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Evaluation of the prevalence and liver function tests in patients with Sickle cell disease and Sickle cell trait in Taif Province, Saudi Arabia

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ABSTRACT

Background: Sickle cell disease (SCD) is the most common monogenic condition, impacting millions of people. This study aimed to estimate the prevalence of SCD and sickle cell trait (SCT) and evaluated the levels of liver function tests in SCD individuals.

Methods: This case-control study was conducted between January and December 2023, and data were collected from Armed Forces Hospitals in Al-Hada in Taif. The study included all patients with SCD and SCT using hemoglobin electrophoresis. Demographics, hemoglobin variants, and liver function tests were evaluated and a one-way analysis of variance (ANOVA) was used to assess significance between groups. The correlation was conducted using Pearson's correlation coefficient.

Results: The prevalence of SCD was 11.1%, while the prevalence of SCT was 40.9%. The majority of patients were females. The data showed that alkaline phosphatase (ALP) and total proteins were increased in patients with SCD and SCT. The results showed that albumin levels were not significantly different between groups. In addition, the levels of ALT and AST were elevated in both diseases, but a significant difference was observed only in SCD patients. The results also indicated that there was negative correlation between several liver function tests and age in SCD and SCT patients.

Conclusions: The prevalence of SCD and SCT is high in the study population. Discrepancies in standard liver function tests are frequently observed in patients with SCD and SCT and are correlated with age. These observations suggest that the liver tests may be affected in both disorders, therefore further investigation is needed to validate these findings.

Keywords: liver function tests, sickle cell disease, sickle cell trait

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INTRODUCTION

Sickle cell disease (SCD) is a hereditary illness caused by a single-nucleotide mutation encoding the β-globin subunit of hemoglobin (HBB), leading to the formation of an abnormal form of hemoglobin, known as hemoglobin S (HbS). It is the most prevalent severe monogenic disorder worldwide [1]. SCD occurs when an individual inherits two copies of the hemoglobin S gene (HbSS), resulting in the homozygous genotype (SS). Sickle cell trait (SCT) results when an individual inherits one normal hemoglobin allele (A) and one sickle hemoglobin allele (S), resulting in the heterozygous genotype (AS). Despite their connection, SCT and SCD are distinct [2].

SCD and its variants are the most prevalent hematological disorders, affecting millions of people globally [1]. The number of individuals affected by SCD is determined to be approximately 4.4 million, although statistical reports vary. Annually, around 300,000 infants globally are born with the condition [1]. SCD was initially recorded in the Eastern Province of Saudi Arabia during the 1960s. This prompted the commencement of many regional and national screening investigations to ascertain the clinical characteristics and prevalence of SCD genes across various locations in Saudi Arabia [3]. The prevalence of SCD differs significantly throughout the Kingdom of Saudi Arabia, with the Eastern and Southern Provinces exhibiting the greatest incidence. Moreover, the disease exhib-

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its diversity in both genotypes and clinical manifestations [4]. However, the number of SCD and SCT cases and their clinical manifestations in Taif Province is limited.

SCD is a persistent condition marked by many acute and chronic consequences, including recurrent vaso-occlusive crises, persistent hemolytic anemia, and extensive organ destruction [5] [4]. Vaso-occlusive crises represent the predominant morbidity associated with SCD and are a primary reason for hospitalization in approximately 95% of cases [6]. The liver is involved in the multiorgan failure associated with SCD, and the pathophysiology of liver disease in this disorder is complex due to its associated multifactorial etiology [7]. Liver damage in people with SCD may arise from the sickled cells within the hepatic vasculature [8].

A significant organ damage in SCD and SCT, especially in the liver, remains asymptomatic for decades and can be identified with comprehensive investigations [9]. Therefore, the discovery of early indicators of organ damage may facilitate targeted therapy for affected organs, avoid further deterioration, and enhance SCD care [9]. Thus, this study estimated the prevalence of SCD and SCT and evaluated levels of liver function tests in patients and healthy people in Taif Province, Saudi Arabia.

