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Genetic Variation of Hemoglobin Gene and Its Impact on Disease Severity

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Abstract. Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia and associated with severe complications, including neuropathy, nephropathy, and retinopathy. Oxidative stress plays a crucial role in the progression of these complications. Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) are essential in mitigating oxidative stress; however, their activity is often impaired in diabetic patients. Despite global research on oxidative stress in diabetes, there is limited evidence from Iraq examining the relationship between antioxidant enzyme activity and glycemic control. This study aimed to assess the levels of antioxidant enzymes (SOD, CAT, and GPx) and their association with glycemic indices (fasting blood glucose and HbA1c) in patients with type 2 diabetes mellitus compared to healthy controls. A case-control study including 60 diabetic patients and 30 healthy controls revealed significantly reduced activities of SOD, CAT, and GPx in diabetic patients ($p < 0.05$). In contrast, fasting blood glucose and HbA1c were significantly elevated in diabetic subjects compared to controls. A negative correlation was observed between antioxidant enzyme activity and glycemic indices, indicating that poor glycemic control exacerbates oxidative stress. This is among the first studies in Iraq to demonstrate the association between impaired antioxidant defense mechanisms and hyperglycemia in type 2 diabetes mellitus. The findings emphasize the importance of monitoring oxidative stress biomarkers alongside glycemic indices to improve management strategies and prevent diabetic complications.

Highlights:

1. Vitamin D deficiency was prevalent in 62% of patients with type 2 diabetes mellitus.
2. Low vitamin D levels were significantly associated with poor glycemic control and longer disease duration.
3. Age, obesity, and limited sun exposure were identified as key risk factors for vitamin D deficiency in diabetic patients.

Keywords: Type 2 diabetes mellitus, Oxidative stress, Antioxidant enzymes, Glycemic control, Iraq

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Background

A monogenic condition known as sickle cell anemia (SCA) results from the production of sickle hemoglobin (HbS) due to a single nucleotide mutation in the β-globin gene (HBB). The sickle shape that red blood cells take on as a consequence of polymerization of deoxygenated HbS—caused by this mutation—obstructs blood flow and causes various clinical issues. There is substantial clinical diversity in SCA, despite the fact that it is a single-gene disorder; this suggests that other genetic factors influence the severity of the illness. Severity of sickle cell anemia (SCA) is mostly determined by the amount of fetal hemoglobin (HbF), a kind of hemoglobin that some individuals have even after they're born. Because HbF prevents HbS polymerization, higher levels of HbF are associated with milder illness symptoms. The following are examples of the many genetic loci that have been identified as having an effect on HbF levels and, by extension, the severity of SCA:

BCL11A: This gene is essential for the repression of fetal γ-globin genes. Variants in BCL11A are correlated with elevated HbF levels and reduced disease severity in SCA patients.

HBS1L-MYB Intergenic Region: A polymorphism in this intergenic region has been associated with increased HbF levels and a milder clinical progression in SCA.

HBB Cluster Variants: Polymorphisms within the β-globin gene cluster, including the Xmn1-HBG2 variant, have been linked to increased HbF production and improved clinical manifestations.

HMIP-2A and HMIP-2B: These loci have been recognized as supplementary genetic regulators of HbF levels, influencing the diversity in SCA severity.

α-Thalassemia: The co-inheritance of α-thalassemia, which reduces the quantity of α-globin chains, may result in elevated HbF levels and a less severe SCA phenotype.

Comprehending the genetic moderators of SCA is essential for forecasting illness severity and customizing treatment approaches. Patients with elevated HbF levels often encounter fewer vaso-occlusive crises and have a more favorable outcome. Therapeutic strategies designed to enhance HbF production, including hydroxyurea administration, have shown efficacy in diminishing disease consequences.

The clinical diversity seen in SCA highlights the significance of genetic modifiers in illness manifestation. Recognizing and comprehending these genetic characteristics not only improves our knowledge of the illness's pathogenesis but also creates opportunities for tailored treatment therapies designed to optimize disease outcomes.

