabdomyolysis

Successful treatment of ER includes early detection, and immediate measures to prevent renal failure by rapid rehydration, and correction of hypovolemia and metabolic derangements [16,17].

#### 5. The splenic syndrome in sickle cell trait

Acute splenic syndrome is a rare but well-documented complication of SCT that can present in the setting of low oxygen tension that occurs with major changes in altitude, either by

unpressurized air flight or ground travel such as mountain climbing [20,21].

### 5.1. Pathophysiology and clinical manifestations of the splenic syndrome

The standard scenario of splenic syndrome in patients with SCT is as follows: patients usually do not know about their sickle cell genetic status, and most of them have never had any problems. Shortly after arrival to an area of high altitude, upper abdominal pain develops that soon localizes itself to the splenic region in the left hypochondrium. The spleen is usually enlarged from sequestration of red cells and becomes very tender from vaso-occlusion by sickled red cells, resulting in splenic infarction. The abdomen becomes rigid, with muscle guarding and, often, rebound tenderness [22,23]. In many of these patients pleural effusion can develop, especially on the left side, and a few can even have pulmonary infiltration [24]. Breathing thus becomes shallow, difficult and often painful, especially at the end of inspiration. Anemia may accompany this presentation, and reticulocyte count and serum lactate dehydrogenase enzyme levels may increase [24]. However, there are few reports describing acute splenic infarction in SCT patients in the absence of hypoxia, possibly related to infection, dehydration, drugs, and/or muscular exertion [25,26].

### 5.2. Management of SCT related splenic syndrome

Once a diagnosis of SCT is established, conservative measures could obviate surgical management [22]. Splenectomy should be discouraged in SCT patients presenting with splenic syndrome at high altitude. Supportive care should always be the primary treatment [21,24].

## 6. Renal complications in sickle cell trait

Renal abnormalities are among the most widely acknowledged complications of SCT [3]. They include hematuria, papillary necrosis, hyposthenuria, renal medullary carcinoma and asymptomatic bacteriuria in pregnancy [9].

### 6.1. Hematuria in SCT: pathophysiology and management

The renal medulla represents an acidotic environment characterized by low oxygen tension and high interstitial osmolarity. As blood traverses the slow-moving circuit of the medullary vasa recta, the hyperosmolar milieu may enhance dehydration of erythrocytes, allowing sickling in sickle cell disease and probable vaso-occlusion and medullary microinfarctions [27].

Hematuria is the most common manifestation of SCT, but its true incidence remains uncertain [28]. Spontaneous sickling can occur in the renal papilla (normally under low oxygen pressure) in patients with renal papillary necrosis; therefore, 5% of patients with sickle cell trait can suffer episodes of hematuria at some point during their lives [27,29]. Bleeding, is typically painless, presents as microscopic or gross bleeding and may be associated with renal papillary necrosis [30].

Conservative management of bleeding with bed rest and aggressive hydration is usually sufficient [28]. In refractory

cases, medical intervention with desmopressin, antifibrinolytic agents such as aminocaproic acid, aprotinin, oral urea or even invasive intervention with ureteroscopy or angiography, has been advocated. [31,32].

### 6.2. Hyposthenuria in sickle cell trait

The majority of SCT patients develop a progressive deterioration in the capacity for concentrating urine (hyposthenuria) and even isosthenuria which is directly related with the percentage of intra-erythrocyte HbS. Isosthenuria refers to the excretion of urine in which specific gravity is neither greater nor less than that of protein-free plasma, typically 1.008–1.012. Isosthenuria reflects renal tubular damage/failure of renal medullary function [27,33]. The degree of impairment of urinary concentration is also variable among subjects with SCT, and may be related to the percentage of hemoglobin S [3,8].

Microradiographs of the SCT kidney reveal reduction and disruption of the vasa recta, the intricate vascular system of the kidney responsible for generating an osmolar gradient. Although not as severe as those seen in SCD, these vascular changes likely lead to the observed impairment of urinary concentration in patients with SCT [34].

### 6.3. The risk of progressive nephropathy in sickle cell trait

Conflicting reports exist as to whether sickle cell trait is a risk factor for the progression of nephropathy and the risk of end stage renal disease [35–37].

Derebail et al. [36] reported that among 5319 African–American patients with end-stage renal disease (ESRD) on hemodialysis, 542 (10.2%) patients had sickle cell trait. Sickle cell trait was more common in this cohort than the general African–American population (10.2% vs. 6.5–8.7%, respectively,  $P < 0.05$ ). They suggested that the higher prevalence of SCT in the ESRD population raises the possibility that these hemoglobinopathies contribute to a decline in kidney function, either alone or in conjunction with other known risk factors for renal disease.

