

Blood transfusion and iron overload in patients with Sickle Cell Disease (SCD): Personal experience and a short update of diabetes mellitus occurrence

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Abstract. *Introduction:* In patients with sickle cell disease (SCD), vaso occlusive crisis (VOCs) and iron intoxication due to repeated blood transfusion may cause damages in many organs, including the kidneys, lungs and brain, and pancreas. *Aim of our study:* To evaluate the iron status, hepatic functions and fasting plasma glucose (FPG) in non transfusion dependent (NTD-SCD) patients and transfusion dependent (TD-SCD) patients yearly for 5 years. Cardiac status was evaluated using echocardiography. *Results:* 16 adults with NTD-SCD and six with TD-SCD were studied. 6/16 NTD-SCD had serum ferritin (SF) > 500 ng/mL, and 5/16 patients had high LIC (> 36 $\mu\text{mol Fe/kg}$ dry weight). 2/16 had impaired fasting glucose (IFG). The TD-SCD patients were on top-up transfusion and oral iron chelation therapy (Exjade). All had high LIC, but 2/6 had SF <500 ng/mL. Liver enzymes were high in 2/6 patients. One had IFG. Five years after the initial assessment, 3/16 NTD-SCD developed diabetes mellitus (DM) and 2/16 IFG. In TD-SCD, 2/6 developed DM and 1/6 had IFG. Echocardiography revealed abnormalities in 5/22 (22.7%). *Conclusions:* A significant number of our patients with ND-SCD and TD-SCD develop dysglycemia, hepatopathy, and echocardiographic abnormalities during the follow-up that need effective early detection and management. However, the prevalence of DM in our SCD remains lower than in the general population in Qatar. TD-SCD patients who developed DM were younger and had high LIC and SF compared to those who developed DM in the NTD-SCD (www.actabiomedica.it).

Key words: Sickle cell disease, blood transfusion, iron overload, complications, glucose homeostasis, diabetes mellitus, metformin.

Introduction

Sickle cell disease (SCD) is an inherited autosomal recessive disease genetic disease caused by a single mutation in the β -globin gene, leading to the production of an abnormal hemoglobin called hemoglobin S (HbS), which polymerizes under reduced oxygenation conditions (such as stress, infection, dehydration, or lower temperature), causing rigid sickle-shaped red blood cells (RBCs) and hemolytic anemia. Sickled

RBCs are very fragile and rigid, and patients consequently become anemic and develop frequent and recurrent vaso-occlusive crises (1). Furthermore, the presence of impaired vasodilation, vasomotor hyper-responsiveness, chronic inflammation and oxidative stress participate to the development of vaso-occlusive processes and chronic vasculopathy (2,3). Remarkable variability of the clinical severity of SCD is widely acknowledged, from those with very mild disease to individuals with severe complicated disease with multiple

disabling symptoms leading to premature death.

Disease-modifying therapies such as hydroxyurea (HU) and chronic blood transfusions can reduce the rate of complications and may prolong survival, but hematopoietic stem cell transplantation (HSCT) is the only curative treatment available for patients with SCD; however, its use is limited by lack of suitable human leukocyte antigen (HLA)-matched donors and decreased application in older patients with significant morbidity (4).

HU, a cytotoxic drug, provides clinical benefit through the induction of fetal globin (HbF, $\alpha_2\gamma_2$) which competes with sickle globin; thus, reducing SCD symptoms, but response to HU is not uniform among patients and concerns for long term use persist (5-7). HU therapy is recommended for adults with 3 or more severe vaso-occlusive crises (VOC) during any 12-month period, with SCD pain or chronic anemia interfering with daily activities, or with severe or recurrent episodes of acute chest syndrome (ACS) (8), although it can contribute to subfertility in adult men with SCD (9).

Multiple other drugs (L-glutamine, crizanlizumab, and voxelotor) have recently been approved for the treatment of SCD, with several others at various stages of clinical testing (10,11). However, more studies are required before definitive recommendations can be made regarding their use for SCD-related complications (12).

Several key studies have proven the efficacy of red blood cells (RBCs) transfusion therapy in the prevention as well as treatment of acute and chronic complications of SCD. Transfusion with RBCs can be administered by a simple (top-up) or exchange transfusion. Acute transfusion is more frequently used to increase tissue oxygenation by correcting anaemia, while exchange transfusion (automated or manual) is used to prevent or reduce the complications of sickling by reducing the HbS % content of the blood. Chronic transfusions are predominantly used to treat patients with severe complications of SCD when HU is ineffective (13-15). The age of starting RBCs transfusion, the rate of RBCs transfusion, and the nature of the transfusional regime affect the rate and extent of iron overload (IOL) in SCD (16). In patients receiving episodic transfusion, IOL is usually not recognized and

often not treated while repeated simple blood transfusions will inevitably lead to IOL, especially in adults with SS. In this context, iron chelation therapy has become a critical component of the transfusion program to prevent complications of iron accumulation in patients receiving multiple transfusions (17-19).

The objective of this study was to evaluate IOL, assessed by ferritin level (SF), liver iron concentration (LIC) and cardiac T2*, in two groups of SCD patients depending on whether they were not or top-up frequent transfusion requiring. As a secondary aim, we evaluated to glucose homeostasis in relation to hepatic and cardiac iron overload. A short update of diabetes mellitus occurrence is also reported.

Patients and methods

Twenty-two patients homozygous for SCD (SS), as documented by hemoglobin electrophoresis, attending to Department of Medical Oncology, Hematology Section, National Centre for Cancer Care and Research of Doha (Qatar) were included in the study. 16 SCD patients (10 males and 6 females; mean age 33 ± 14 years) were non transfusion dependent (NTD-SCD) and 6 patients (4 males and 2 females; mean age 25 ± 10 years) required chronic blood transfusions (TD-SCD).

