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Pharmacological and Nursing Perspectives on the Management and Counseling of Individuals with Sickle Cell Trait

Abdulghafur Abdu A Arishi[(1)], Waleed Ibrahim Ali Alfarhan[(2)], Hind Mohammed Ghaythan Alshehri[(3)], Abdullah Mohammed Bariq Al-Qarni Al-Suhaimi[(4)], Ghaida Adel Safta[(5)], Samirah Ali Ali Mahnashi[(6)], Thekra Bandar Khalid Albahuth[(7)], Ayed Shabeeb Sh Almotairy[(8)], Munirah Ayedh Abdullah Alhuzari[(9)], Naif Mdhi Rafa Al Shammari[(10)], Adel Saad Saeed Alzahrani [(11)], Zahraa Mohammed Alshehri[(12)], Awatif Wli Hakami[(13)]

[(1)]*Emergency Operation Center of Jazan, Ministry of Health, Saudi Arabia*
[(2)]*Eastern Province Branch, Ministry of Health, Saudi Arabia*
[(3)]*Aseer Health Cluster,Alnamas General Hospital, Primary Healthcare Sector, Ministry of Health, Saudi Arabia*
[(4)]*King Abdulaziz Hospital, Jeddah, Ministry of Health, Saudi Arabia*
[(5)]*King Abdullah Medical Complex, Jeddah, Ministry of Health, Saudi Arabia*
[(6)]*Ministry of Health, Saudi Arabia*
[(7)]*King Salman Hospital, Ministry of Health, Saudi Arabia*
[(8)]*Rumah Hospital, Ministry of Health, Saudi Arabia*
[(9)]*Second Health Cluster Riyadh, Ministry of Health, Saudi Arabia*
[(10)]*Irada Mental Health Complex Hail, Ministry of Health, Saudi Arabia*
[(11)]*Mental Health Hospital In Jeddah, Ministry of Health, Saudi Arabia*
[(12)]*Long Care Hospital, Ministry of Health, Saudi Arabia*
[(13)]*Ahad Almasarha, Ministry of Health, Saudi Arabia*

Abstract

Background: Sickle cell trait (SCT) is a common inherited hemoglobin variant, traditionally considered a benign condition. It is caused by heterozygosity for the hemoglobin S (HbS) gene. While most carriers are asymptomatic, emerging evidence indicates that specific physiological stressors can unmask serious complications.

Aim: This article synthesizes the current understanding of SCT, aiming to clarify its pathophysiology, epidemiology, and potential health risks. It seeks to outline best practices for the management, counseling, and interdisciplinary care of individuals with SCT to prevent morbidity and mortality.

Methods: A comprehensive review of SCT was conducted, encompassing its genetic etiology, pathophysiology of sickling under stress, and epidemiological distribution. The evaluation and management strategies are detailed, including laboratory diagnosis, differential diagnosis, patient education, and the specific roles of pharmacists and nurses in an interprofessional team.

Results: Under conditions like dehydration, hypoxia, or extreme exertion, individuals with SCT are at risk for complications including exertional rhabdomyolysis, renal papillary necrosis, hematuria, splenic infarction, and thromboembolic events. While life expectancy is normal, targeted education and preventive strategies are crucial to mitigate these risks. Effective management hinges on genetic counseling, especially for reproductive planning, and proactive surveillance for renal and exertional issues.

Conclusion: SCT is not a benign state but a condition with conditional risks. A proactive, interprofessional healthcare approach is essential for patient education, complication prevention, and genetic counseling to improve outcomes.

Keywords: Sickle Cell Trait, Hemoglobin S, Vaso-occlusion, Genetic Counseling, Exertional Rhabdomyolysis, Patient Education, Interprofessional Care.

1. Introduction

Sickle cell trait arises when a person inherits one hemoglobin A gene and one hemoglobin S gene producing an AS genotype. Sickle cell disease results when a person inherits two sickle hemoglobin genes producing an SS genotype. Variants of sickle cell disease include hemoglobin SS HbSS hemoglobin SC HbSC and hemoglobin S beta-thalassemia. These genotypes can produce red blood cell sickling and vaso-occlusion. HbSS accounts for the largest share of severe disease. HbSC occurs when a person inherits HbS from one parent and HbC from the other. HbC reflects a single amino acid substitution in the beta chain from glutamic acid to lysine. HbS beta-thalassemia denotes coinheritance of HbS and a beta-thalassemia allele. The presence of abnormal hemoglobin alone does not cause vaso-occlusion. Vaso-occlusion emerges from a chain of pathophysiologic events that include red cell deformation altered membrane stability increased

*Corresponding author e-mail: Abdulghafura@moh.gov.sa (Abdulghafur Abdu A Arishi).

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cation flux and enhanced cell adhesion. [1] Sickle cell disease constitutes a persistent public health burden. Clinicians first described the disorder in 1910. Genetic analysis clarified the molecular basis in the mid twentieth century. The disease produces chronic anemia progressive organ injury and reduced life span. Patients with disease experience recurrent vaso-occlusive episodes that impair daily functioning and lower quality of life. By contrast sickle cell trait usually follows a benign course. Most people with the trait do not develop vaso-occlusive crises. Life span approximates that of the general population. Clinical absence of frequent crises explains the customary view that the trait lacks major health impact. Reports have documented however that specific stressors can unmask sickling related complications in carriers. [1]