METHODS

Study population

This case-control research was undertaken at the College of Applied Medical Sciences, Taif University. Data were collected from the records of armed forces hospitals in Al-Hada, Taif, which serve most of the residents of the Western region. The study included all patients with a confirmed diagnosis of SCD and SCT using the hemoglobin electrophoresis technique, between January and December 2023. A control group with normal results at Hb electrophoresis was also included. The data were stratified according to age, gender, hemoglobin variants, and liver profile analysis. Ethical approval was obtained from the research and ethics committee of the hospital (application number: 2024-899). All participants signed an informed consent form. This research was performed in line with the principles of the Declaration of Helsinki.

Inclusion and exclusion criteria

Patients with confirmed diagnoses of SCD and SCT through hemoglobin electrophoresis were included in the study. However, patients diagnosed only by screening methods, such as solubility tests, as well as those with incomplete demographic data, were excluded. In addition, patients with liver diseases were excluded from the study.

Measurement of hemoglobin variants

Two milliliters of whole blood, collected in an ethylenediaminetetraacetic acid (EDTA) tube, were used for hemoglobin electrophoresis testing with a Sebia capillarys 3 device to estimate the percentage of SCD and SCT. The prevalence of SCD was determined by dividing the number of affected patients by the total number of healthy individuals screened.

Measurement of liver function tests

Estimation of liver function tests, including alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), total protein, and albumin, was performed using blood samples collected in plain tubes and analyzed using an Architect Abbott analyzer. Albumin was measured using the Bromocresol green procedure, whereas the biuret method was used to measure total proteins.

Statistical analysis

The clinical data were collected and organized using an Excel spreadsheet. Subsequently, the data were analyzed using GraphPad Prism software. Descriptive data were presented as percentages and numbers. A one-way analysis of variance (ANOVA), followed by Tukey's post hoc test, was performed to assess the significance of all hemoglobin variants and liver function tests between patients and the control groups. Correlation analysis was conducted using Pearson's correlation coefficient between age and liver function tests. Statistical significance was set at a p-value of less than 0.05.

RESULTS

A total of 730 participants were recruited in this study based on the number of hemoglobin electrophoresis tests performed during the study period. Eighty-one patients were diagnosed with SCD, 299 with SCT, and 350 people served as healthy controls. Thus, the prevalence of SCD was 11.1%, while that of SCT was 40.9%. The mean age of patients with SCD and SCT was 22.5 ± 13.3 and 24.5 ± 14.9 years, respectively. Most patients with SCD and SCT were female (54.3% and 55.2%, respectively) (Table 1). The levels of HbA2 were higher in both SCD (3.47 ± 0.92) and SCT patients (3.25 ± 0.34), compared to the healthy individuals (2.49 ± 0.25). Similarly, HbF levels were higher in both SCD (15.50 ± 7.24) and SCT patients (2.61 ± 7.44), compared to the controls (1.49 ± 1.07). HbA was reduced in SCT patients (61.6 ± 5.09) and absent in SCD patients. Furthermore, HbS levels were higher in SCD patients (79.4 ± 9.80) than in those with SCT (33.8 ± 5.40).

Table 1. Demographic characteristics and hemoglobin variants (% of total hemoglobin)

	Healthy	Sickle cell disease	Sickle cell trait
Age (mean)	30.9 ± 16.2	22.5 ± 13.3	24.5 ± 14.9
Female	180 (51.4%)	37 (45.7%)	134 (44.8%)
HbA2	2.49 ± 0.25	3.47 ± 0.92	3.25 ± 0.34
HbF	1.49 ± 1.07	15.50 ± 7.24	2.61 ± 7.44
HbA	97.3 ± 1.23	0.0 ± 0.0	61.6 ± 5.09
HbS	0.0 ± 0.0	79.4 ± 9.80	33.8 ± 5.40

Several liver function tests were evaluated in both SCD and SCT patients (Figure 1). The results showed that ALP levels were elevated in patients with SCD and SCT (p<0.01). Furthermore, total protein was increased in patients with SCD (p<0.001) and SCT (p<0.0001). The results showed that albumin levels were not significantly different between groups. In addition, ALT levels were elevated in both groups, but SCD patients exhibited a statistically significant difference (p<0.05) compared with healthy individuals. Similarly, AST levels were elevated in both conditions, with a significant difference only noted in SCD patients (p<0.0001) compared with SCT patients and healthy individuals.