The study was initiated after the approval of Institutional Medical Ethics and review Committee of Hamad Medical Centre of Doha (Qatar) (15281/15 – and MRC-01-22-155) Retrospective Evaluation of Patients with Iron Overload by Ferriscan® T2* MRI). As per the Declaration of Helsinki, confidentiality, deidentification, and anonymity of personal data were strictly maintained.

An extensive medical history, including transfusion and chelation therapy, and a physical examination was performed for each patient. Lab. investigations included measurement of their serum concentrations of iron, serum ferritin (SF), fasting plasma glucose (FPG), HbA1c, alkaline phosphatase (ALP), alanine transferase (ALT), aspartate transferase (AST) and albumin concentrations. Anthropometric evaluation and biochemical tests were assessed yearly for 5 years.

Height and weight were measured using a standard technique. BMI was calculated as weight in kil-

ograms divided by the square of height in meters. Height and weight were measured according to international recommendations (20). An adult patient was considered obese when BMI was $\geq 30 \text{ kg/m}^2$, overweight when BMI was $25 - 30 \text{ kg/m}^2$ (20). Those with impaired fasting glucose [fasting plasma glucose (FPG) between 100 to 125 mg/dL (5.6-6.9 mmol/L)], according to ADA criteria, were tested by standard oral glucose tolerance test (OGTT: 75 g glucose). Patients with 2 h-PG values, after OGTT, between 140–199 mg/dL (7.8–11.0 mmol/L) were defined impaired glucose tolerance (IGT). Newly diagnosed diabetes mellitus (DM) was those with FPG $\geq 126 \text{ mg/dL}$ or 2 h-PG $\geq 200 \text{ mg/dL}$ (FPG: $\geq 7.0 \text{ mmol/L}$ or 2h-PG: $\geq 11.1 \text{ mmol/L}$) (21). In addition, an HbA1c level below 5.7% is considered normal, between 5.7% and 6.4% is considered prediabetes and $\geq 6.5\%$ on two separate tests indicate type 2 diabetes (T2DM) (21).

Iron overload was assessed by direct and indirect methods by SF and Magnetic Resonance Imaging (MRI) T2* MRI of liver and heart. SF was measured by immune enzymatic and chemiluminescence immunoassays. The manufacturer's normal reference range values were 30-350 ng/mL in males and 15-150 ng/mL in females. A cut-off value of 300 ng/mL in males and 200 ng/mL in females is usually consistent with iron overload (22). Generally, a cut-off value of SF concentration higher than 800 ng/mL indicate significant IOL (22).

Liver iron concentration (LIC) by MRI was measured using Ferriscan[®] following the method of St Pierre et al. (23). Normal LIC ranges from 0.2 mg Fe/g dry weight (d.w.) (3.6 $\mu\text{mol Fe/kg d.w.}$) to 2 mg Fe/g d.w. (36 $\mu\text{mol Fe/kg d.w.}$). The severity of LIC was graded as follows: normal (LIC $< 36 \mu\text{mol Fe/kg d.w.}$); mild (LIC > 37 and $< 126 \mu\text{mol Fe/kg d.w.}$), moderate (LIC > 126 and $< 252 \mu\text{mol Fe/kg d.w.}$) and severe overload (LIC $> 252 \mu\text{mol Fe/kg d.w.}$) (23,24).

All patients underwent an echocardiographic examination. Normal systolic function was defined as ejection fraction $>55\%$. Cardiac MRI T2* was evaluated in 8 patients (6 TD-SCD, and 2 NTD-SCD) using a 1.5 T scanner (GE Signa/Excite HD, Milwaukee, WI, USA). A cut-off value of cardiac T2* $> 20 \text{ ms}$ was considered normal. The cut-off points in the cardiac MRI instrument for iron load were as follows: Low

risk: 14-20 ms; Intermediate risk: 10-14 ms, and High risk: $< 10 \text{ ms}$ (24,25).

Statistical analysis

The data collected were analyzed using excel statistical pack. Quantitative variables are presented as mean and SD. Correlations of variables were evaluated using the Pearson's or Spearman's correlation analysis. Data were analyzed using the chi-square test or Student's t test, and the level of significance was set as P value < 0.05 .

Results

At baseline

The diagnosis of homozygous for SCD (SS) was documented by hemoglobin electrophoresis and the analysis for hemochromatosis genes C282Y and H63D was negative in all patients.

Sixteen adult patients with NTD-SCD who received no or occasional blood red blood cells (RBCs) transfusions for at least 5 years were studied. Twenty five percent of patients were females and all patient genotypes consisted of HbSS. None of them was splenectomised. Their Hb level varied between 7 to 10.5 g/dL. Hepatitis screening tests for HBV, HCV and HIV were negative in all patients. Patients were tested for gene for hemochromatosis genes C282Y and H63D and both mutations were negative.

Six patients with TD-SCD were selected for comparison. They were on chronic RBCs transfusions since the age of 5.5 ± 3.5 years to keep their Hb $> 10 \text{ g/dL}$ and iron chelation therapy (Deferoxamine: 20-40 mg/kg/ body weight, given subcutaneously using a small portable pump, days a week, starting from the age of 5 years). Deferoxamine was replaced by daily oral chelation therapy (Deferasirox: 30 mg/Kg/ body weight (6 days a week) for the past 6 years. Their calculated total iron received through RBCs transfusions ranged from 52.400 to 201.600 mg. A unit of RBCs, processed from 420 mL of donor blood, contains ~200 mg of iron (0.47 mg iron/mL of whole donor blood or 1.08 mg iron/mL

of pure RBCs). Chronic blood transfusions were indicated for severe symptomatic anemia in 2/6, and history of stroke in 4/6 patients. None was splenectomized. All were on HU treatment (20-30 mg/kg daily, from the age of (10: 18 years). Their BMI ranged from 20.2 to 28.8 kg/m² (mean:25.9 kg/m²). Hepatitis screening for HBV, HCV and HIV were negative in all patients. Four patients were cholecystectomized.