Physiologic stressors that favor red cell sickling include severe hypoxia volume depletion and abrupt shifts in autonomic tone. Thermal extremes and marked changes in 2 3-diphosphoglycerate levels can also promote polymerization of deoxygenated hemoglobin S. Inflammatory states that release activated leukocytes or alter the microvascular environment may further increase the risk of localized sickling. Under these conditions carriers may develop muscle ischemia that presents cramping weakness or a dull deep ache within minutes of exertion. This pain results from reduced perfusion to skeletal muscle and differs clinically from exertional heat illness. Athletes who have these symptoms require assessment for a sickling exacerbation until that diagnosis is excluded. Additional presentations linked to intra vascular sickling include left upper quadrant abdominal pain pleuritic chest pain chest tightness and dyspnea. Clinicians must treat these symptoms with the possibility of red cell sickling in mind. [1] Diagnosis of sickle cell trait relies on screening followed by confirmatory testing. Newborn screening programs expanded after enactment of the Sickle Cell Anemia Act in 1972. Today each state in the United States typically performs universal newborn screening before hospital discharge. Screening tests that yield positive results require confirmation. Hemoglobin electrophoresis remains the standard confirmatory method in clinical laboratories. Genetic testing can establish genotype when electrophoresis results are equivocal or when counseling requires precise molecular detail. [2]

Management of sickle cell trait focuses on reversing the circumstances that trigger sickling and on treating complications when they arise. Routine therapy aimed at preventing vaso-occlusion is not indicated for carriers. Interventions should target dehydration hypoxemia and other modifiable triggers. Clinicians must also identify and manage medical conditions that coexist with the trait and that may precipitate sickling related events. When a patient presents with hematuria renal papillary necrosis or other organ specific manifestations clinicians should initiate condition specific treatment promptly and address underlying contributors to red cell sickling. [1][3] Awareness of the potential complications associated with sickle cell trait supports timely diagnosis and effective management. Health professionals must incorporate screening results into counseling renal and sports medicine recommendations and perioperative planning. Providers should educate carriers about exposure risks that may increase their chance of sickling under stress. They should also maintain a low threshold for targeted evaluation when carriers present with compatible signs or symptoms. These steps permit early intervention and reduce the likelihood of preventable morbidity. [1][3]

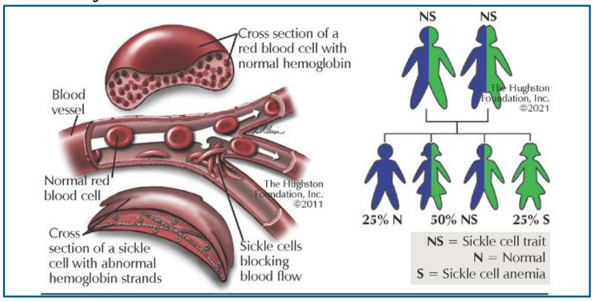

Figure-1: Sickle cell trait.

Etiology:

Sickle cell trait results from a specific mutation in the beta-globin gene that alters the structure of hemoglobin. A single nucleotide substitution at codon six of the beta-globin gene replaces adenine with thymine. This base change converts the codon that normally encodes glutamic acid into a codon that encodes valine. The resulting hemoglobin variant is designated hemoglobin S. When hemoglobin S is present alongside normal hemoglobin A the genotype is heterozygous and is termed sickle cell trait. Individuals with this genotype inherit the HbS allele from one parent and the HbA allele from the other. The valine residue introduced by the mutation alters the physicochemical properties of the beta chain. Under conditions of reduced oxygen tension the deoxygenated form of hemoglobin S undergoes a conformational change that promotes polymer formation. Polymerized hemoglobin S distorts the red blood cell membrane and produces the characteristic sickled shape. Sickling in trait carriers occurs more readily when red cells are exposed to low oxygen levels or other environmental stressors that reduce intracellular oxygen content. In the heterozygous state the proportion of hemoglobin S is lower than in homozygous disease, which reduces the baseline risk of widespread polymerization and clinical vaso-occlusion. Nonetheless the molecular mechanism that links the point mutation to polymer formation and cell deformation is the same in trait and disease [3]. Genetic transmission follows Mendelian inheritance. A parent who carries the HbS allele has a 50 percent probability of transmitting that allele to each child. When both parents carry HbS the risk of having a child with sickle cell disease increases.

Genetic testing and hemoglobin analysis permit definitive identification of the HbS allele and distinction between trait and disease [3].

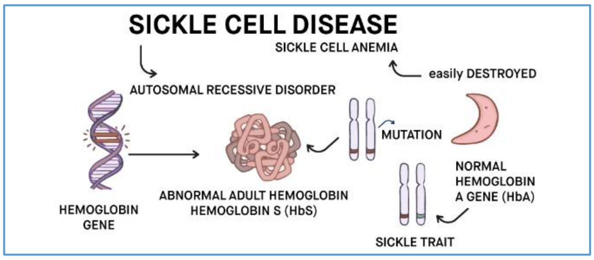

Figure-2: Sickle cell etiology.

Epidemiology:

Sickle cell trait concentrates in populations whose ancestors lived where Plasmodium falciparum malaria was endemic. Natural selection favored the heterozygous genotype because it confers relative protection against severe malaria. As a result, the trait persists at high frequency in parts of sub Saharan Africa the Arabian Peninsula and portions of the Indian subcontinent and Mediterranean basin. Migration from these regions distributed the trait more widely and produced measurable prevalence in diasporic communities across Europe the Americas and other regions. In the United States the trait occurs disproportionately among African American individuals. Large population surveys estimate a prevalence near nine percent in this group and a substantially lower prevalence among persons of European ancestry, near 0.2 percent. Population specific screening programs and newborn screening data document these differences and provide the primary sources for national prevalence estimates [4]. Global estimates project that roughly three hundred million people carry the sickle cell allele. These carriers predominate in sub Saharan Africa where approximately one third of the global SCT burden is located. Country level surveys and community based studies in Africa frequently report heterozygosity rates that approach or exceed twenty five percent in focal areas with intense malarial selection pressure [5].