The correlations between age and liver function tests were evaluated in both SCD and SCT patients. In SCD patients, the results indicated a negative connection between age and all liver function tests. However, a significant difference was only observed between age and ALP (p<0.0001), ALT (p=0.0321), and AST (p=0.0128) (Figure 2). In SCT patients, a negative correlation was observed between ALP ($p < 0.0001$), albumin ($p= 0.0020$), ALT ($p= 0.3157$), and AST ($p < 0.0001$) and age. In contrast, no correlation was shown between age and total proteins ($p= 0.6474$) (Figure 3).

DISCUSSION

SCD is an autosomal recessive hematological disorder that results in the formation of abnormal red blood cells. This genetic disorder is initiated due to a mutation in the gene encoding hemoglobin, causing a high mortality rate [10]. The prevalence of abnormal genetic variants causing HbS in at least 40 nations ranges from 2% to 30%, resulting in significant morbidity [10]. The frequency of SCD and SCT cases in Taif Province is limited. Therefore, this study was performed to assess the frequency of SCD and SCT and to measure liver function tests in affected individuals and healthy controls in Taif Province. Understanding the prevalence of both SCD and SCT and the potential liver involvement is essential for implementing specific management strategies.

In the present study, we first assessed the prevalence of both SCD and SCT. Data demonstrated that the prevalence of SCD was 11.1%, while the prevalence of SCT was 40.9%. A nationwide community-based survey indicated a high prevalence of SCD, with the condition being most prevalent in the eastern and southern areas, followed by the Western region of Saudi Arabia [11]. Another study showed that the number of SCD cases was higher (22.6%) in Jazan, Saudi Arabia. However, this study did not estimate the number of SCT cases [12]. Another retrospective study conducted in Riyadh reported a total of only 160 patients diagnosed with SCD between 2016 and 2021 [13]. The frequency of SCD in this study was low, which may be related to the study design, as they excluded patients with SCT and patients younger than 14 years. It was reported that the incidence in the adult population was 4.2% for SCT and 0.26% for SCD [3]. However, in newborn screening, the incidence of SCT was approximately 21%, while that of SCD was 2.6% [3].

