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Evaluating the Relationship between Ferritin and Renal Function Tests in Adult Sickle Cell Anemia Patients Who Do not Take Iron Chelating Agents

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ABSTRACT

Background: *Sickle cell anemia (SCA) patients are exposed to increased iron levels due to frequent blood transfusions and hemolysis, which can lead to organs damage.* ***Objective:*** *This study explored the significance of iron effects on the kidneys in SCA patients who were not taking iron chelating agents (ICA).* ***Materials and Methods:*** *A case-control study involved 42 patients with SCA (14-55 years), who were not taking ICA, and 50 age- and sex-matched apparently healthy individuals. Hemoglobin analysis was done by Bio-Rad D10 analyzer. Ferritin was quantitated by Roche cobas e411 analyzer; urea and creatinine were evaluated by Abbott ARCHITECT c4000 analyzer. The correlations between these biomarkers were determined using Pearson's correlation.* ***Results:*** *Significantly higher ferritin levels in SCA patients compared to healthy controls were found (642.75±254.02 vs. 40.56±37.11 ng/mL, p = <0.001; respectively), whereas no significant difference between patients and controls was recorded in urea (p = 0.305) or creatinine levels (p = 0.192). No significant correlation was found between ferritin and urea levels (p = 0.423) or between ferritin and creatinine levels (p = 0.29).* ***Conclusions:*** *Iron's effect on kidney function may be less pronounced than on other organs.*

Keywords: Sickle Cell Anemia, Iron Overload, Renal Function Tests, Ferritin.

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INTRODUCTION

Sickle cell anemia is one of the most prevalent genetic diseases, inherited in autosomal recessive pattern [1]. Between the years 2000 and 2021, the worldwide prevalence of SCA increased by about 41%, from about 5.5 million people to about 7.7 million [2,3]. Every year, approximately 300000 newborns are born with SCA globally. There were nearly 5100 SCA patients reported in 2015 in Iraq, of which Basra province had the highest prevalence, with 124 cases per 100,000 (Sadeq *et al.*, 2024). Sickle cell anemia results from a single nucleotide polymorphism (SNP) at the 6th position in the beta-globin gene's first exon. This SNP causes the change from glutamic acid to valine (GAT to GTT) [4]. When this type of beta-globin chain binds to an alpha-globin chain, hemoglobin S (HbS) is formed [5].

Red blood cells can change from their typical biconcave disc-shape to a half-moon or sickle shape when exposed to hypoxic conditions, due to the hemoglobin S's polymerization during deoxygenation [6]. This changes the shape and function of the membrane of RBCs and makes them more fragile. Eventually, this causes RBC destruction (hemolysis) and hemoglobin release, leading to anemia [7,8]. Regular blood transfusions

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are one of the most used treatments for anemia in SCA, but they can lead to iron overload, which can damage organs through oxidative stress, inflammation and ferroptosis [9]. Chronic hemolysis also increases iron levels, as the hemoglobin released and broken down into heme and globin. The heme is further metabolized into iron and bilirubin [10,11]. Ferritin is the principal protein for iron storage, with each ferritin molecule has the ability of containing 4000 to 4500 atoms of iron [12].

Serum ferritin is an essential test in the diagnosis of iron status and iron overload in SCA patients. It is an affordable and widely available [13,14], and in the absence of inflammation, there is a positive correlation between the total stored body iron and the serum ferritin concentration [15]. Renal function tests include urea and creatinine, which are two important measures for the evaluation of kidney health and decision making about drugs and their dosages, as many of them may cause harmful consequences if the kidneys are not working properly [16]. Iron chelating agents are used to mitigate the effect of increased iron, but they have adverse effects, including possible hepatic and renal damage [17]. This study aimed to evaluate kidney functions in adult SCA patients who were not affected by the side effects of ICA. It also examined the association between kidney function tests and serum ferritin levels, in order to determine the relationship between iron status and renal function.

MATERIALS AND METHODS

Study design

In this case–control study, forty-two SCA patients, aged between fourteen and fifty-five years old were involved. These patients were not taking ICA; they did not have any other blood, acute or chronic diseases, autoimmune or malignant diseases; they had no major surgery in the last 3 months, no recent drug or alcohol intake and were not pregnant or lactating. As a controls group, fifty apparently healthy volunteers, who matched the sex and age of the patients, were chosen. They did not have a family history of any blood disorder; they had no acute, chronic, autoimmune or malignant diseases; they had not undergone any blood transfusion or recent major surgery; they were not smokers, taken alcohol or have any recent intake of any drug; also, they were not pregnant or lactating.