Regional pockets with exceptionally high trait frequencies occur where historical malaria exposure was intense and where population structure limited gene flow. Epidemiologic surveys published from the Arabian Peninsula reported unusually high carriage rates in selected communities consistent with founder effects and local demographic history. One study cited carrier rates that reached up to sixty percent in particular subpopulations in Saudi Arabia though such high figures represent localized clusters rather than national averages [4]. These data indicate that national prevalence measures can mask substantial within country variation. Contemporary population movement amplifies the public health importance of SCT outside traditionally affected regions. International migration refugee movements and labor mobility transport the HbS allele to low prevalence settings and increase the number of heterozygotes who encounter health systems unaccustomed to S hemoglobin disorders. Demographic projections therefore predict a rise in the absolute numbers of carriers and affected births in parts of Europe and the Americas driven by migration from Africa and the Middle East [6]. This shift has implications for screening counseling reproductive planning and the allocation of clinical resources in host countries.

Pathophysiology:

Sickle cell trait generally remains asymptomatic because the proportion of hemoglobin S in red cells is low and insufficient to promote widespread polymerization under normal oxygen tension. In the heterozygous state, red blood cells contain both hemoglobin A and hemoglobin S, and hemoglobin A exerts a protective dilutional effect that reduces hemoglobin S polymer formation. Consequently, vaso-occlusive crises, which characterize sickle cell disease, are uncommon in individuals with sickle cell trait. However, under certain environmental or physiological stresses, sickling can occur and produce clinical manifestations similar to those observed in sickle cell anemia. [1] When oxygen tension decreases beyond a critical threshold, deoxygenated hemoglobin S undergoes a conformational change that promotes polymer formation within the erythrocyte. This intracellular polymerization distorts the normally pliable biconcave shape of the red cell into a rigid, elongated sickle form. Sickled cells demonstrate reduced deformability, impaired passage through the microvasculature, and a tendency to adhere to the endothelium. These changes promote mechanical obstruction within small vessels, limiting tissue perfusion and oxygen delivery. Hypoxia, dehydration, and acidosis exacerbate this process by increasing intracellular hemoglobin concentration and favoring polymerization. The consequence is localized ischemia that can affect multiple organs, including skeletal muscle, kidneys, lungs, and the spleen. Systemic stressors such as intense physical exertion, exposure to high altitude, or extreme temperatures can precipitate sickling episodes in individuals with the trait. Hyperthermia or hypothermia disrupts red cell metabolism, while increased sympathetic activation elevates circulating catecholamines, leading to vasoconstriction and reduced tissue oxygenation. Elevated levels of 2,3-diphosphoglycerate (2,3-DPG) shift the oxygen dissociation curve to the right, further decreasing oxygen affinity and enhancing deoxygenation of hemoglobin S. These physiologic disturbances create a microenvironment that facilitates sickling even in carriers who otherwise maintain normal function under baseline conditions. [1]

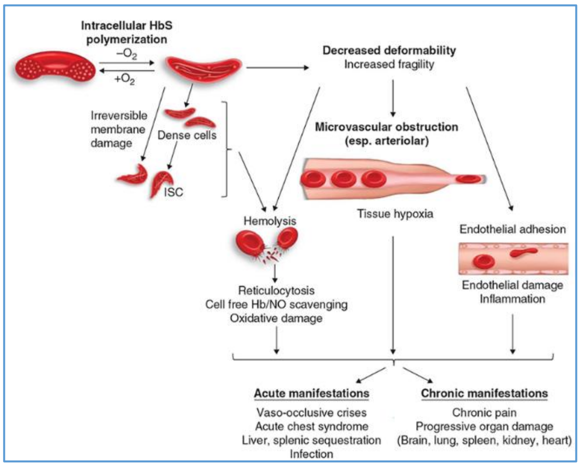

Figure-3: Sickle cell pathophysiology.

Beyond the erythrocytes, endothelial and inflammatory cell interactions amplify vascular occlusion. Activated leukocytes and platelets release adhesion molecules and inflammatory mediators that enhance the binding of sickled cells to the vascular endothelium. This adhesion initiates a cascade of vascular obstruction and local inflammation. Repeated ischemic episodes can lead to microinfarction and organ dysfunction, most commonly affecting the kidneys, muscles, and lungs. In severe or prolonged stress, tissue necrosis may develop due to sustained hypoperfusion. [1] Over time, recurrent microvascular obstruction may produce subclinical organ damage. Renal medullary hypoxia, for example, predisposes to papillary necrosis and microscopic hematuria, which are recognized complications of sickle cell trait. Musculoskeletal ischemia may manifest exertional pain, weakness, or rhabdomyolysis, particularly during intense physical activity. Although the condition remains largely benign, the same molecular mechanism underlying sickle cell disease—hemoglobin S polymerization—serves as the foundation for potential complications when environmental or physiological stressors exceed the adaptive capacity of red cells containing hemoglobin S. [1]

Histopathology

In individuals with sickle cell trait, microscopic examination of peripheral blood typically reveals red blood cells with a normal biconcave disk morphology under resting physiological conditions. The presence of hemoglobin A alongside hemoglobin S maintains normal cell deformability and prevents spontaneous sickling under adequate oxygenation. The peripheral smear of an asymptomatic carrier is therefore indistinguishable from that of a healthy individual without the sickle allele. No morphologic abnormalities are usually evident unless the sample is subjected to deoxygenation or other forms of oxidative stress. When erythrocytes from a carrier are exposed to hypoxic or oxidative conditions, structural changes become apparent. Under such stress, hemoglobin S molecules within the red cells undergo polymerization, which distorts the normal cytoskeletal structure. The affected cells assume an elongated or crescent-like configuration known as a drepanocyte or sickle cell. These morphological changes are reversible in the early stages if oxygen levels are restored. However, repeated or prolonged episodes of deoxygenation cause irreversible membrane damage, resulting in a subpopulation of permanently sickled cells even after reoxygenation. Such findings are more pronounced in individuals with a higher proportion of hemoglobin S or during severe physiologic stress.