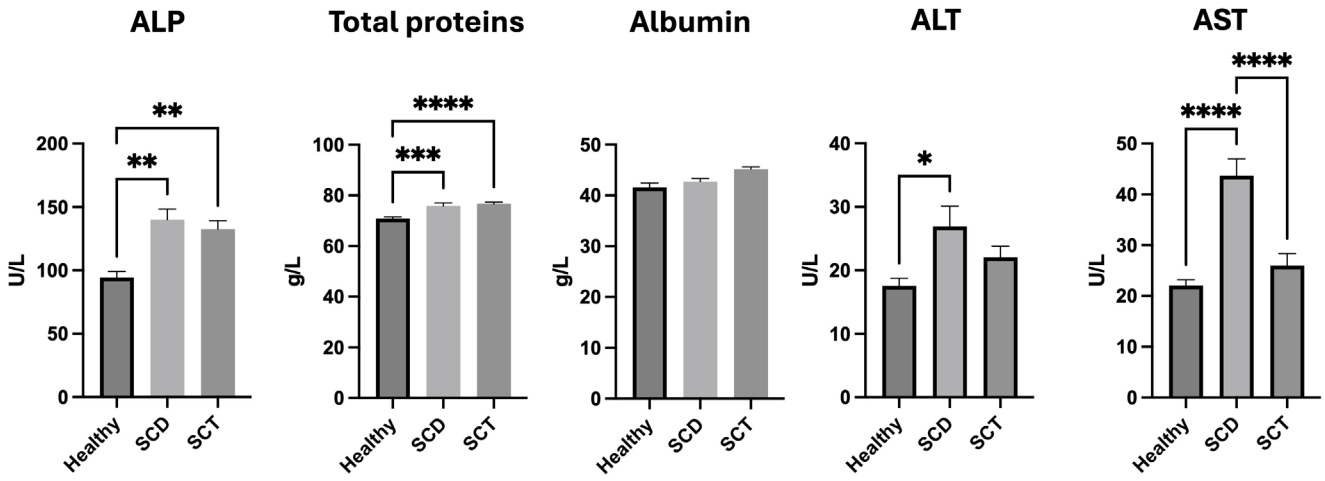

Figure 1. One-way ANOVA evaluation of liver function tests in all groups
Significance: *p≤0.05. **p≤0.01, ***p≤0.001 and ****p≤0.0001.

High HbF levels are linked to a generally milder disease phenotype and survival advantage, making them possibly the most significant genetic driver of severity in SCD [14]. A previous study found that higher HbF% provides an overall survival advantage and it is linked to decreased vaso-oclusive episodes (VOEs), dactylitis, acute coronary syndrome (ACS), leg ulcers, osteonecrosis, and cholelithiasis [14]. In our study, the levels of HbF were 15.50 and 2.61% in patients with SCD and SCT, respectively. It was reported that HbF levels in patients with SCD are higher, ranging from roughly 3% – 25%, with an average of about 7% [14]. Consistent with our study, the majority of patients in Saudi Arabia's Eastern Province have extremely high HbF levels [15]. Symptoms in patients with SCD persist despite elevated HbF levels, possibly as a result of the heterogeneous cellular distribution of HbF, which may not equally shield all erythrocytes from the damage caused by polymerization [15]. For better understanding, HbF levels should be interpreted in combination with other data, such as the total hemoglobin level and reticulocyte count [14]. It was demonstrated that elevated HbF levels may occasionally arise from deletions of the β-globin gene or point mutations in the HbF promoters [16]. Another study suggests that