Introduction

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A hereditary hematologic disorder known as sickle cell anemia (SCA) results from a single nucleotide mutation in the HBB gene. This mutation causes the β-globin chain to produce sickle hemoglobin (HbS) by substituting valine for glutamic acid at position 6. Hypoxia promotes hemoglobin polymerization due to this mutation, which deforms red blood cells into a sickle shape. This, in turn, causes hemolysis, vaso-occlusion, and a host of other clinical symptoms [1, 2]. Despite SCA being a monogenic condition, there is a lot of clinical variation, which suggests that other genetic factors play a role. Important genetic modifiers include the BCL11A gene, which is necessary to suppress the production of fetal hemoglobin (HbF); the HBS1L-MYB intergenic region, which is associated with higher levels of HbF; and the α-thalassemia trait, which can lessen the severity of the disease by reducing the supply of α-globin chains for the polymerization of HbS. The phenotypic variability seen in SCA patients is influenced by these genetic variations. If we want to understand how diseases develop and create effective treatments, we need to have a firm grasp on these modifiers [4]. New developments in genome editing and gene therapy hold great promise for improving patient outcomes by correcting underlying genetic defects. The genetic basis of SCA is still a mystery, but recent studies have shed light on potential treatment targets and tailored treatment plans [5].

Genetic variations that govern fetal hemoglobin (HbF) levels, which in turn influence the polymerization of sickle hemoglobin (HbS) and the clinical manifestations of sickle cell anemia (SCA), have a significant impact on the severity of sickle cell anemia (SCA) [6]. The presence of elevated HbF levels inhibits the polymerization of HbS, which in turn reduces the sickling of red blood cells and lessens the severity of many illnesses [7]. The BCL11A, HBS1L-MYB, and HBG2 genetic loci are the most important ones that are associated with increased HbF production. Polymorphisms, such as the Xmn1 -158 Gγ variation, have been linked to higher levels of hemoglobin and a less severe clinical presentation on the part of people with sickle cell anemia (SCA). Furthermore, it has been shown that the co-inheritance of α-thalassemia, which is characterized by deletions in the α-globin gene, is associated with increased amounts of hemoglobin and a reduction in the consequences of illness, such as stroke [8]. It should be noted, however, that not all HbF-modifying mutations provide protective mechanisms [9]. It has been shown that the HBG2 rs7482144 polymorphism is associated with elevated levels of HbF, although it does not correlate with a reduction in the severity of infection. [10, 11] These findings highlight the complex interaction that exists between genetic factors and the consequences of sickness in SCA, highlighting the need of doing comprehensive genetic profiling in order to get an understanding of the disease and effectively manage it.

Diagnosis of Sickle Cell Anemia

Sickle cell anemia (SCA) is diagnosed with a combination of clinical assessment and laboratory testing that detect sickle hemoglobin (HbS). Preliminary evaluation often involves a blood smear to identify sickled erythrocytes and a solubility test to determine the presence

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of HbS [12]. Nonetheless, these approaches may fail to differentiate between carriers and afflicted persons. A confirmatory diagnosis is often obtained by more precise methods such hemoglobin electrophoresis, isoelectric focusing, high-performance liquid chromatography (HPLC), and DNA analysis. These sophisticated techniques can precisely distinguish among different hemoglobinopathies and detect particular mutations in the HBB gene [13]. In resource-constrained environments, novel methodologies like as smartphone-based microscopy integrated with deep learning algorithms have been devised to automate the identification of sickle cells, providing a cost-efficient and accessible diagnostic instrument. Moreover, ultraviolet-visible (UV-Vis) absorbance spectroscopy, evaluated by automated machine learning (AutoML) methodologies, has shown potential in diagnosing SCA with elevated sensitivity and specificity, hence enabling early diagnosis and screening across various populations. The improvements in diagnostic methods are essential for enhancing the care and therapy results of people with sickle cell anemia [14].