Sample collection

Five milliliters of blood were collected from each participant by venipuncture. Two milliliters were collected in ethylenediaminetetraacetic acid (EDTA). Three milliliters were collected in gel-containing serum separating blood collection tubes and centrifuged to separate serum.

Laboratory analysis

The whole blood collected in EDTA tubes was used for hemoglobin analysis by the high performance liquid chromatography (HPLC) analyzer D10 from Bio-Rad to determine the hemoglobin variant of each subject. The serum was used for urea and creatinine measurement by chemiluminescence immunoassay via Abbott ARCHITECT c4000, and ferritin measurement by Roche cobas e411 (CLIA).

STATISTICAL ANALYSIS

The version 26 of SPSS software was used for statistical analysis. Categorical data were compared using chi-square test, numerical data were compared by independent samples t-test and the correlations between urea, creatinine and ferritin were assessed by Pearson correlation.

RESULTS

Table 1 shows the demographical characteristics of the patients and healthy controls. No significant age (p = 0.358) or sex (p = 0.882) differences were noticed between the patients and the controls.

The levels of urea, creatinine and ferritin were demonstrated in **Table 2**. There was no significant difference in urea and creatinine levels between study groups (p = 0.305 and 0.192,

respectively), whereas ferritin levels had demonstrated significant difference (p <0.001).

Figure 1 shows the distribution of ferritin levels among SCA and healthy subjects.

As shown in **Table 3**, there was a significant positive correlation between urea and creatinine levels (r = 0.23, p = 0.03). However, there was no significant correlation between ferritin and urea levels (p = 0.423) or between ferritin and creatinine levels (p = 0.29).

Table 1: Demographical characteristics across study groups.

Groups	Males No. (%)	Females No. (%)	P-value	Age (Mean±SD)	P-value
SCA	25 (59.5%)	17 (40.5%)	0.882	26.38 ± 12.3	0.358
Controls	29 (58%)	21 (42%)		24.42 ± 7.92	

Independent samples t-test, SD = standard deviation.

Table 2: Levels of Urea, Creatinine, and Ferritin in sickle cell anemia patients and healthy controls.

Items	SCA group (Mean±SD)	Control group (Mean±SD)	P-value
Urea (mg/dL)	24.67±5.11	25.84±5.68	0.305
Creatinine (mg/dL)	0.53±0.26	0.60±0.25	0.192
Ferritin (ng/mL)	642.75±254.02	40.56±37.11	<0.001

Independent samples t-test.

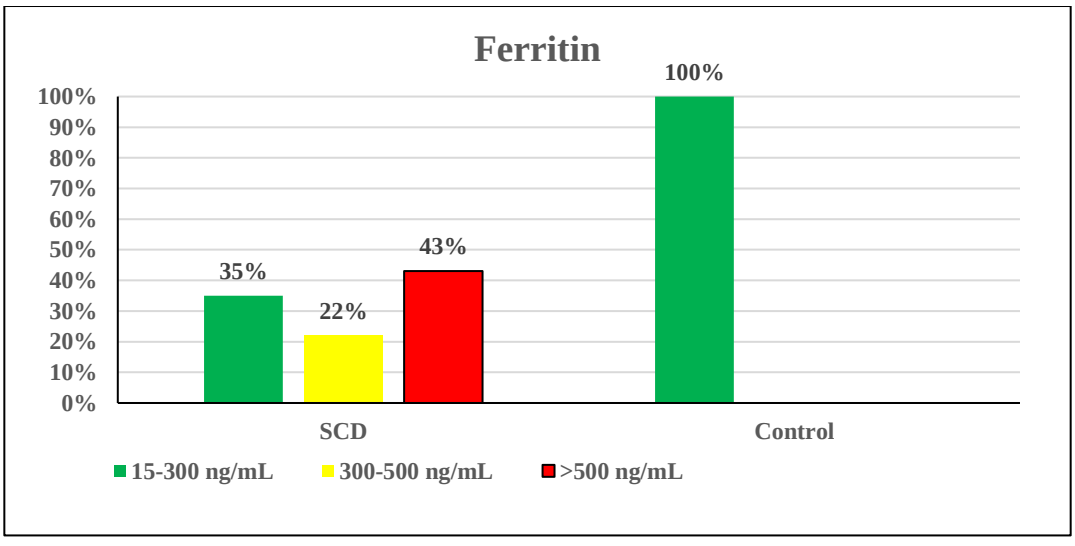

Figure 1: Ferritin levels in the study groups.