6/16 patients with NT-SCD had a SF level > 500 ng/mL, and 5 patients had a LIC concentration > 36 mmol /kg d.w. One patient had high LIC despite a concomitant SF concentration < 500 ng/mL. 5 patients had elevated ALT and/or AST concentrations. Two patients had impaired fasting glucose (IFG) but none had IGT or diabetes (DM).

3/6 patients with TD-SCD had moderate and 1 had severe LIC. Two patients had a SF level <500 ng/mL. Liver enzymes (ALT, AST) were high in two patients. One patient had IFG.

After 5 years of follow up:

Biochemical data and LIC in patients with SCD at the beginning of the study and at last observation (after 5 years of follow up) are presented in tables 1, 2 and 3. One patient developed hepatic cirrhosis with a LIC level of 59 mmol/Kg d.w. and had normal FPG level.

Table 1 compares the biochemical data and LIC in TD-SCD at the beginning of the study (A) and after 5 years of follow-up (B). FPG increased significantly and serum albumin concentration decreased significantly after 5 years of follow-up. LIC increased, but the difference was not statistically significant (P =0.46).

Table 2 compares the biochemical data and LIC in NTD-SCD at the beginning of the study (A) and after 5 years of follow-up (B). FPG and LIC increased significantly after 5 years of follow up. These patients were not on treatment with iron chelating therapy. Some of them had high SF values (range 112- 3.337, mean = 772 ± 1.200). Those with SF > 1.500 were offered chelation therapy but were not compliant.

Table 3 compares the biochemical data and LIC in patients with TD-SCD vs. NTD-SCD at the beginning of the study (A) and after 5 years of follow-up (B).

Table 1. Biochemical data and liver iron content (LIC) in TD-SCD at the beginning of the study (A) and after 5 years of follow-up (B)

(A)	Age yr	Hb g/dL	SF ng/mL	ALT U/L	AST U/L	ALP U/L	Albumin g/L	FPG mmol/L	LIC mmol/kg d.w.
TD-SCD Mean (SD)	24.8±10.2	8.56±0.85	3.310±3.078	33.0±25.1	35.0±12.7	165.8±106.0	44.8±1.3	4.6±0.7	11.1±13.3
(B)	Age yr	Hb g/dL	SF ng/mL	ALT U/L	AST U/L	ALP U/L	Albumin g/L	FPG mmol/L	LIC mmol/kg d.w.
TD-SCD Mean (SD)	30.6±9.9	8.9±0.9	2.767±2.925	55.4±31.6 *	51.8±17.5 *	136.8±73.5 *	38.8±5.1	5.9±1.1	16.1±8.9
P value	0.38	0.43	0.75	0.20	0.08	0.59	0.019	0.047	0.46

Legend: Hb = hemoglobin; SF = serum ferritin; ALT = alanine aminotransferase (normal values: < 40 U/L); AST = aspartate aminotransferase (normal values: < 40 U/L); ALP = alkaline phosphatase (normal values 40 to 129 U/L); FPG = fasting plasma glucose; LIC = liver iron concentration.

Table 2. Biochemical data and liver iron content (LIC) in patients with NTD-SCD at the beginning of the study (A) and after 5 years of follow-up (B)

(A)	Age yr	Hb g/dL	SF ng/mL	ALT U/L	AST U/L	ALP U/L	Albumin g/L	FPG mmol/L	LIC mmol/kg d.w.
NTD-SCD Mean (SD)	33.0±14.3*	10.1±1.9	772±1300	23.8±14.7	37.5±18.6	90.3±31.7	43.6±4.3	4.7±0.7	1.9±1.7
(B)	Age yr	Hb g/dL	SF ng/mL	ALT U/L	AST U/L	ALP U/L	Albumin g/L	FPG mmol/L	LIC mmol/kg d.w.
NTD-SCD Mean (SD)	38.3±14.3*	9.5±1.2	550±467	31.4±33.1	30.5±12.6	91.7±34.8	39.2±6.2	6.4±2.0	2.9±0.4
P value	0.32	0.36	0.51	0.44	0.21	0.93	0.06	0.001	0.02

Legend: Hb = hemoglobin; SF = serum ferritin; ALT = alanine aminotransferase (normal values: < 40 U/L); AST = aspartate aminotransferase (normal values: < 40 U/L); ALP = alkaline phosphatase (normal values: 40 to 129 U/L); FPG = fasting plasma glucose; LIC = liver iron concentration.

Table 3. Biochemical data and liver iron content (LIC) in patients with NTD-SCD versus TD-SCD at the beginning of the study (A) and after 5 years of follow-up (B)

(A)	Age yr	Hb g/dL	SF ng/mL	ALT U/L	AST U/L	ALP U/L	Albumin g/L	FPG mmol/L	LIC mmol/kg d.w.
NTD-SCD Mean (SD)	33.0±14.3	10.1±1.9	772±1,300	23.8±14.7	37.5±18.6	90.3±31.7	43.6±4.3	4.7±0.7	1.9±1.7
TD-SCD Mean (SD)	24.8±10.2	8.5±0.8	3,310±3,078*	33.0±25.1	35.0±12.7	165.8 ±106.0 *	44.8±1.3	4.6±0.7	11.1±13.3*
(B)	Age yr	Hb g/dL	SF ng/mL	ALT U/L	AST U/L	ALP U/L	Albumin g/L	FPG mmol/L	LIC mmol/kg d.w.
NTD-SCD Mean (SD)	38.3±14.3	9.5±1.2	550±467	31.4±33.1	30.5±12.6	91.7±34.8	39.2±6.2	6.4±2.0	2.9±0.4
TD-SCD Mean (SD)	30.6±9.9	8.9±0.9	2,767±2,925*	55.4±31.6*	51.8±17.5*	136.8±73.5	38.8±5.1	5.9±1.1	16.1±8.9*

Legend: Hb = hemoglobin; SF = serum ferritin; ALT = alanine aminotransferase (normal values: < 40 U/L); AST = aspartate aminotransferase (normal values: < 40 U/L); ALP = alkaline phosphatase (normal values: 40 to 129 U/L); FBG = fasting plasma glucose; LIC = liver iron concentration; * P: <0.05 NTD-SCD vs. TD-SCD.