Individuals with sickle cell anemia (SCA) display a spectrum of clinical and laboratory characteristics that vary in intensity and prevalence, shaped by variables including age, sex, genotype, and environmental factors [15]. A study of 166 genetically verified SCA patients in Kinshasa, DR Congo, classified illness severity as mild in 28.9%, moderate in 64.5%, and severe in 6.6%. The severity of the disease was significantly connected with age ($p < 0.001$) and was more evident in men ($p = 0.012$), with priapism recognized as a major factor in males ($p = 0.045$) [12]. Sickle Cell Anemia (SCA) is clinically defined by repeated vaso-occlusive crises that result in severe pain episodes, often occurring in the chest, back, limbs, or belly. These crises may lead to problems including acute chest syndrome, stroke, organ damage, and infections resulting from functional asplenia. Chronic hemolytic anemia arises from the reduced lifetime of sickled erythrocytes, resulting in weariness and pallor. Furthermore, individuals may encounter priapism, leg ulcers, and gallstones [13]. Laboratory results often reveal decreased hemoglobin and hematocrit levels, with elevated fetal hemoglobin (HbF) values in some cases. Research indicated mean HbF levels of 12 ± 7% in SCA patients, with higher levels correlated with milder clinical characteristics. Hydroxyurea treatment has been shown to elevate HbF levels, thus enhancing hematologic parameters and diminishing problems [14].

Genetic factors significantly influence illness manifestation. α-thalassemia and certain β-globin gene haplotypes, including Arab-Indian (AI), are correlated with elevated HbF levels and reduced disease severity [16]. In a cohort from the Eastern Province of Saudi Arabia, patients with the AI/AI haplotype had mean HbF levels of 16.6 ± 7.5%, which correlated with a slower illness progression. In summary, SCA manifests a range of clinical and laboratory characteristics shaped by hereditary and environmental influences. Timely recognition and intervention of these characteristics are essential for enhancing patient outcomes and quality of life [12, 13].

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Symptoms of Patients with Sickle Cell Anemia

Sickle cell anemia (SCA) is an inherited hematological illness marked by the synthesis of sickle hemoglobin (HbS), resulting in red blood cell sickling, vaso-occlusion, and a range of consequences impacting several organ systems. These consequences substantially increase morbidity and death in afflicted patients.

1. In Sickle Cell Anemia (SCA), Vaso-Occlusive Crises (VOC) occur when sickled red blood cells block blood flow, causing extreme agony. These crises cause most SCA emergency department visits and hospitalizations.
2. Acute Chest Syndrome (ACS): A serious complication characterized by new pulmonary infiltrates on chest imaging, often accompanied by fever, cough, and respiratory distress. SCA patients die most from this disorder, the second leading cause of hospitalization.
3. Children with Sickle Cell Anemia (SCA) are at higher risk of both overt and quiet brain infarcts, leading to long-term neurological impairments. Strokes affect 11% of this group, whereas silent cerebral infarcts affect 37%.
4. Sickle cell nephropathy may lead to renal complications such hyposthenuria, proteinuria, and chronic kidney disease. Microvascular obstruction and ischemia cause glomerular injury and renal failure in certain people.
5. Sickle cell retinopathy, caused by retinal vascular blockage and neovascularization, may lead to visual impairment or blindness. Early identification and treatment of eye diseases need regular ophthalmologic screening.
6. Functional asplenia in Sickle Cell Anemia (SCA) patients increases their susceptibility to infections, particularly those caused by encapsulated organisms like Streptococcus pneumoniae. Antibiotics and vaccines are crucial prophylactic measures.
7. Priapism: A painful and protracted penile erection caused by poor venous drainage is a common consequence of sickle cell anemia in male patients. Erectile dysfunction might develop from uncontrolled episodes.
8. Chronic vaso-occlusion may cause avascular necrosis, causing bone infarctions in the femoral and humeral heads and joint dysfunction.
9. Elevated bilirubin levels from hemolysis may lead to gallstone development, biliary colic, and cholecystitis.
10. Sickle Cell Anemia during pregnancy may lead to complications such preeclampsia, intrauterine growth restriction, and spontaneous miscarriage. Throughout pregnancy, close supervision and collaboration are essential. To improve patient outcomes and quality of life, SCA treatment must involve preventative care, early identification, and individualized therapeutic approaches [17-21].