Table 3: The Correlation between Ferritin, Urea and Creatinine in Sickle Cell Anemia Patients.

Items		Creatinine	Ferritin
Urea	**R**	0.23	-0.09
	P-value	0.03	0.423
Creatinine	**R**		-0.117
	P-value		0.29

DISCUSSION

Significantly higher levels of ferritin in SCA patients is attributed to frequent blood transfusions for anemia treatment [18]. Patients receiving three or more transfusions annually had elevated iron stores [19]. Each unit of transfused blood introduces about 250 mg of iron, whereas the human body do not have an efficient physiologic pathway to eliminate the accumulated iron, which leads to iron overload that causes substantial effects on liver, heart, and endocrine glands [20,21]. Another cause of increased iron in SCA patients is the increased bone marrow production of erythroferrone during the process of RBCs production (erythropoiesis) to compensate for the destructed RBCs. Erythroferrone can inhibit hepcidin, leading to increased gastrointestinal iron absorption [22]. Chronic hemolysis also drives iron overload via increased iron release from heme metabolism [10,11]. Iron overload is one of the main predictors of death in SCA patients [23].

No significant difference found in urea and creatinine levels between patients and controls. Aldwaik *et al.* found that renal function tests exhibit no significant correlation with serum ferritin levels in patients with hemoglobinopathies [24]. Tammadondar *et al.* also found no significant correlation between creatinine and ferritin levels in hemoglobinopathies patients [25]. These results suggest that iron effect is not pronounced on the kidneys. The kidneys show lower iron deposition due to their role in iron reabsorption, not iron storage, as Mohammad *et al.* noted that ferroportin in the kidneys is implicated in increased renal tubular iron reabsorption in cases of iron overload, and that increased kidney iron absorption helps protecting the kidney, but increases iron availability in the circulation leading to increased deposition in the liver and other organs [26,27].

In contrast, some studies had found decreased urea and creatinine levels attributed to kidney hyperfiltration, where the kidney increases the glomerular filtration rate to compensate for the increased demand, due to chronic hemolysis and due to medullary hypoxia with reduced kidney concentration ability [28]. Moreover, Qadah *et al.* reported that in SCA patients hepatic dysfunction lowers urea and decreased muscle mass lowers creatinine [29]. Oppositely, Ismail *et al.* found increased creatinine levels in SCA patients with nephropathy [30]. This contrast may stem from difference in cohort disease stage and patient selection criteria. However, hyperfiltration in the kidneys of SCA patients could mask early declines in renal health by transiently reducing initially elevated urea and creatinine levels, potentially obscuring early signs of kidney damage. Hyperfiltration is defined by a glomerular filtration rate (GFR) exceeding normal limits [31]. Although hyperfiltration can initially reflect a physiological response to increased renal workload, sustained

hyperfiltration may predispose individuals to glomerular damage and progressive kidney disease [32,33]. Therefore, in case of high clinical suspicion or high risk patients, measurement of GFR [34] using reference methods had to be considered in SCA patients for early detection of any kidney damage, which may be missed by depending on routine serum creatinine and urea.

Limitations and future directions

The cross-sectional design prevents establishing causal relationships between ferritin levels and renal function parameters over time. Longitudinal studies with larger sample sizes are needed to track changes in ferritin levels and renal function over time. More sensitive markers of kidney function, such as cystatin C and direct measurement of glomerular filtration rate using reference methods, should be employed to detect subtle renal changes that might be missed by conventional renal function tests.

CONCLUSIONS

Adult SCD patients who do not take ICA have iron overload primarily due to frequent blood transfusions and hemolysis. However, that iron's effect on kidney function may be less pronounced than on other organs such as the liver and heart. Measuring GFR is recommended to detect early kidney dysfunction as the conventional measures of renal functions may be affected by renal hyperfiltration.

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