Glucose homeostasis in relation to LIC:

3/16 patients with NTD-SCD had an OGTT compatible with the diagnosis of DM (at 46, 59 and 60 years of age). They were overweight and had positive family history of T2DM. 2/16 had IFG. Those who developed DM had had, a LIC level of 13, 22 and 75 mmol/kg d.w., respectively, five years before developing DM. Two patients who developed IFG had LIC of 27 and 39 mmol/kg d.w., respectively (Table 5).

In TD-SCD, 2 developed DM (at 18 and 25 years of age) and 1 had IFG. Those who developed DM had a LIC of 25 and 161 mmol/kg d.w. and a normal FPG five years before the development of DM. The patient with IFG had a LIC of 22 mmol/kg d.w. and a normal FPG five years before the development of IFG.

The diagnosis of DM was made on the base of fasting and 2-h PG after OGTT. All patients with DM had family history of T2DM. They had polyuria and polydipsia at presentation. None had ketosis. Patients with DM (both NTD-SCD and TD-SCD) were treated with oral hypoglycemic agents (metformin and/or gliclazide). Only 1 patient was on insulin glargine (basal) and lispro (prandial). In TD-SCD, diabetes occurred earlier compared to those with NTD-SCD and was associated with higher serum ferritin concentration (Table 4).

IFG was detected from 1 to 4 years (2.1± 1.3 years) after baseline.

3/8 SCD patients with dysglycemia were overweight and all patients with DM had positive family history of T2DM (Table 5). HbA1c was low < 4% in 3 patients who had abnormal fasting glucose (103, 103 and 153 mg/dL).

Anthropometric data (Table 5) revealed no statistical difference in age, height, weight or BMI between the two groups before and after 5 years of follow up.

Echocardiography and global cardiac T2*:

In 13/16 patients with NTD-SCD, the echocardiography showed a normal global left ventricular (LV) function and systolic ejection fraction (SEF%). One patient had left ventricular hypertrophy (LVH) and dilated left atrium (LAD), abnormalities of the left ventricle, dilated left atrium and dyskinesia were documented in 2/6 patients (Table 5). One TD-SCD had left atrial dilatation, tricuspid incompetence and

Table 4. Echocardiographic changes of patients with SCD and associated glucose abnormalities in relation to their BMI and iron load status (SF and LIC)

Type of hemoglobinopathy	Age (yr)	BMI (kg/m ²)	LIC (mmol/kg d.w)	SF (ng/mL)	Glucose abnormality	Echocardiographic changes
1. NTD-SCD	60	22	13	650	DM	Normal
2. NTD-SCD	46	23	72	800	DM	LVH Normal systolic EF
3. NTD-SCD	40	25.8	27	655	IFG	Severe LAD
4. NTD-SCD	59	24	22	400	DM	LAD, LV hypokinesia
5. NTD-SCD	28	21	39	1.995	IFG	Normal
6. TD-SCD	18	19.5	161	1.500	DM	LAD, Tricuspid incompetence, reduced systolic EF (49%)
7. TD-SCD	30	29	33	2.600	IFG	Normal
8. TD-SCD	25	26.5	25	9.100	DM	Normal

Legend: BMI = body mass index; LIC = liver iron concentration; SF = serum ferritin; IFG = Impaired fasting glucose; IGT = Impaired glucose tolerance; DM = diabetes mellitus; LVH = Left ventricular hypertrophy; LAD = left atrial dilatation.

Table 5. Anthropometric data of SCD patients (NTD-SCD and TD-SCD) and body mass index (BMI) before and after 5 years of follow-up.

Before	Age (yr)	Height (cm)	Weight (Kg)	BMI (kg/m ²)
NTD-SCD Mean (SD)	33.0 ± 14.3	160.3 ± 8.6	57.1 ± 12.8	22.7 ± 3.5
TD-SCD Mean (SD)	24.8 ± 10.2	163.0 ± 6.5	69.1 ± 7.4*	24.8 ± 4.2
After 5 yrs of follow-up	Age (yr)	Height (cm)	Weight (Kg)	BMI (kg/m ²)
NTD-SCD Mean (SD)	38.3 ± 14.4 *	162 ± 9	62.5 ± 8.7	23.5 ± 4.1
TD-SCD Mean (SD)	30.1 ± 9.2	166 ± 7.8	74.5 ± 8.8*	25.9 ± 4.2

*P < 0.05 NTD-SCD vs. TD-SCD.

reduced systolic EF (49%). All the 3 TND-SCD patients with cardiac abnormalities had global cardiac T2* > 20 ms (Table 4). All TD-SCD patients had a global cardiac T2* > 20 ms despite high LIC.

Correlations

After 5 years of follow up the group of TD-SCD had significantly higher LIC, SF, ALT, AST and ALP compared to the NTD-SCD (Table 2). LIC was correlated significantly with SF (r = 0.89, P: < 0.001) and both SF and LIC were correlated significantly with ALT level (r = 0.34 and 0.37 respectively, P = < 0.01). FPG was correlated significantly with the age of patients (r = 0.68, P < 0.01) but did not correlate with SF, LIC and BMI (Table 6).

Discussion

SCD is an important cause of morbidity and mortality worldwide. The complications of disease are numerous, affect every organ and/or tissue in the body and vary considerably among patients over the time which challenge its management. Although blood transfusion is one of the most effective ways to deal with specific acute and chronic complications of SCD, this approach is often associated with alloimmunization, iron overload, hemolytic reactions, and iron overload (26). Erythropheresis is currently the safest and the most efficient method, but it is costly, complex, and cannot be implemented everywhere, nor is it suitable for all patients (26).

It is worth noting that iron deposition in patients with SCD oc-

curs predominantly in the liver and less so in the heart and the endocrine organs (27-29). Iron deposition in patients with SCD generally follows the traditional pattern of transfusional iron overload; however, parenchymal hepatocyte deposition also occurs early, and chelation removes iron preferentially from the reticuloendothelium (30).