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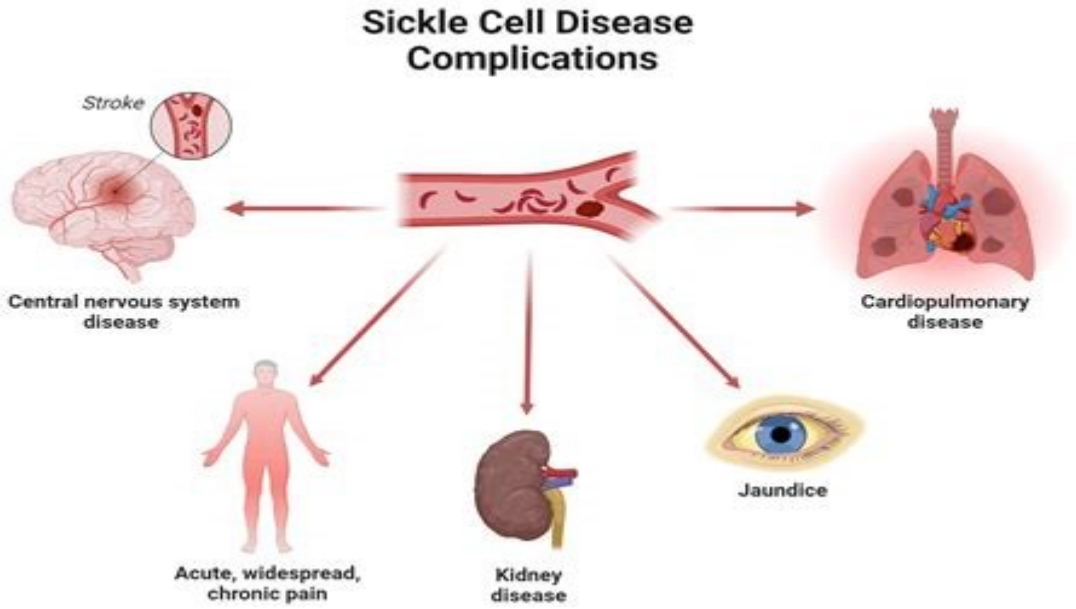

Figure 1: Effect of Sickle cell anemia in other organs
https://www.biorender.com/template/complications-of-sickle-cell-disease

Complication of Sickle Cell Anemia

A hereditary hematological disorder known as sickle cell anemia (SCA) causes abnormalities in red blood cell shape and function as well as the development of vaso-occlusive events. A cascade of organ-specific consequences, triggered by this pathophysiological process, significantly impacts mortality and morbidity rates.

1. Neurological Complications: SCA is linked to an increased risk of both overt and silent cerebrovascular events. About 10–15% of children with sickle cell anemia (SCA) experience strokes, with silent cerebral infarcts occurring more frequently in younger patients. Such events may result in persistent neurological deficits, highlighting the necessity for prompt detection and intervention [22].
2. Renal Involvement: Sickle cell nephropathy includes various renal complications such as glomerular hyperfiltration, proteinuria, and chronic kidney disease. The pathogenesis includes microvascular occlusion and ischemia in the renal medulla, resulting in progressive renal dysfunction [23].
3. Ocular Manifestations: Sickle cell retinopathy arises from retinal vascular occlusion and neovascularization, which may result in vision impairment or blindness. Regular ophthalmologic screening is crucial for the early detection and management of conditions.

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4. Pulmonary Complications: Sickle cell anemia patients exhibit an elevated risk of acute chest syndrome, a critical condition marked by the presence of new pulmonary infiltrates and respiratory distress. Chronic pulmonary hypertension is common and contributes to right ventricular strain and heart failure [25].
5. Cardiovascular Issues: Chronic hemolysis and vaso-occlusion may result in cardiomyopathy and left ventricular diastolic dysfunction. These conditions lead to pulmonary hypertension and reduced exercise capacity [26].
6. Hepatic Complications: Chronic hemolysis in sickle cell anemia (SCA) results in elevated bilirubin production, increasing the risk of gallstones and cholecystitis. Furthermore, hepatic iron overload may arise from recurrent blood transfusions, contributing to liver dysfunction [27].
7. Involvement of the Musculoskeletal System Ischemia may lead to avascular necrosis of the hip and other major joints, which can result in joint dysfunction and pain [28].
8. Effects on the Hematologic and Immune System: Functional asplenia, which is a consequence of splenic infarction, increases the likelihood of infections, particularly those caused by encapsulated bacteria like Streptococcus pneumoniae. Antibiotics used as preventative measures and vaccines are both considered to be crucial preventive techniques [29]. A multisystem illness that is marked by substantial organ involvement is what we mean when we talk about SCA. In order to lessen the burden of these consequences and improve patient outcomes, it is essential to implement efficient management techniques that include preventative care, early identification, and individualized treatment interventions.