In experimental laboratory settings, sodium metabisulfite or other reducing agents can induce sickling in vitro, demonstrating the latent potential for hemoglobin S polymerization in carriers. During significant sickling episodes, bone marrow response to hemolysis may lead to a transient increase in reticulocyte count, reflecting compensatory erythropoietic activity. The bone marrow architecture itself remains normal unless repeated ischemic insults occur, which is rare in trait carriers. The absence of chronic hemolysis or marrow hyperplasia distinguishes sickle cell trait from sickle cell disease. Tissue sections from individuals with sickle cell trait seldom show pathologic alterations unless an ischemic event has taken place. When present, histologic examination of affected organs may demonstrate focal vascular congestion, localized microinfarction, or evidence of hypoxic injury within the renal medulla, skeletal muscle, or splenic tissue. These findings result from transient microvascular occlusion by sickled erythrocytes during episodes of extreme physiologic stress. Overall, the histopathologic hallmark of sickle cell trait remains the potential for red cell sickling under deoxygenated conditions, rather than persistent structural abnormality in the absence of stress.

History and Physical:

The clinical evaluation of a patient with suspected sickle cell trait begins with a comprehensive history and physical examination aimed at identifying risk factors, precipitating conditions, and potential complications. A detailed family history is essential, as many patients with sickle cell trait have relatives diagnosed with sickle cell disease (HbSS) or other hemoglobinopathies. This background often provides the first indication of carrier status, especially in individuals from high-prevalence populations or with ancestral origins in regions where malaria was historically endemic. [7] Unlike patients with sickle cell disease, individuals with sickle cell trait are usually asymptomatic. Their hemoglobin S levels generally remain below 35%, which limits the extent of hemoglobin polymerization and red cell sickling under normal oxygen conditions. As a result, their clinical presentation resembles that of individuals with normal hemoglobin genotypes. They do not experience vaso-occlusive crises, chronic anemia, or recurrent pain episodes characteristic of sickle cell disease. In most cases, the diagnosis of sickle cell trait is incidental, discovered through routine screening, pre-employment evaluations, or blood donation testing. [7]

However, under specific stress conditions—such as intense physical exertion, dehydration, high ambient temperature, hypoxia, or high altitude—individuals with sickle cell trait may develop symptoms resulting from transient red cell sickling. The most common presentations include hematuria and exertional rhabdomyolysis. Hematuria arises from renal papillary necrosis caused by localized microvascular occlusion within the renal medulla, an area highly susceptible to hypoxia and acidosis. Exertional rhabdomyolysis, on the other hand, results from ischemic injury to skeletal muscle during strenuous activity, especially in hot or high-altitude environments. [8][9] A careful history should explore the nature and timing of symptoms, their relationship to physical exertion, hydration status, environmental temperature, and altitude exposure. Patients may describe early fatigue, muscle cramps, weakness, or a dull ache developing within minutes of vigorous activity. This pattern of pain differs from that of heat stroke, which is associated with confusion, loss of consciousness, or core temperature elevation. In contrast, sickling-related pain reflects reduced muscle perfusion and hypoxia rather than systemic hyperthermia. Clinicians should also inquire about prior similar episodes, as recurrence under similar conditions supports a diagnosis of sickling exacerbation. [1]

On physical examination, patients with sickle cell trait undergoing a sickling episode may appear alert but fatigued, with localized muscle weakness affecting large muscle groups such as the calves, quadriceps, hamstrings, or gluteal muscles. These muscles are often firm but not diffusely tender or hypertonic, distinguishing the condition from exertional heat cramps. Signs of dehydration, such as dry mucous membranes, tachycardia, or hypotension, may also be present and are important contributing factors to sickling-related complications. [1] Cardiorespiratory assessment may reveal tachypnea, mild chest discomfort, or chest tightness due to transient pulmonary microinfarction or vascular occlusion. However, confusion, syncope, or altered mental status is uncommon and should prompt evaluation for alternative diagnoses such as heat stroke, cardiac arrhythmia, or electrolyte imbalance. Abdominal examination may identify tenderness in the upper left quadrant, reflecting splenic ischemia or infarction. In rare cases, splenic enlargement or acute splenic sequestration may occur in unacclimatized individuals exposed to high altitudes. [1]

Clinicians should also consider the broader spectrum of complications associated with sickle cell trait during assessment. Findings suggestive of venous thromboembolism, pulmonary embolism, or chronic kidney disease warrant further evaluation, as these conditions occur at higher frequencies among individuals with the trait. [10] Laboratory investigations may include urinalysis to detect hematuria or myoglobinuria, serum creatine kinase for rhabdomyolysis, and imaging studies if thromboembolic events are suspected. Pulse oximetry and arterial blood gas analysis can help assess oxygenation status, especially in cases involving exertional collapse. Overall, the history and physical examination play a pivotal role in identifying symptomatic sickle cell trait. A precise understanding of the patient's activities, environmental exposures, and hydration status, combined with targeted examination findings, allows clinicians to distinguish sickling events from other exertional or metabolic disorders. Early recognition and intervention can prevent progression to serious complications such as renal failure, rhabdomyolysis, or sudden death. [1][7][8][9][10]

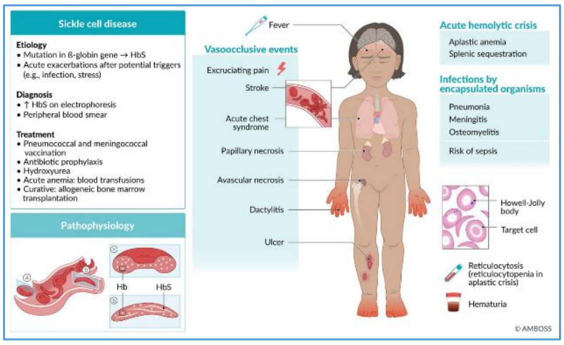

Figure-4: Sickle cell overview.