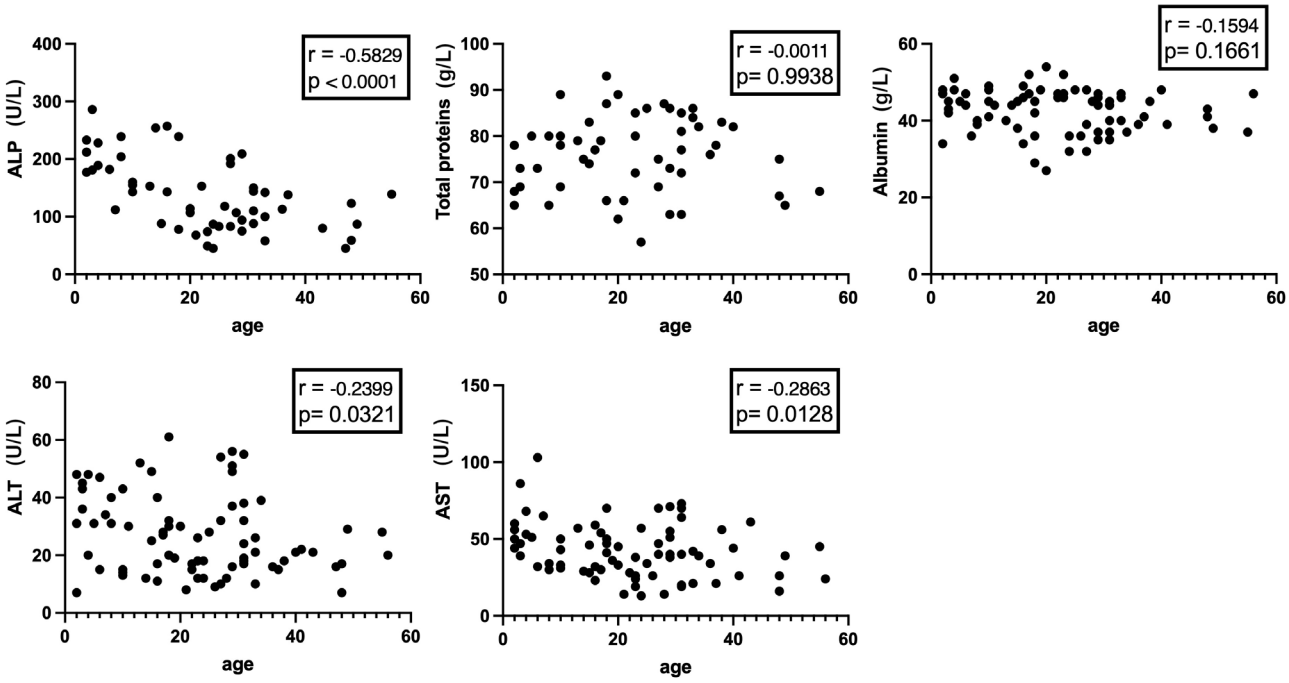

Figure 2. Association between age and liver function tests in SCD patients (Pearson correlation)

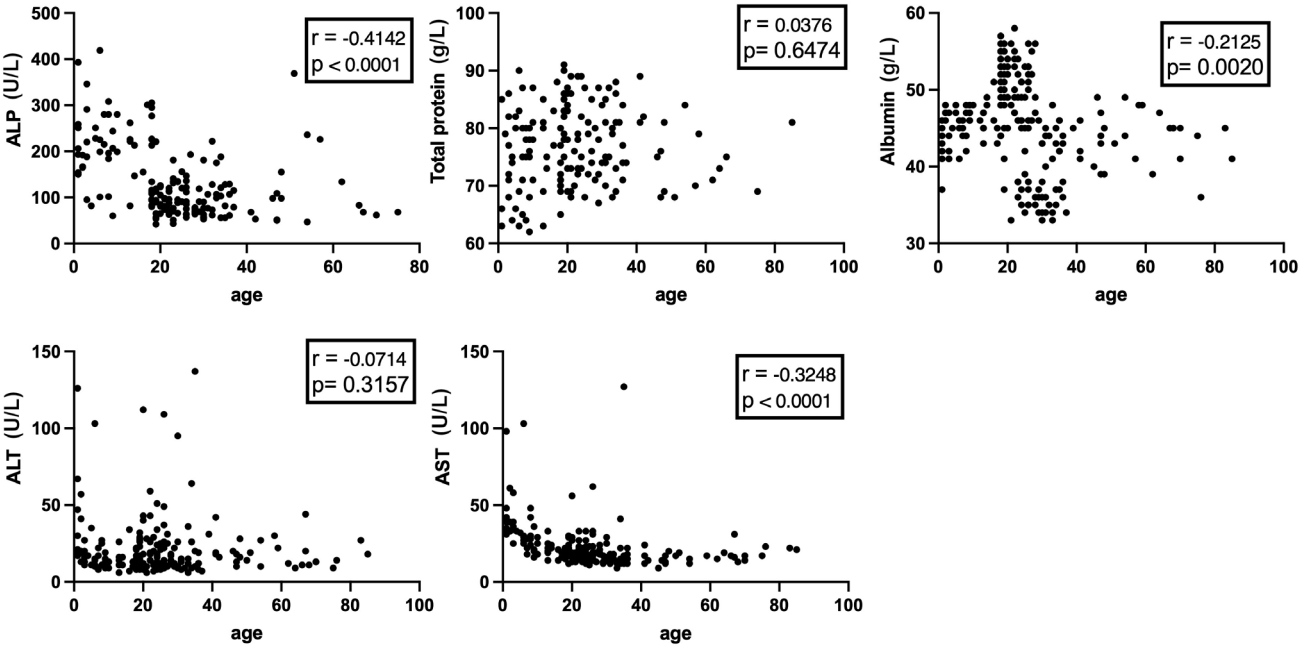

Figure 3. Association between age and liver function tests in SCT patients (Pearson correlation)

patients with elevated HbF may still experience severe disease due to the unequal distribution of HbF among F-cells, resulting in certain cells having inadequate amounts to prevent HbS polymerization [17].