Factors Association with Sickle Cell Anemia

A complex interplay of genetic, environmental, and socioeconomic variables is responsible for determining the prevalence of sickle cell anemia (SCA). It is vital to have a solid understanding of these factors in order to have a better understanding of the worldwide distribution and clinical diversity of the illness.

- Sickle cell anemia (SCA) is an autosomal recessive illness that is caused by mutations in the HBB gene. These mutations are responsible for the production of sickle hemoglobin (HbS), which is the hallmark of sickle cell anemia. those who are homozygous, or contain two copies of the HbS gene, are the ones that exhibit symptoms of the illness. On the other hand, those who only have one copy of the HbS gene are considered carriers and are therefore referred to as having sickle cell trait. In regions where malaria is widespread, notably in sub-Saharan Africa, the prevalence of sickle cell anemia (SCA) is highest. This may be related to the fact that the sickle cell trait provides a protective advantage against malaria. There has been a rise in the prevalence of the sickle cell gene among these groups as a result of the selection that has occurred evolutionarily [30].

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- Environmental conditions significantly influence the clinical manifestations of SCA. Cold weather, high altitudes, and dehydration can trigger vaso-occlusive crises, resulting in acute pain episodes and subsequent hospitalizations. Moreover, air pollution, specifically heightened concentrations of nitrogen dioxide and particulate matter, correlates with a rise in emergency admissions among SCA patients. Environmental stressors intensify disease severity and complicate management strategies [31].
- Socioeconomic status significantly influences the incidence and severity of sudden cardiac arrest (SCA). In low-income countries, restricted healthcare access, insufficient nutrition, and absence of preventive measures lead to elevated morbidity and mortality rates. In high-income countries, early diagnosis via newborn screening and access to comprehensive care have enhanced outcomes, underscoring the significance of healthcare infrastructure in disease management [32]. In conclusion, the prevalence of sickle cell anemia is influenced not only by genetic inheritance but also by environmental exposures and socioeconomic factors. Addressing these determinants via public health initiatives, enhanced healthcare access, and environmental controls is crucial for mitigating the global burden of SCA.

Association Between Consanguineous marriages and Occurrence of Disease

Consanguineous marriages, defined as unions between closely related individuals, are common in various regions and are linked to a heightened risk of genetic disorders, such as sickle cell anemia (SCA). This relationship holds particular significance in populations characterized by a high prevalence of SCA and elevated consanguinity rates.

Genetic Basis of Sickle Cell Anemia

Mutations in the HBB gene, which is responsible for the production of sickle hemoglobin (HbS), cause sickle cell anemia, an autosomal recessive condition. Sickle cell anemia (SCA) is a condition that affects people who are homozygous for the HbS gene, whereas individuals who are heterozygous for the gene are considered carriers and are known as having sickle cell trait. When two people get married from the same family, the odds of their children acquiring sickle cell anemia (SCA) are higher since both parents are more likely to have the same genetic mutation [33].

Prevalence of Consanguinity and Sickle Cell Anemia

In regions where the frequency of SCA is high, studies show that consanguineous marriages are more common. Consanguinity rates in Saudi Arabia range from 20% to 50%, while sickle cell trait frequency is between 2% and 27%. The prevalence of sickle cell

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anemia (SCA) is estimated to reach 2.6% in certain areas. Of all families in Sudan, 67.5% are consanguineous, while the incidence of SCA varies from 0.8% to 30.4% across different areas [34, 35].

Impact of Consanguinity on Sickle Cell Anemia Risk

The probability of a kid getting two copies of the hemoglobin S gene increases when parents are consanguineous because it is more likely that both parents contain the sickle cell gene. Because of this inherited tendency, SCA is more common among highly related groups. Despite premarital screening programs in Saudi Arabia, many couples still choose to tie the knot despite being at high-risk for sexually transmitted infections (SCA) [36]. This decision is likely influenced by cultural and socioeconomic reasons. Sickle cell anemia is more common in families when both parents inherit the same genetic mutation, which is why consanguineous marriages are so common. This correlation emphasizes the need for premarital screening and genetic counseling in regions with high prevalence of consanguinity in order to lower the probability of SCA and other hereditary diseases [31, 36].