Evaluation

Assessment of sickle cell trait involves both genetic and laboratory-based testing strategies designed to identify carriers and guide appropriate counseling and clinical management. In the United States, a comprehensive screening framework has been established that differs from many developing countries. Pregnant women are routinely offered genetic testing to determine whether they or their fetuses carry the sickle cell allele. This approach allows for early identification of at-risk pregnancies and informed reproductive decision-making. Additionally, all fifty states mandate universal newborn screening for sickle cell disease and sickle cell trait before hospital discharge. This national public health measure ensures that affected infants are identified shortly after birth, enabling early follow-up, counseling, and preventive care interventions [5]. Initial laboratory screening for sickle cell trait commonly employs the sickling test, a simple procedure that detects the presence of red cells capable of forming sickled shapes under deoxygenated conditions. In this test, a drop of blood is mixed with a reducing agent and examined microscopically. The observation of sickled cells suggests the presence of hemoglobin S. While this method is inexpensive and rapid, it lacks specificity and requires confirmation. Confirmatory testing is performed using hemoglobin electrophoresis, which separates hemoglobin fractions based on their electrical charge. This analysis quantifies the proportions of hemoglobin A, hemoglobin S, and other variants within the sample. Individuals with sickle cell trait typically exhibit both hemoglobin A and hemoglobin S, with the latter representing less than 40% of the total hemoglobin. Modern diagnostic laboratories may also use high-performance liquid chromatography (HPLC) or molecular genetic testing for greater accuracy, particularly in prenatal and confirmatory testing [5].

Screening of blood donors for sickle cell trait was historically routine; however, many transfusion services have discontinued this practice, as the presence of hemoglobin S in donor blood is no longer regarded as a contraindication to transfusion. The focus has shifted toward ensuring that blood products meet safety and compatibility standards rather than excluding donors based on carrier status [11]. Beyond diagnosis, evaluation of patients with sickle cell trait should include assessment for potential comorbidities, as the condition is associated with increased risk of certain complications. Chronic kidney disease represents one of the most significant long-term risks. Carriers may develop renal medullary ischemia and papillary necrosis due to intermittent sickling in the hypoxic environment of the renal medulla. Consequently, annual renal function testing—including serum creatinine, urinalysis, and blood pressure monitoring—is recommended for early detection of renal impairment. Persistent hematuria warrants further evaluation with renal ultrasound or contrast-enhanced computed tomography (CT) to exclude structural lesions. Notably, sickle cell trait has been linked to an elevated incidence of renal medullary carcinoma, a rare but aggressive malignancy that occurs almost exclusively in individuals with hemoglobin S. Therefore, any unexplained hematuria or flank pain should prompt immediate imaging and urologic consultation [12]. Comprehensive evaluation of sickle cell trait extends beyond identification of carrier status. It requires ongoing surveillance for renal and vascular complications, particularly in individuals exposed to physiologic stress or with additional comorbidities. Through systematic screening, confirmatory testing, and preventive assessment, clinicians can reduce the risk of undetected complications and provide accurate counseling for patients and their families [5][11][12].

Treatment / Management

Patients with sickle cell trait require no baseline therapy when they lack symptoms. Care focuses on preventing and reversing factors that provoke red cell sickling. Clinicians intervene when dehydration hypoxia or other stressors threaten oxygen delivery. Treatment targets restoration of volume oxygenation and correction of metabolic derangements. Clinicians also treat medical conditions that interact with the trait and raise the risk of complications. When sickling occurs, management follows standard supportive measures. Rapid assessment of airway breathing and circulation precedes specific actions. Provide supplemental oxygen if hypoxia is present. Initiate intravenous fluids to restore intravascular volume and reduce blood viscosity. Monitor electrolytes and acid base status and correct abnormalities that promote sickling. Manage pain with analgesics and escalate care if pain control fails. Evaluate rhabdomyolysis and treat with aggressive hydration and renal monitoring. Admit patients who show progressive organ dysfunction or markers of severe injury [12].

Clinicians must identify and treat organ specific complications linked to the trait. Hematuria warrants evaluation for renal papillary necrosis and imaging when indicated. Flank pain or persistent hematuria requires urologic assessment and renal imaging. Suspect venous thromboembolism when clinical features match and perform diagnostic testing without delay. Manage confirmed thrombotic events according to accepted anticoagulation protocols. Screen for and address chronic kidney disease through laboratory testing and blood pressure control. Early intervention limits progression of organ injury. Preventive strategies reduce risk in at risk populations. Athletes and military recruits should follow graded acclimation programs before exposure to high altitude or intense exertion. Emphasize steady hydration avoidance of exertion in heat and staged increases in activity intensity. Counsel patients to avoid situations that produce severe hypoxia dehydration or thermal extremes. Children with the trait should undergo annual clinical review that includes renal function assessment and nutritional laboratory tests such as iron folate and vitamin D when indicated. These measures support early detection of comorbidity and permit timely therapy. [12]

Pregnant women with sickle cell trait require targeted surveillance and prompt treatment of urinary tract infection. Perform urine culture each trimester to detect asymptomatic bacteriuria. Treat suspected or confirmed pyelonephritis early and with appropriate antibiotics. Assess hemoglobin levels and provide folic acid and iron supplementation when anemia or increased demand exists during pregnancy and lactation. Consider hemoglobinopathy testing for women planning pregnancy or presenting with anemia microcytosis or a family history of hemoglobin disorders or origin from regions with high prevalence of hemoglobinopathies. These steps inform reproductive counseling and perinatal management. [12] Counseling forms a central element of management. Offer genetic counseling to carriers and to partners when either parent carries the HbS allele. Communicate risks for offspring and options for prenatal diagnosis. Provide practical advice on activity hydration and fever management. Coordinate care across primary care sports medicine obstetrics nephrology and hematology when patients present with complications or complex needs. Documentation of carrier status assists future care planning and reduces diagnostic delay when acute events occur [12].