However, Hicks et al. [37] demonstrated that sickle cell trait was not associated with diabetic or non-diabetic ESRD in a large sample of African Americans.

## 7. Renal medullary carcinoma in sickle cell trait

Renal medullary carcinoma (RMC) is a rare neoplasm of the kidney that has been first described in 1995 [38]. It is almost exclusive to young patients and associated with sickle cell hemoglobinopathy, mainly sickle cell trait and hemoglobin SC disease [39].

### 7.1. Pathogenesis and clinical presentation of renal medullary carcinoma

Chronic ischemia has been suggested as a predisposing factor related to constant regeneration of the distal collecting duct epithelium giving rise to malignant transformation [3,35], although reports of RMC in sickle cell anemia are very rare [40].

Although initially described in adults with mean age of 21 years, there are increasing reports of this rare cancer in childhood age [41]. Most patients present with the triad commonly seen in renal carcinoma, that is, gross hematuria, flank pain, and a palpable abdominal mass. Regional lymphadenopathy is common at presentation, as is distant metastatic disease to liver, lung, pleura, or omentum [42].

### 7.2. Prognosis of renal medullary carcinoma

The prognosis of RMC is very poor because of the highly aggressive behavior of this neoplasm and its resistance to conventional chemotherapy [38]. Metastatic disease is almost universal at the time of presentation, and the malignancy is minimally responsive to a variety of regimens and/or modalities, including surgery, radiotherapy, chemotherapy, and biological immune-modulation therapy. [42,43].

## 8. Thrombo-embolic events and sickle cell trait

Sickle cell disorders, such as Hb SS and Hb SC, are associated with a hypercoagulable state that may contribute to the vaso-occlusive episodes observed in these disorders [44]. However, the epidemiologic evidence to support increased thromboembolic events in SCT has been sparse until recently [8].

### 8.1. Coagulopathy in sickle cell trait

An interesting study [45] demonstrated that individuals with SCT had increased coagulation activity, with d-dimers, thrombin-antithrombin (TAT) complexes, prothrombin fragment 1.2 being consistent indicators of coagulation activation. However, the measured markers of coagulation activity in SCT (Hb AS) were lower than in patients with Hb SC and Hb SS disease. Their findings suggested that monocytosis, with the possible expression of monocyte-derived tissue factor, are contributing factors to the associated hypercoagulable state. A recent study [46] demonstrated elevated soluble CD163 as a marker of monocyte activation in asymptomatic SCT individuals, although the levels were less than in sickle cell disease (HbSS) patients, in whom it was significantly related to the severity of sickle cell vasculopathy and vaso-occlusive crises.

Lawrie et al. [47] investigated two sibs, a set of monozygotic twins with SCT, to establish their procoagulant activity status as a potential indicator of thrombotic risk. Markers of coagulation activation were markedly elevated in one patient but within the normal in the other patient, although flow cytometric analysis for RBC-derived microparticles showed elevated levels in both patients on two occasions. They suggested that there may be two levels of hypercoagulability in SCT. Measurement of such differences would allow for separation of individuals at high or low-risk for serious complications.

### 8.2. Epidemiological studies of thrombo-embolic events in SCT

Recent published data [33] including analysis of a total of 13,964 adult African Americans registered in the Kaiser Permanente Northern California (KPNC) health system (Oakland, CA, USA), including 2642 with sickle cell trait, 11,183 with normal hemoglobin (Hb) and 139 with sickle cell

disease revealed that the adjusted relative risk of pulmonary embolism in sickle cell trait patients compared to patients with normal Hb was 1.37 [95% confidence interval (CI) 1.07–1.75].

Austin 2007 [48] conducted a case-control study of venous thromboembolism that included 515 hospitalized black patients and 555 black controls obtained from medical clinics. They found that the risk of venous thromboembolism is increased approximately 2-fold among blacks with sickle cell trait compared with those with the normal genotype (odds ratio = 1.8 with 95% confidence interval, 1.2–2.9). The odds ratio for pulmonary embolism and sickle cell trait was higher, 3.9 (2.2–6.9). They concluded that sickle cell trait is a risk factor for venous thromboembolism (VTE) and that the proportion of venous thromboembolism among blacks attributable to the mutation is approximately 7%. Later on [49] the authors reported that hormonal contraceptive use increases venous thromboembolism risk among women with sickle cell trait.