Effect of Sickle Cell Anemia on the Hematological Parameters
Hematological Parameters

- Sickle cell anemia (SCA) is characterized by low hemoglobin (Hb) and hematocrit (Hct) levels, which may lead to chronic anemia in patients. The phenomenon occurs because sickled red blood cells have a shorter lifetime and hemolysis is more intense. During steady-state phases, Patel et al. (2025) found that compared to healthy controls, SCA patients had significantly lower levels of Hb and Hct [37].
- Sickle cell anemia (SCA) patients often have high levels of MCV and MCH, two markers of red blood cell health. As a defense strategy against anemia, the presence of reticulocytes causes this macrocytosis. Another indicator of a diverse red blood cell population is an increased red cell distribution width (RDW) [38].
- • Reticulocyte Count: When hemolysis and red blood cell turnover are increased, the bone marrow usually responds by increasing the reticulocyte count. As an indication of disease activity and treatment response, this is often used [39].
- Patients with sickle cell anemia often have thrombocytosis, particularly during vaso-occlusive crises. As a defense mechanism against inflammation and damaged tissues, this is thought of as a reactive process [38].

Biochemical Parameters

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- Elevated levels of Lactate Dehydrogenase (LDH) indicate increased red blood cell turnover and tissue hypoxia. Studies indicate that LDH levels do not consistently correlate with directly measured red blood cell survival, highlighting the necessity for caution when employing LDH as the sole marker of hemolysis [40].
- Elevated levels of total and indirect bilirubin are commonly observed in patients as a result of increased hemolysis. This may result in jaundice and facilitate gallstone formation [41].
- Urea and Electrolytes: Patients with SCA may exhibit changes in renal function, resulting in fluctuations in urea and electrolyte concentrations. Patel et al. [37] conducted a study that found reduced urea and sodium levels in patients with SCA during steady-state phases when compared to healthy controls.
- Sickle cell anemia (SCA) is characterized by the presence of elevated levels of C-reactive protein (CRP) and other acute phase proteins, even when the patient is in a steady state. This presents evidence of a prolonged inflammatory state as well as injury to the tissue under the surface [40, 42].
- One of the characteristics of SCA is a decreased bioavailability of nitric oxide (NO), which therefore results in endothelial dysfunction and vasculopathy at the same time. Genetic study has shown that there are relationships between hematological parameters and nitric oxide-related genetic variations in people who have sickle cell anemia.

Clinical Implications Association with Alteration in Hematological and Biochemical Levels

The changes in hematological and biochemical parameters in SCA are not only diagnostic but also have direct clinical implications. The severity of anemia and elevated reticulocyte counts assist clinicians in evaluating disease severity and determining the necessity for interventions, including blood transfusions or hydroxyurea administration. Monitoring biochemical markers such as LDH, bilirubin, and CRP offers insights into hemolysis extent, organ involvement, and subclinical inflammation presence, thus guiding treatment strategies and prognostic assessments.

Prevention of Disease

Traditional methods of preventing sickle cell anemia (SCA) have not been successful in "curing" this hereditary disease. There are a number of approaches that may lessen the impact of the condition and make life better for those who suffer from it. Genetic counseling, early detection, screening during pregnancy, and preventative healthcare are all part of the plans. Here are the main techniques for prevention:

1. Genetic Counseling and Screening

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- Expectant parents, especially those living in regions where SCA is common, should get genetic counseling. Here we find out if people have sickle cell trait, also known as being carriers (heterozygous) of the sickle cell gene. Decisions on family planning may then be made with this information in hand.
- People from high-risk communities or with a family history of sickle cell anemia (SCA) should undergo carrier screening before becoming pregnant. That way, if both parents have the SCA gene, it won't be passed on to their kid.
- Screening for sickle cell trait and other hemoglobinopathies before marriage is suggested or mandated in countries with high rates of sickle cell anemia. As a result, couples may make educated choices about having a family. As part of their public health programs, several nations, including Saudi Arabia, have made premarital screening obligatory in an effort to reduce the number of cases of sexually transmitted infections [44].