Differential Diagnosis

The diagnostic evaluation of an individual with suspected sickle cell trait requires systematic exclusion of hemoglobinopathies and myopathic or renal conditions that can mimic exertional or renal presentations. Laboratory differentiation begins with hemoglobin electrophoresis or high performance liquid chromatography to quantify hemoglobin fractions and distinguish heterozygous HbS carriage from homozygous sickle cell disease and compound heterozygous states such as HbSβ-thalassemia and HbSC. Beta thalassemia minor and beta thalassemia major produce microcytosis and alter hemoglobin A2 and F proportions; these patterns permit separation from isolated HbS heterozygosity when interpreted alongside red cell indices and genetic testing. Clinical overlap with sickle cell disease must be assessed by correlating genotype and phenotype because patients with HbS-related compound genotypes manifest recurrent vaso-occlusion and chronic hemolysis unlike typical carriers. Beyond hemoglobinopathies, differential considerations include causes of exertional muscle injury and collapse such as heat stroke, exertional rhabdomyolysis from metabolic myopathies, and exertional collapse related to cardiac arrhythmia or structural cardiac disease. These entities produce exertional pain, weakness, or collapse and require targeted evaluation including creatine kinase measurement, electrocardiography, and cardiac imaging when indicated. Hematuria in a carrier warrants exclusion of urologic sources including nephrolithiasis, urinary tract infection, glomerulonephritis, and malignancy; imaging and urinary analyses assist in this discrimination. Finally, thromboembolic disease should be considered in cases with unexplained chest pain or dyspnea; pulmonary embolus may mimic acute thoracic sickling and demands prompt diagnostic imaging. A combined approach using hemoglobin quantification, targeted laboratory assays, imaging, and clinical correlation ensures accurate differentiation between sickle cell trait and alternative diagnoses.

Prognosis

Sickle cell trait generally confers a favorable long term outlook when compared with sickle cell disease. Population studies indicate that carriers have life expectancy estimates that approximate those of the general population despite an elevated risk for a discrete set of complications such as renal papillary necrosis, hematuria, renal medullary carcinoma, exertional rhabdomyolysis, and increased risk of certain venous thromboembolic events. The absolute incidence of these outcomes remains low in most carrier cohorts. Mortality analyses demonstrate that the marked increase in in-hospital and disease related mortality observed in sickle cell disease is not seen in heterozygous carriers, which supports a generally benign prognosis for the majority of individuals with the trait [13][14]. Prognostic stratification rests on identification and mitigation of exposure to precipitating conditions. Carriers who avoid severe dehydration, prolonged hypoxia, high altitude without acclimation, and extreme exertional stress retain baseline health comparable to noncarriers. Conversely, exposure to known triggers increases the risk of acute events that can produce morbidity and, rarely, mortality. Long term renal monitoring is prudent because progressive renal impairment may develop insidiously in a subset of carriers; early detection and blood pressure control reduce progression to advanced kidney disease. Reproductive counseling also shapes prognosis for offspring by clarifying parental carrier status and informing prenatal diagnostic options. Overall, risk counseling should emphasize the low absolute probability of severe outcomes while acknowledging specific elevated risks. This balanced message guides clinical surveillance, occupational and athletic recommendations, and reproductive planning without overstating hazard. Empiric evidence supports a prognosis for carriers that aligns closely with population norms when patients receive appropriate preventive advice and targeted evaluation for symptoms. [13][14].

Complications

Although sickle cell trait is frequently characterized as a benign carrier state, accumulating clinical evidence indicates a spectrum of potential complications that can affect multiple organ systems. Carriers remain at risk for renal manifestations including hematuria resulting from papillary necrosis, progressive renal impairment culminating in chronic kidney disease, and a rare but highly aggressive neoplasm of the renal medulla. Extra-renal complications include splenic infarction, exertion-related morbidity such as rhabdomyolysis and sudden death, and an increased incidence of venous thromboembolic events in some cohorts. Female carriers also demonstrate a higher prevalence of asymptomatic bacteriuria. The absolute risk for many of these outcomes is low in population terms, however the presence of hemoglobin S in heterozygotes confers vulnerability to microvascular injury under physiologic stressors that reduce oxygen delivery or augment blood viscosity [5]. Renal papillary necrosis represents one of the more commonly reported complications among carriers. The lesion arises when red cell sickling occurs within the vasa recta and the microcirculation of the renal medulla, producing microthrombi and focal ischemic infarction of papillary tissue. Case series and observational data suggest that the likelihood of papillary necrosis correlates with the proportion of hemoglobin S present in the erythrocyte population, with higher HbS percentages associated with greater risk; patients with HbS fractions near or above one third have demonstrated a higher incidence relative to those whose HbS approximates one fifth [15]. Clinically affected individuals typically present with gross hematuria and variable flank or abdominal pain. Initial management is usually conservative and supportive, focusing on rehydration, analgesia, and avoidance of further hypoxic exposure. Prognosis is generally favorable when necrosis is limited to a single papilla owing to the preserved reservoir of viable renal tissue.