Classically, SF has been used to monitor patients with iron overload and assess their response to chelation therapy. SF has the advantage of being widely available, but not always correlate with body iron stores (31). Therefore, MRI has emerged as the standard of care for effective detection and quantification of iron in the heart and the liver (32).

Our study confirms an increased LIC (>36 mmol/Kg d.w.) and high SF in a considerable number of patients with TD-SCD (4/6; 66.6%) and NTD-SCD (5/16; 31.2%). Four NTD-SCD patients had a normal LIC despite a high SF level (> 500 ng/mL). In support of our data, Drasar et al. (33), observed that even sporadically transfused patients developed heavily iron overloaded, on par with those on transfusion programs.

The higher serum ALT, ALP, SF concentrations and increased LIC in TD-SCD compared to the TND-SCD, and the significant correlation between LIC, SF and ALT concentration in patients with SCD supported the concept of harmful effect of iron overload on hepatocytes (34-36).

It has been believed that TD-SCD patients appear to have lower risk of myocardial iron overload (MIO) than comparably transfused thalassemia major (TM) patients. In our study, none of the five patients who developed clinical and/or echocardiographic abnormalities had low global cardiac T2* values despite variable LIC. In support to our findings, Wood et al. (37), studied 17 patients with SCD and 19 patients with TM, who were receiving long-term transfusions, all SCD patients had normal cardiac T2* while 8/19 TM patients had high cardiac iron load.

Meloni et al. (38) reported five SCD patients who developed MIO after more than 11 years, but all their patients had poor compliance to chelation therapy with very high SF level (>4.600 ng/mL) and LIC (> 22 mg/g d.w.).

Our TD-SCD patients had significantly lower SF and LIC compared to their patients. Moreover, in

Table 6. Correlations between biochemical data and fasting plasma glucose before (1) and after 5 years of follow-up (2) in 21 SCD patients

	Age	BMI	Ferritin	LIC	ALT	AST	ALP	Albumin	FBG1	Age 2	Hb	Ferritin2	ALT2	AST2	ALP2	Albumin2	FBG2
Age	1.00																
BMI	0.15	1.00															
Ferritin	-0.27	-0.09	1.00														
LIC	-0.30	-0.19	0.89	1.00													
ALT	-0.50	-0.47	0.34	0.47	1.00												
AST	-0.41	-0.35	0.02	0.11	0.73	1.00											
ALP	-0.25	-0.14	0.34	0.25	0.54	0.20	1.00										
Albumin	-0.35	-0.01	-0.11	0.01	0.30	0.20	0.04	1.00									
FBG1	0.45	0.01	-0.02	0.05	0.05	-0.14	-0.04	-0.02	1.00								
Age 2	1.00	0.16	-0.25	-0.28	-0.50	-0.42	-0.23	-0.35	0.45	1.00							
Hb	0.12	0.26	-0.23	-0.31	-0.47	-0.51	-0.24	-0.19	0.07	0.12	1.00						
Ferritin2	-0.37	0.18	0.13	0.11	-0.05	-0.15	0.09	0.01	-0.25	-0.35	-0.02	1.00					
ALT2	-0.20	0.27	0.02	0.12	0.24	0.51	-0.13	0.17	-0.11	-0.20	-0.37	0.15	1.00				
AST2	0.10	0.36	0.24	0.18	0.04	0.25	0.17	-0.14	-0.03	0.11	-0.47	0.21	0.64	1.00			
ALP2	0.14	0.26	0.14	0.18	0.06	0.13	0.17	-0.18	-0.13	0.14	-0.24	0.06	0.40	0.70	1.00		
Albumin2	-0.59	0.03	-0.03	0.03	-0.06	-0.14	-0.19	0.19	-0.11	-0.60	0.00	0.21	0.09	-0.22	-0.37	1.00	
FBG2	0.66	0.05	-0.16	-0.09	-0.06	-0.24	0.12	-0.06	0.47	0.67	-0.25	-0.18	-0.10	0.00	0.05	-0.32	1.00

Legend: BMI = body mass index; LIC = liver iron concentration; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; FBG = fasting plasma glucose.

our patients with TD-SCD, cardiac manifestations occurred late in life (> 40 years). In addition, cardiac dysfunction occurred in 3 patients (2 with NTD-SCD and one with TD-SCD) who had normal LIC.

In the study of Wood et al. (37), abnormal T2* was observed only in TM patients who were receiving transfusions for 13 years or longer and was correlated with SF but not LIC. Cardiac dysfunction was present in 3/8 patients with low T2*.

Echocardiography abnormalities were identified in our 5/22 (22.7%) patients with SCD; all had global cardiac T2* > 20 ms. Bawor et al. (39) reviewed studied 123 cardiac MRI scans in 82 SCD patients. 68% of patients were female and the mean age at time of scan was 37 years. The average left ventricular ejection fraction was 57% (n=82). Cardiac abnormalities were identified in 60% of patients. Coates et al. (40) documented the occurrence of iron cardiomyopathy in a patient with SCD who presented at the age of 24 years with congestive heart failure (CHF), a cardiac T2* < 10 ms and an ejection fraction, assessed by MRI, of 45%. After aggressive chelation therapy for 3

weeks with deferiprone, she became asymptomatic. On the other hand, Alkindi et al. (41) confirmed the cardiac sparing effect in 58 chronically transfused patients with SCD (aged 35 ± 9 yr), even with the significant transfusion-related iron burden. Longitudinal studies investigating progression of echocardiographic abnormalities across the pediatric age spectrum in SCD are lacking. A retrospective longitudinal analysis of 829 echocardiograms from pediatric patients with SCD at steady state was performed by Harrington et al. (42). Cardiac abnormalities began early in childhood and progressively increased with age.