2. Prenatal Screening and Diagnosis

- Carrier screening of newborns can identify individuals affected by or carriers of sickle cell anemia. Timely diagnosis facilitates improved management and strategic planning for interventions, including blood transfusions and hydroxyurea administration.
- Prenatal Testing: Prenatal screening methods, including amniocentesis and chorionic villus sampling, can be conducted during pregnancy to assess whether a fetus has inherited SCA. Early detection enables parents to make informed decisions concerning the pregnancy. This testing is especially beneficial for couples who are carriers of sickle cell trait.

3. Avoiding Risk Factors and Improving Care

- Patients with Sickle Cell Anemia (SCA) are at an increased risk of dehydration, which may precipitate vaso-occlusive crises. Maintaining adequate hydration, particularly during periods of illness or physical activity, is essential. Vaccinations for pneumococcal infections and other preventable diseases are crucial, given that SCA patients exhibit an increased susceptibility to infections due to functional asplenia [46].
- Hydroxyurea is a pharmacological agent utilized to enhance fetal hemoglobin (HbF) synthesis in individuals with sickle cell anemia (SCA). It decreases the incidence of pain crises and mitigates complications such as stroke. This approach is commonly employed in preventive medical management for individuals diagnosed with SCA [47].

4. Gene Therapy

Although there is now no common way to avoid sickle cell anemia, researchers are looking at new treatments, including gene therapy, that may be able to treat or cure the

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condition. In order to cure the condition, gene therapy aims to fix the faulty copy of the HBB gene. In order to avoid sickling of red blood cells, this involves either directly altering the gene or stimulating the organism to boost synthesis of fetal hemoglobin (HbF). Many promising gene-editing technologies, such as CRISPR/Cas9, are now being studied in clinical studies [48].

5. Education and Awareness Programs

- Public health initiatives that raise awareness of sickle cell anemia may encourage screening for carrier status and allow for early discovery, especially in areas where the disorder is prevalent. In areas where consanguineous marriages are common, education is key to understanding the dangers of the practice [44].
- Advancing Health-Conscious Lives: Regular checkups, avoiding excessive temperatures, and pain management are all important parts of a healthy lifestyle that may greatly improve the health of people with sickle cell anemia and reduce the risk of problems [45].

6. Public Health Initiatives

- In order to undertake public health measures centered on illness prevention, some nations with high SCA rates have set up national and regional programs. Several countries in Africa and the Middle East mandate newborn screening for sickle cell anemia so that it may be treated early.
- Some governments have instituted programs that require couples to undergo premarital testing in order to reduce the likelihood of having a child with a hereditary disorder, such as sickle cell anemia, by providing genetic screening and counseling [49, 50].

Control of Sickle Cell Anemia

Management of sickle cell anemia (SCA) encompasses preventive strategies and therapeutic interventions designed to alleviate symptoms, decrease complications, and enhance quality of life. As SCA is a genetic disorder, it is incurable; however, it can be effectively managed through early intervention and suitable medical care. The main objectives of SCA management include pain control, complication prevention, and enhancement of overall health outcomes. The following are the essential components of SCA control:

1. Early Diagnosis and Screening

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- Early diagnosis via newborn screening is essential for the management of SCA. In numerous nations, the screening of newborns for sickle cell anemia facilitates early interventions that can markedly diminish complications. This may also assist in genetic counseling and early intervention.
- Carrier screening is essential for individuals at risk of having offspring with SCA, especially in areas with elevated prevalence. Genetic counseling assists couples in comprehending risks and making informed decisions regarding family planning. Early genetic counseling can inform individuals about preventive strategies to reduce the risk of having children with the disease. [45, 46].

2. Pain Management and Crisis Prevention

- Dehydration and extreme temperatures can induce vaso-occlusive crises, resulting in significant pain. Maintaining proper hydration and steering clear of extreme environmental conditions can decrease the incidence of pain crises.
- Medications for Pain Relief: Non-steroidal anti-inflammatory medications (NSAIDs) and opioids are often used for the treatment of pain in various emergency scenarios. In most cases, opioids are prescribed for the treatment of severe pain episodes; nevertheless, the administration of these medications needs careful monitoring in order to avoid the development of dependency.
- Regular monitoring of SCA patients is essential to detect signs of acute crises during routine check-ups. Prompt interventions can mitigate pain escalation and facilitate faster recovery [47].