Splenic infarction in carriers follows the same pathophysiologic principle of deoxygenation induced polymerization of hemoglobin S and resultant vaso-occlusion. Exposure to hypoxic environments such as high altitude, combined with dehydration and acidemia, increases blood viscosity and favors red cell sickling within splenic microvasculature. Unlike many other manifestations that require precipitants, splenic infarction has been documented to occur at relatively low altitude in some individuals, suggesting that individual susceptibility and local hemodynamic conditions modulate risk [16]. Biochemical markers of hemolysis or splenic injury including elevated bilirubin and lactate dehydrogenase may accompany clinical events. Although occasional cases require splenectomy, most reports indicate that surgical removal is necessary in a minority of patients. Renal medullary carcinoma constitutes a distinct and ominous association with sickle cell trait. This malignancy typically presents with advanced local disease and early metastasis, often affecting young patients and showing an aggressive clinical course. Case reports document presentations with diffuse abdominal pain and widespread nodal involvement at initial diagnosis, underscoring the tumor’s rapid progression and poor prognosis when detected at late stages [17]. The pathogenesis is not fully elucidated but is hypothesized to relate to chronic hypoxia and recurrent microinfarction in the renal medulla creating a pro-oncogenic milieu. Chronic kidney disease among carriers has been increasingly recognized in epidemiologic studies, particularly in populations of African descent. Longitudinal analyses reveal a modest but statistically significant excess decline in glomerular filtration rate and a greater incidence of albuminuria in carriers compared with noncarriers [18]. Mechanistically, recurrent reversible sickling within the hypoxic renal medulla provokes microinfarction and tubular injury. This ischemic insult triggers release of vasoactive mediators induces glomerular hyperfiltration and ultimately promotes glomerulosclerosis and proteinuria. Quantitative estimates indicate an accelerated rate of GFR loss in carriers, supporting the need for periodic renal surveillance and early intervention to mitigate progression.

Exertional morbidity in carriers ranges from symptomatic muscle ischemia and rhabdomyolysis to rare instances of sudden death during intense physical exertion. Observational data in athletic populations report a markedly elevated relative risk of exertional death among affected individuals when compared with noncarriers in similar environments, a finding that prompted institutional screening policies in some athletic organizations [19]. Exertional rhabdomyolysis appears more frequent in carriers, with studies demonstrating a significantly higher incidence during strenuous activity [8]. These events likely arise from the confluence of increased metabolic demand, local hypoxia within skeletal muscle, dehydration, and enhanced red cell sickling. The relationship between sickle cell trait and outcomes in infectious or systemic inflammatory states has also drawn attention during the COVID-19 pandemic. Emerging analyses suggest an association between carrier status and increased mortality in COVID-19, with reported effect sizes indicating an elevated risk of death among heterozygotes [21][22]. The mechanisms may involve synergistic effects of viral hypoxemia, inflammation mediated endothelial activation, and an increased tendency for microvascular occlusion in the presence of hemoglobin S.

Taking together, these complications establish sickle cell trait as a condition with clinical relevance beyond simple genetic carriage. Risk is conditional, rising in contexts that provoke deoxygenation, hemoconcentration, acidemia, or inflammatory activation. Recognition of these vulnerabilities informs targeted preventive strategies, including avoidance of severe dehydration and hypoxic exposures, graded acclimatization to altitude, tailored exercise programs, and vigilant renal monitoring. While the population-level prognosis for carriers remains favorable relative to individuals with sickle cell disease, clinicians should maintain awareness of the specific, albeit infrequent, complications that can produce significant morbidity and occasionally mortality in heterozygous individuals [5][15][16][7][17][18][19][20][8][21][22].

Patient Education

Sickle cell trait affects many people of African descent. About nine percent of African Americans carry the trait. [4] Most carriers learn their status from newborn screening. Many never receive follow up testing as adults. As a result, most people of childbearing age do not know their status. Only sixteen percent know they carry the trait. [23] You need clear, direct information about what the trait means for your health and your family. Explain that carrying the trait usually does not cause frequent crises. Explain the specific situations that raise risk. These include severe dehydration extreme exertion and low oxygen exposure. Explain the signs that require urgent care. These include sudden muscle pain dark urine persistent hematuria or chest pain. Emphasize when seeking immediate medical attention. Offer practical steps you can take to reduce risk. Advise steady hydration before, during and after exercise. Advise gradual acclimation to altitude when travel or work requires it. Advise avoiding sudden intense exertion in hot or hypoxic settings. Recommend talking with sports medicine or occupational health before starting high intensity training or military service. These actions reduce the chance of exertional complications. Provide reproductive counseling to you and your partner. Offer hemoglobinopathy testing to partners when either person is a carrier or has a family history. Explain inheritance patterns and the risk to offspring. Discuss prenatal diagnostic options for those who wish them. Tailor the discussion to your language and cultural context. Use plain language. Use teach back to confirm understanding.

Address the gap in knowledge with structured education. Caregiver education programs increased baseline knowledge from thirty eight percent to over ninety percent in one study. [23] Use short handouts videos and face to face counseling. Repeat key points at multiple visits. Provide written results of newborn screening in formats the family can keep and share. Screen routinely for associated conditions when indicated. Explain the need for periodic renal function checks and for evaluation of unexplained hematuria. Advise pregnant women to report urinary symptoms promptly. Recommend referral to nephrology or urology when tests show abnormalities. [24][25] Adapt education to literacy and language needs. Use interpreters when needed. Use simple visual aids. Encourage questions. Ask you to repeat the main points in your own words. Provide contact information for follow up and local genetic services. Good education improves self care and reduces preventable harm. [4][23][24][25]

Enhancing Healthcare Team Outcomes

The global burden of sickle cell trait (SCT) remains substantial, with an estimated three million African Americans and over three hundred million people worldwide carrying the trait. [4] Despite being commonly regarded as a benign genetic condition, SCT has demonstrated potential for clinical complications under certain physiologic stresses such as hypoxia, dehydration, or extreme exertion. These complications underline the need for a proactive healthcare approach in which pharmacists and nurses play vital and complementary roles. Their coordinated efforts are essential for improving patient outcomes, promoting education, and reducing the intergenerational transmission of sickle-related disorders through effective counseling and preventive programs. Pharmacists are positioned to contribute at multiple stages of patient care. Their role begins with patient education and risk communication. Pharmacists interact with patients during medication dispensing, chronic disease management, and community health programs, providing valuable opportunities to identify individuals at risk for SCT-related complications. They should educate carriers about the physiological effects of sickling, the importance of hydration, and the avoidance of environmental triggers such as high altitude or excessive physical exertion. By incorporating SCT awareness into counseling on hydration and over-the-counter medication use—particularly drugs affecting renal perfusion such as NSAIDs—pharmacists can help prevent kidney-related complications like papillary necrosis and hematuria [26].