Iron overload is clearly an important factor responsible for the development of cardiac abnormalities (as in our patients) but other factors, such as levels of effective erythropoiesis, frequency of sickling episodes (hypoxic insult) and diffuse myocardial fibrosis, can contribute to cardiac risk (43-46). These observations have implications for both the diagnosis and subsequent management of cardiac abnormalities in this population of patients and support the need for further investigations in these patients.

In our TD-SCD, on chronic blood transfusion and iron chelation, LIC and SF did not change signifi-

cantly after 5 years of therapy. Compliance issue can explain part of this finding. However, recently, Alkindi et al. (41) evaluated a cohort of 44 SCD patient on long-term blood transfusion and iron chelation therapy. Similar to our results, after 5 years of follow up, the mean SF changed marginally from a baseline value of 4.311 to 4.230 ng/mL, LIC level dropped from 12 to 10.3 mg/gm d.w. and the mean value of cardiac T2*MRI improved marginally from 36.8 to 39.5 ms.

Effective iron chelation therapy is an important part of treatment in patients with SCD and iron overload. Previous studies have indicated that heavy iron overload may be responsible for up to 11% of deaths (47), particularly in the 25-34-year-old age range (48), thus highlighting the importance of monitoring and reducing body iron load in this patient group. Therefore, compliance with the prescribed treatment regimen is important for treatment efficacy and long-term reduction of body iron. Our results further reinforce the importance to monitor iron overload to address adherence to chelation therapy and improve management decisions.

Past studies have suggested a low (ranging from 3.5% to 7%) or zero prevalence of DM in patients with SCD (49-58). In our series, 5/75 patients followed with TD-SCD and NTD-SCD (6.6%) developed DM. However, DM occurred relatively early in TD-SCD versus TND-SCD. This finding pointed out to the negative effect of iron overload (oxidative injury) in the early development of DM in these patients. However, it must be noted that the prevalence of DM in the Qatari population is 12.6% in males and 13.2% in females, according to the World Health (59) and therefore the prevalence in our SCD patients is relatively lower than in the population. The cause of infrequent occurrence of DM in SCD patients was previously attributed to low BMI and lower patients' life span (49,60). However, our diabetic SCD patients were not underweight and all had family history of T2DM. TD-SCD patients who developed DM were younger and had high LIC and SF compared to those who developed DM in the NTD-SCD.

FPG was correlated with the age of the patients suggesting a progressive dysglycemia with age. In support of our findings, a multicenter study of Fung et al. (61) reported that for every 10 years of transfusion

therapy, subjects with SCD have a 2.5 times greater probability to develop diabetes (while patients with thalassemia have a double risk).

Yavropoulou et al. (62) and Smiley et al. (63) studied normoglycemic patients with SCD and demonstrated an impaired β -cell function with reduced insulin secretion even before OGTT was impaired. Conversely, an Italian study found that 11.5% of children and adolescents with SCD had insulin resistance (IR), which occurred even in subjects with normal BMI (64). The IR was attributed to malondialdehyde (MDA, the membrane lipid peroxidation products) and to carbonyl contents (the oxidative products of proteins). In addition, both SF and oxidative products (expressed as MDA and carbonyl levels) were significantly correlated with blood glucose, insulin level, and HOMA-IR (65).

Al Harbi et al. (66) suggested that patients with SCD and those with sickle cell trait were protected from development of diabetes as well its complications. These observations were not confirmed in a recent study of Zhou et al. (67). Compared to SCD patients without T2DM, SCD patients with T2DM had more frequently a diagnosis of nephropathy (28.0% vs. 9.5%; $P < 0.001$), neuropathy (17.7% vs. 5.2%; $P < 0.001$), and stroke (24.1% vs. 9.2%; $P < 0.001$). The prevalence of T2DM in SCD patients was similar to the general African American population with an increasing trend in recent years. These findings support the indication of a routine screening for T2DM in aging patients with SCD, and especially in those with comorbid hypertension and/or dyslipidemia (67) and an aggressive treatment in the affected population.

Moreover, a comparative study was performed on healthy individuals with T2DM or sickle cell trait (SCT), and patients with both T2DM and SCT (T2DM-SCT) comparing vascular function, hemorheological profile, and biomarkers of oxidative stress, inflammation, and nitric oxide metabolism. Results showed that oxidative stress, advanced glycation end products, and inflammation (interleukin-1 β) were greater in patients with T2DM-SCT compared with the other groups. Blood viscosity was also higher in T2DM-SCT patients compared to other groups. The authors concluded that SCT with T2DM. should be viewed as a risk factor for further cardiovascular dis-

orders (68). In support of this view, our patients with SCD and dysglycemia had relatively high cardiac abnormalities (4/7) compared to SCD without dysglycemia (1/67).

Recently, metformin was found to increase HbF, which may have a beneficial effect in SCD patients. Badawy et al. (69) studied 457 adult patients (age 33-52 years) with SCD, and DM. 142 (31%) were treated with metformin. The Authors found that metformin might have protective effects with less frequent hospital treated clinical events. They also recommended further prospective studies to evaluate metformin efficacy and cost-effectiveness in relation to clinical outcomes, quality of life, mortality, and health care utilization in adults with SCD.

It must be mentioned that in our study the use of HbA1c, as a parameter of monitoring glycemia, appeared to be misleading as we encountered many low HbA1c values ($< 4\%$) in patients with DM and high fasting plasma glucose level. These findings are supported by previous studies in SCD patients (70-72). Moreover, in two large, well-established cohorts, participants with sickle cell trait (SCT) had lower levels of HbA1c at any given concentration of fasting or 2-hour plasma glucose compared with participants without SCT (73,74). These findings suggest that HbA1c is an unreliable screening test for hyperglycemia and DM in SCD patients as well as those with sickle cell trait.