### 8.3. Thromboembolic events and pregnancy in sickle cell trait

A recent retrospective cohort study [50] included 22,140 black American women with hemoglobin (Hb) AA status, and 2037 women with SCT studied during pregnancy or the puerperium. They reported that the relative risk (RR) of VTE for the association with SCT status = 1.6; 95% confidence interval (CI) 0.5 to 5.5 compared to RR = 32.2, 95% CI 9.7 to 107 in the presence of Hb SS or SC disease. They concluded that sickle cell trait may be associated with a modest increase in VTE in the setting of pregnancy

However, in a large recent study, Pintova et al. [51] studied 12,429 women, 679 non-Hispanic SCT black women, 5465 non-Hispanic Hemoglobin AA black women and 1162 non-Hispanic HbAA white women were included in the analysis. Proportions with VTE were similar for black SCT and black HbAA groups. There was no increase in the incidence of pulmonary embolism in the SCT group. They could not detect a meaningful difference in peripartum VTE incidence between women with and without sickle cell trait.

## 9. Perinatal and maternal outcomes in women with sickle cell trait

Although early studies [6,9] reported increased fetal loss and preeclampsia in women with SCT. In a recent large study, perinatal mortality and preeclampsia were not increased in carriers of sickle cell trait, as well as the risks of stillbirths and pregnancy-associated hypertension were not increased [10]. Similarly, a systematic search study in the Cochrane Library, Medline, EMBASE and CINAHL databases reported no significant effect of SCT for low birth weight, growth retardation, or hypertension; only the risks of anemia and bacteriuria were increased [11].

## 10. Sickle cell trait and the eyes

Sickle trait is traditionally considered a benign condition by ophthalmologists. Patients with sickle trait are at risk of retinopathy if coincident ocular trauma or systemic disease is present [52,53].

### 10.1. Pathogenesis of complicated hyphemas in sickle cell trait

Sickle cell trait is a significant risk factor for complicated traumatic hyphemas following blunt trauma, because of increased risk of secondary hemorrhage, anterior and posterior synechiae, increased intraocular pressure, and glaucomatous optic atrophy, and permanent visual impairment [54,55].

The possible explanation is that there is more sickling of erythrocytes in the aqueous humor of the eye in vivo and in vitro than in venous blood. This difference is dependent on the concentration of HbS in the erythrocytes as well as the anterior chamber environment. In SCT, there is delay in the resolution of anterior chamber hyphema due to sickling of erythrocytes and subsequent obstruction within the trabecular meshwork and Schlemm's canal leading to rise in intraocular pressure and the production of secondary glaucoma [6].

## 11. Other potential morbidities in sickle cell trait

### 11.1. Priapism

Priapism reported in SCT is rare, the recently reported cases in literature were associated with another predisposing factor mostly drugs or co-morbid conditions like surgery or thrombophilia [56–59].

### 11.2. Cerebral stroke

The increased risk of cerebral stroke in sickle cell trait is a subject of debate [60,61]. In a large retrospective study, Bucknor [33] reported no increased risk of ischemic stroke in sickle cell trait patients compared to patients with normal Hb. Most reported cases in the literature are adults, very few childhood cases, co-morbidities could play important additional predisposing factors [62,63].

### 11.3. Acute chest syndrome

There are sporadic reports in the literature of acute chest syndrome in SCT individuals, mostly precipitated by exposure to heat, dehydration or infection. In these situations high fatality is related to previously undiagnosed SCT condition delaying proper management mainly with hydration, metabolic corrections and in severe conditions, exchange transfusion is life saving [64,65].

### 11.4. Osteonecrosis

Osteonecrosis of the femoral head and leg ulcers caused by sickle cell trait are very rarely reported and only in old references [66–69].

## 12. Conclusions

Although the average life span of individuals with sickle cell trait is similar to that of the general population, the condition may be associated with serious life threatening morbidity. Awareness of the individual and the treating physician of the sickle cell carrier state is important, to take preventive measures and to intervene properly and early in critical situations.

Early accurate diagnosis and proper management will reduce the risk of long term morbid sequelae and mortality. Further research studies are needed to identify the potential genetic modifiers of phenotypic expression of SCT and the impact of co-morbid conditions such as asthma or diabetes mellitus on the clinical outcomes in individuals with SCT, as well as possible genetic or non genetic risk factors that predispose SCT individuals to thrombotic events. Other potential complications and aspects of SCT morbidity should be further investigated, including renal and coagulation complications and the importance of access to genetic counseling.

## Conflict of interest

The author has nothing to declare.

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