3. Hydroxyurea Therapy

- One of the best pharmacological drugs for sickle cell anemia (SCA) treatment is hydroxyurea. The process works by increasing the synthesis of fetal hemoglobin (HbF), which in turn reduces the formation of sickled red blood cells and stops sickle hemoglobin (HbS) from polymerizing. Fewer pain crises, fewer blood transfusions, and fewer cases of acute chest syndrome are seen with this medication. That is considered the gold standard for treating SCA in many settings, and it applies to both children and adults.
- By reducing hospitalizations and incidences of severe pain, hydroxyurea treatment improves quality of life. It also reduces the risk of stroke and other related problems [51].

4. Blood Transfusions

- Blood transfusions are used to treat severe instances of sickle cell anemia (SCA) in order to reduce the risk of consequences, such as organ damage and stroke.

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Transfusions of healthy red blood cells may increase the number of healthy cells in circulation and decrease the proportion of sickled cells by regular transfusions.

- Iron chelation treatment is essential because long-term blood transfusions may lead to an excess of iron and potential harm to vital organs like the heart and liver. In order to reduce iron buildup, iron chelation treatment is often used with blood transfusions.
- To quickly lower the fraction of sickled cells in circulation, exchange transfusions replace a patient's blood with donor blood. Patients suffering from severe pain crises or acute consequences like stroke are ideal candidates for this surgery [52, 53].

5. Preventing and Managing Complications

- Infections or vaso-occlusive events may cause Acute Chest Syndrome (ACS), a serious consequence of sickle cell anemia (SCA). Acute chest syndrome (ACS) care relies on prompt diagnosis and administration of antibiotics, oxygen treatment, and blood transfusions. Preventing illnesses caused by pneumococcal bacteria and other respiratory pathogens requires vaccination.
- A substantially increased risk of stroke is seen in children with sickle cell anemia (SCA). To reduce the likelihood of stroke, children whose transcranial Doppler ultrasounds indicate they are at high risk get blood transfusions.
- Preventing Infections: People with sickle cell anemia (SCA) are more likely to have infections, especially those caused by streptococcus pneumoniae and other encapsulated bacteria. Vaccination is highly recommended to protect against avoidable diseases such as pneumonia and meningitis. Antibiotics, particularly penicillin, are given to children less than five years old as a preventative measure against infections.
- In order to intervene early, it is vital to check for sickle cell retinopathy and kidney disease (sickle cell nephropathy) on a regular basis. Managing proteinuria is one possible treatment for kidney damage, while laser therapy may help individuals with retinal problems avoid vision loss [17, 20, 25].

6. Bone Marrow Transplantation (BMT)

- • The only treatment that has the ability to cure sickle cell anemia is bone marrow transplantation, which is also called hematopoietic stem cell transplantation (HSCT). Research suggests that HSCT, which involves transferring healthy stem cells from a donor who is genetically compatible with the patient (often a sibling), has the potential to alleviate or even cure the illness in some cases. However, not many people can get this therapy since it needs a suitable donor. A plethora of serious risks are linked to it, including graft-versus-host disease.
- • Gene Therapy: Novel therapeutic approaches, including as gene therapy, are under development with the aim of resolving the HBB gene mutation. These therapies modify the patient's own stem cells so that they can produce healthy red blood cells.

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Gene therapy is still in its early stages and is not available to the public, despite promising results in clinical trials [48].

7. Psychosocial Support

- A person's mental health may take a major hit while they deal with a chronic condition like SCA. Psychological treatment, such as counseling and support groups, is crucial for improving patients' and their families' quality of life and helping them cope with the stresses brought on by the disease.
- Better condition management and treatment adherence may result from providing patients, especially children, and their families with educational resources and support [54].

Conclusion

The findings of this study demonstrate that English language teachers in Riyadh widely adopt blended learning strategies, with usage levels rated as high, particularly among teachers holding postgraduate qualifications and those specializing in English language education. These results indicate that academic background and specialization play a significant role in shaping teachers' ability to integrate technology effectively into their instructional practices. The implications of this study emphasize the necessity for policymakers and educational institutions to design targeted professional development programs and provide adequate digital resources to ensure equitable adoption of blended learning across different teacher groups. Furthermore, future research should expand to larger and more diverse populations across different regions, explore the long-term impact of blended learning on student performance, and investigate the challenges that may hinder teachers' engagement with this approach to provide more comprehensive strategies for sustainable implementation.

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