Sickle cells tend to become trapped in blood vessels, causing damage to several organs, and the incidence of organ dysfunction increases with age [18]. In the present study, several liver tests (total protein, ALP, AST, and ALT) were found to be abnormally elevated in patients with SCD and SCT. All of these tests, except albumin, were significantly higher in SCD patients. In contrast, only the total protein and ALP were found to be elevated in SCT patients. A previous study suggested that the higher serum total protein levels found in SCD and SCT patients were attributed to hypergammaglobulinemia reported in those patients [19]. Discrepancies in routine liver function tests are common in patients with SCD and do not in themselves indicate actual liver disease [20]. A report has shown that 74% of patients with SCD have abnormal levels of ALT, AST, and ALP enzymes [7]. Furthermore, patients diagnosed with SCD frequently exhibit high levels of ALP, possibly due to cholestasis or bone pathology [7]. A further study revealed that one-third of individuals with SCD exhibited abnormal liver function tests [8]. In the present study, we have also found a negative correlation between liver function tests and age, meaning that these markers are high in patients with younger age. In agreement with our findings, patients with SCD exhibit liver function test abnormalities, with the severity of these abnormalities diminishing with increasing age [21]. In contrast, liver impairment in people with SCD is 10% and is projected to rise in the aging SCD patients [18]. It should be noted that severe liver disease in children is infrequently documented due to misinterpretation of liver function tests and potential confusion between hemolysis and indicators of liver damage [8]. Additionally, the clinical manifestation of SCD varies throughout age groups and is influenced by a number of factors, including genetic background, environmental circumstances, and accessibility to healthcare [22].

Liver disease significantly contributes to morbidity and death in individuals with SCD [20]. However, the natural history of liver illness remains poorly defined, and there is insufficient evidence to support specific therapeutic interventions [20]. Sinusoidal blockage, caused by sickled erythrocytes and hyperplasia, leads to hepatocyte ischemia, resulting in subsequent damage of neighboring hepatocytes and cholestasis [18]. Chronic hemolysis causes hyperbilirubinemia, leading to an elevated bilirubin burden in the biliary ducts, and the release of heme, which may exacerbate SCD-related liver damage by triggering proinflammatory activation of liver macrophages [18]. In addition, liver damage may be due to iron overload, which is a worrisome consequence of prolonged transfusion in SCD patients. Excess iron accumulates in the hepatic parenchyma and other organs, leading to end-organ damage via reactive oxygen species (ROS)-mediated lipid peroxidation [23]. Therefore, it is recommended that serum ferritin levels and liver biopsy be utilized to follow up with individuals with excess iron and to evaluate the therapeutic response [24].

Not all the standard liver tests, such as bilirubin, were evaluated in this study. In addition, a history of blood transfusions was lacking in patients with SCD. This missing information would provide comprehensive information about the causes of abnormal liver function tests. It is difficult to claim liver dysfunction without a proper liver biopsy analysis. Future studies should include these parameters to provide comprehensive insights into the effect of SCD and SCT on the liver, ultimately leading to their optimal management.

CONCLUSIONS

The prevalnce of SCD and SCT is high in the study population. Elevations in routine liver function tests are frequently observed in both SCD and SCT patients and are correlated with age. These observations suggest that the liver may be involved in both disorders, but further investigation and comprehensive liver function testing are warranted to confirm these findings and enhance generalization.

ABBREVIATIONS

ACS – Acute coronary syndrome
ALP – Alkaline phosphatase
ALT – Alanine aminotransferase
AST – Aspartate transaminase
HbF – Fetal hemoglobin
HbS – Hemoglobin S
SCD – Sickle cell disease
SCT – Sickle cell trait
VOE – Vaso-oclusive episode

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AUTHORS' CONTRIBUTION

MA – Conceptualization, methodology, formal analysis, writing original draft and review, final revision
TA – Methodology, data management, final revision

GA – Methodology, data management, final revision

HMA – Formal analysis, data curation, final revision

MAA – Data curation, final revision

NA – Investigation, software, final revision

HA – Investigation, software, final revision

MA – Investigation, software, final revision

MMA – Formal analysis, data management, final revision

ASA – Conceptualization, supervision, data management, final revision

All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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