In addition, pharmacists should take an active role in genetic counseling and screening programs. When SCT carriers are identified, pharmacists can collaborate with physicians and public health workers to provide genetic information about inheritance patterns, clarify misconceptions, and refer patients for formal genetic counseling when indicated. This becomes particularly important for individuals of reproductive age. Pharmacists in clinical and community settings can facilitate voluntary preconception or premarital testing programs. Evidence from Saudi Arabia demonstrates that premarital screening significantly reduces marriages between carriers, thereby lowering the risk of offspring being born with sickle cell disease. [26] Implementing similar programs globally could contribute to breaking the transmission cycle of SCT and its complications. Nurses play an equally crucial and often frontline role in managing SCT outcomes. Their responsibilities encompass patient education, screening coordination, and early detection of clinical complications. Nurses are frequently the first professionals to interact with patients in community clinics, emergency departments, and primary care settings. This gives them the opportunity to identify individuals presenting with symptoms such as exertional pain, hematuria, or fatigue—symptoms that may otherwise be dismissed or misattributed. Through detailed history taking and risk assessment, nurses can initiate appropriate referrals for confirmatory testing such as hemoglobin electrophoresis. Education remains a cornerstone of nursing practice in SCT management. Nurses should deliver structured, culturally sensitive educational sessions that focus on self-care behaviors, recognition of warning symptoms, and strategies to prevent sickling episodes. For example, during pre-employment or athletic physical examinations, nurses can educate individuals about maintaining hydration, avoiding overheating, and pacing physical exertion. For pregnant women with SCT, nurses play a critical role in prenatal and antenatal counseling, emphasizing the importance of regular urine screening for asymptomatic bacteriuria and monitoring for signs of pyelonephritis or anemia. They also ensure adherence to folic acid and iron supplementation protocols to prevent maternal and fetal complications [26].

Both pharmacists and nurses share responsibility for improving awareness through community-based initiatives. Public health campaigns, school-based health education, and workplace wellness programs can incorporate SCT awareness to reach adolescents and young adults—the key demographic for breaking the hereditary transmission chain. In these programs, nurses can coordinate testing drives, while pharmacists can provide medication safety guidance and reinforce the link between genetic knowledge and reproductive health decisions. Their collaboration is essential to ensure that information reaches communities in accessible, comprehensible forms that overcome literacy and language barriers. Interprofessional collaboration between pharmacists, nurses, and physicians enhances surveillance for SCT-related complications. Nurses can perform routine assessments, such as blood pressure monitoring and urinalysis, while pharmacists interpret renal function trends and evaluate medication safety in patients with compromised kidney function. Early recognition of renal impairment or exertional rhabdomyolysis allows timely referral and intervention, reducing long-term morbidity. Moreover, pharmacists can ensure that medications prescribed to SCT carriers do not exacerbate dehydration, hypoxia, or oxidative stress, thus minimizing preventable adverse outcomes. At the policy level, pharmacists and nurses have a shared advocacy role. They can support the implementation of SCT screening policies across schools, universities, and athletic organizations. They can also contribute to the development of educational materials that explain the genetic and clinical aspects of SCT in clear, evidence-based language. By documenting adverse outcomes and participating in research and data collection, they can inform national health strategies aimed at reducing SCT prevalence and improving management standards [26].

Pharmacists and nurses must also focus on continuity of care. Follow-up after newborn screening is often neglected, resulting in adults unaware of their carrier status. Nurses can maintain contact with families after initial screening, ensuring that results are explained, documented, and carried into adolescence and adulthood. Pharmacists can support this continuity by maintaining registries of patients with SCT and flagging them for counseling during future healthcare encounters. This long-term approach helps individuals make informed decisions about health, exercise, and family planning throughout their lives. The success of SCT management depends on coordinated teamwork, consistent education, and a patient-centered approach. Pharmacists and nurses should use every clinical interaction to reinforce awareness, encourage testing, and promote preventive behaviors. Their collaboration ensures that SCT is managed not merely as a benign genetic variant but as a condition requiring lifelong vigilance and informed decision-making. Through these sustained efforts, the healthcare team can reduce morbidity, enhance quality of life, and limit the intergenerational transmission of sickle-related disorders. [4][26][27].

Conclusion:

In summary, while sickle cell trait (SCT) confers a generally favorable prognosis and normal life expectancy, it is inaccurate to classify it as entirely benign. The condition carries conditional risks for significant morbidity under specific physiological stressors. The pathophysiological mechanism—the polymerization of hemoglobin S under deoxygenated conditions—is the same as in sickle cell disease, albeit with a higher threshold for activation. This latent potential can be unmasked by severe dehydration, hypoxia, extreme exertion, or thermal extremes, leading to complications such as exertional rhabdomyolysis, renal papillary necrosis with hematuria, splenic infarction, and an increased risk for thromboembolic events and rare malignancies like renal medullary carcinoma. Consequently, a paradigm shift in the clinical approach to SCT is warranted, moving from passive acknowledgment to proactive, patient-centered management. The cornerstone of care is comprehensive patient education, empowering individuals with SCT to understand their genetic status and recognize and avoid high-risk situations. This includes emphasizing the critical importance of sustained hydration, graded acclimatization to altitude, and avoiding sudden, intense physical exertion. Furthermore, genetic and reproductive counseling is imperative to inform carriers and their partners about the risks of having a child with sickle cell disease. Ultimately, optimizing outcomes for individuals with SCT requires a coordinated, interprofessional healthcare team strategy. Pharmacists, nurses, physicians, and genetic counselors must collaborate to ensure continuity of care, from explaining newborn screening results to providing lifelong counseling and monitoring for potential complications. Through this vigilant, educated, and team-based approach, the healthcare system can effectively mitigate the specific risks associated with SCT, prevent preventable morbidity, and support carriers in making informed health and reproductive decisions.

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