In conclusion, the choice of transfusion method, i.e., simple (top up) or exchange, should be based on clinical judgement of individual cases, considering benefits and risks. While RBCs transfusion may improve disease complications, IOL is a dreaded and inevitable consequence of ongoing transfusion therapy. IOL may also develop in non-transfused SCD patients and is probably related to intravascular hemolysis, which constitutes about a third of the hemolysis in SCD (75). It has been proposed that chelation therapy in SCD should start when patients have received 10-20 transfusions, with a SF > 1.000 ng/mL, or LIC > 3 mg/g d.w. (18, 33,76). Our data also suggest that in SCD monitoring for iron overload (SF and LIC) in relation to hepatic function, echocardiography, and glucose homeostasis, can improve early detection and management of complications.

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References

- Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet* 2017;390:311–23.
- Nader E, Conran N, Romana M, Connes P. Vasculopathy in Sickle Cell Disease: From Red Blood Cell Sickling to Vascular Dysfunction. *Compr Physiol* 2021;11:1785–803.
- Nader E, Romana M, Connes P. The Red Blood Cell-Inflammation Vicious Circle in Sickle Cell Disease. *Front Immunol.* 2020;11:454.
- Kassim AA, Sharma D. Hematopoietic stem cell transplantation for sickle cell disease: The changing landscape. *Hematol Oncol Stem Cell Ther* 2017;10:259–66.
- Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *J Med* 1995;332:1317–22.
- Steinberg MH, Barton F, Castro O, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003;289:1645–51.
- de Montalembert M, Voskaridou E, Oevermann L, et al.; All ESCORT HU Investigators. Real-Life experience with hydroxyurea in patients with sickle cell disease: Results from the prospective ESCORT-HU cohort study. *Am J Hematol* 2021; 96: 1223–31.
- Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA* 2014; 312: 1033–48.
- DeBaun MR. Hydroxyurea therapy contributes to infertility in adult men with sickle cell disease: a review. *Expert Rev Hematol* 2014;7:767–73.
- Ballas SK. The Evolving Pharmacotherapeutic Landscape for the Treatment of Sickle Cell Disease. *Mediterr J Hematol Infect Dis* 2020;12(1):e2020010.
- Rai P, Ataga KI. Drug Therapies for the Management of Sickle Cell Disease. *F1000Res* 2020;9:F1000 Faculty Rev-592.
- Leibovitch JN, Tambe AV, Cimpeanu E, et al. l-glutamine, crizanlizumab, voxelotor, and cell-based therapy for adult sickle cell disease: Hype or hope? *Blood Rev* 2022:100925.
- Davis BA, Allard S, Qureshi A, et al. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. *Br J Hematol* 2017; 176:179–91.
- Wang WC, Dwan K. Blood transfusion for preventing primary and secondary stroke in people with sickle cell disease. *Cochrane Database Syst Rev* 2013;11:003146.
- Howard J. Sickle cell disease: when and how to transfuse. *Hematol Am Soc Hematol Educ Program* 2016;2016:625–31.
- Inati A, Musallam KM, Wood JC, Taher AT. Iron overload indices rise linearly with transfusion rate in patients with sickle cell disease. *Blood* 2010;115:2980–1.
- Inati A. Recent advances in improving the management of sickle cell disease. *Blood Rev* 2009; 23 (Suppl 1): S9–13.
- Kwiatkowski JL, Hamdy M, El-Beshlawy A, et al. Deferiprone vs deferoxamine for transfusional iron overload in SCD and other anemias: a randomized, open-label noninferiority study. *Blood Adv* 2022; 6: 1243–54.
- Porter J, Garbowski M. Consequences and management of iron overload in sickle cell disease. *Hematology Am Soc Hematol Educ Program* 2013;447–56.
- Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of Childhood and Adult Obesity in the United States, 2011–2012. *JAMA* 2014 311(8):806.
- American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes – 2020. *Diabetes Care* 2020;43 Suppl 1:S14–S31.
- Taher AT, Porter J, Viprakasit V, et al. Deferasirox reduces iron overload significantly in nontransfusion-dependent thalassemia: 1-year results from a prospective, randomized, double-blind, placebocontrolled study. *Blood* 2012;120:970–7.
- St Pierre TG, Clark PR, Chua-anusorn W. Single spin-echo proton transverse relaxometry of iron-loaded liver. *NMR Biomed* 2004; 17: 446–58.
- Casale M, Meloni A, Filosa A, et al. Multiparametric Cardiac Magnetic Resonance Survey in Children With Thalassemia Major: A Multicenter Study. *Circ Cardiovasc Imaging* 2015;8(8): e003230.
- He T, Gatehouse PD, Smith GC, Mohiaddin RH, Pennell DJ, Firmin DN. Myocardial T2* measurements in iron-overloaded thalassemia: An in vivo study to investigate optimal methods of quantification. *Magn Reson Med* 2008;60:1082–9.
- Koehl B, Missud F, Holvoet L, et al. Continuous manual exchange transfusion for patients with sickle cell disease: an efficient method to avoid iron overload. *J Vis Exp* 2017; 121:551–72.
- Wood JC, Ghugre N. Magnetic resonance imaging assessment of excess iron in thalassaemia, sickle cell disease and other iron overload diseases. *Hemoglobin* 2008;32:85–96.

28. Hogen R, Kim M, Lee Y, et al. Liver Transplantation in Patients with Sickle Cell Disease in the United States. *J Surg Res* 2020;255:23-32.
29. Oduor H, Minniti CP, Brofferio A, et al. Severe cardiac iron toxicity in two adults with sickle cell disease. *Transfusion* 2017;57:700-4.
30. Hankins JS, Smeltzer MP, McCarville MB, et al. Patterns of liver iron accumulation in patients with sickle cell disease and thalassemia with iron overload. *Eur J Haematol* 2010; 85:51-7.
31. Linder GE, Chao ST. Red cell transfusion and alloimmunization in sickle cell disease. *Haematologica* 2021;06:270546.
32. Abou Zahr R, Burkhardt BEU, Ehsan L, Potersnak A, Greil G, Dillenbeck J, et al. Real-world experience measurement of liver iron concentration by R2 vs. R2 Star MRI in hemoglobinopathies. *Diagnostics* 2020; 10:768.
33. Drasar E, Vasavda N, Igbineweka N, Awogbade M, Allman M, Thein SL. Serum ferritin and total units transfused for assessing iron overload in adults with sickle cell disease. *Br J Haematol* 2012;157:645-47.
34. Banerjee S, Owen C, Chopra S. Sickle cell hepatopathy. *Hepatology* 2001;33:1021-8.
35. Vichinsky E, Butensky E, Fung E, et al. Comparison of organ dysfunction in transfused patients with SCD or beta thalassemia. *Am J Hematol* 2005; 80:70-4.
36. Shah R, Taborda C, Chawla S. Acute and chronic hepatobiliary manifestations of sickle cell disease: A review. *World J Gastrointest Pathophysiol* 2017;8:108-16.
37. Wood JC, Tyszka JM, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. *Blood* 2004;103:1934-6.
38. Meloni A, Puliyl M, Pepe A, Berdoukas V, Coates TD, Wood JC. Cardiac iron overload in sickle-cell disease. *Am J Hematol* 2014;89:678-83.
39. Bawor M, Kesse-Adu R, Gardner K, Marino P, Howard J, Webb J. Prevalence of cardiac abnormalities in sickle cell disease identified using cardiac magnetic resonance imaging. *Eur Heart J* 2020; 41 (Suppl. 2): ehaa946.1026. <https://doi.org/10.1093/ehjci/ehaa946.1026>
40. Coates TD, Wood JC. How we manage iron overload in sickle cell patients. *Br J Haematol* 2017;177:703-16.
41. Alkindi S, Panjwani V, Al-Rahbi S, Al-Saidi K, Pathare AV. Iron Overload in Patients With Heavily Transfused Sickle Cell Disease—Correlation of Serum Ferritin With Cardiac T2* MRI (CMRTools), Liver T2* MRI, and R2-MRI (Ferriscan®). *Front Med (Lausanne)* 2021;8:731102.
42. Harrington JK, Krishnan U, Jin Z, Mardy C, Kobsa S, Lee MT. Longitudinal Analysis of Echocardiographic Abnormalities in Children With Sickle Cell Disease. *J Pediatr Hematol Oncol* 2017;39:500-5.
43. Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. *J Am Coll Cardiol* 2012 59:1123-33.
44. Oduor H, Minniti CP, Brofferio A, et al. Severe cardiac iron toxicity in two adults with sickle cell disease. *Transfusion* 2017;57:700-4.
45. Niss O, Fleck R, Makue F, et al. Association between diffuse myocardial fibrosis and diastolic dysfunction in sickle cell anemia. *Blood* 2017;130:205-13.
46. Kaur H, Aurif F, Kittaneh M, Chio JPG, Malik BH. Cardiomyopathy in Sickle Cell Disease. *Cureus* 2020;12(8):e9619.
47. Darbari DS, Kple-Faget P, Kwagyan J, Rana S, Gordeuk VR, Castro O. Circumstances of death in adult sickle cell disease patients. *Am J Hematol* 2006;81:858-3.
48. Fung EB, Harmatz P, Milet M, et al; Multi-Center Study of Iron Overload Research Group. Morbidity and mortality in chronically transfused subjects with thalassemia and sickle cell disease: A report from the multi-center study of iron overload. *Am J Hematol* 2007;82:255-65.
49. Morrison JC, Schneider JM, Kraus AP, Kitabchi AE. The prevalence of diabetes mellitus in sickle cell hemoglobinopathies. *J Clin Endocrinol Metab* 1979;48:192-5.
50. Ngombe LK, Mulangu AM, Kasole TL, Numbi OL. Sickle cell disease and diabetes: a rare combination in a black teenager in Lubumbashi, Democratic Republic of Congo [in French]. *Pan Afr Med J*. 2014;18:74.
51. Abraham EC, Rao KR. Glycosylated hemoglobins in a diabetic patient with sickle cell anemia. *Clin Physiol Biochem* 1987;5:343-9.
52. Miodovnik M, Hurd WW, Lobel JS, Siddiqi TA. Pregnancy associated with both insulin-dependent diabetes mellitus and sickle cell disease. A report of two cases. *J Reprod Med* 1987; 32:317-9.
53. Reid HL, Photiades DP, Oli JM, Kaine W. Concurrent sickle cell disease and diabetes mellitus. *Trop Geogr Med* 1988;40:201-4.
54. Reid HL, Ene MD, Photiades DP, Famodu AA. Insulin-dependent diabetes mellitus in homozygous sickle-cell anaemia. *Trop Geogr Med* 1990;42:172-3.
55. Mohapatra MK. Type 1 diabetes mellitus in homozygous sickle cell anaemia. *J Assoc Physicians India* 2005;53:895-6.
56. Shoar Z, Rezvani G, De Luca F. Type 1 diabetes mellitus in a patient with homozygous sickle cell anemia. *J Pediatr Endocrinol Metab* 2013;26:1205-7.
57. Jarrett OO, Olorundare EI. Type 1 diabetes mellitus in a known sickle cell anaemia patient: a rare combination in Nigeria. *Afr J Med Med Sci* 2014;43:177-81.
58. Morrison JC, Schneider JM, Kraus AP, Kitabchi AE. The prevalence of diabetes mellitus in sickle cell hemoglobinopathies. *J Clin Endocrinol Metab* 1979;48:192-5.
59. WHO. Diabetes Country Profiles. Qatar, 2016.
60. Mohamed AA, Al-Qurashi F, Whitford DL. Does Sickle Cell Disease Protect Against Diabetes Mellitus?: Cross-sectional study. *Sultan Qaboos Univ Med J* 2015;15:e116-e 9.
61. Fung EB, Harmatz PR, Lee PD, et al. Multi-Centre study of Iron overload research group. Increased prevalence of iron-overload associated endocrinopathy in thalassaemia versus sickle-cell disease. *Br J Haematol* 2006;135:574-82.
62. Yavropoulou MP, Pikilidou M, Pantelidou D, et al. Insulin secretion and resistance in normoglycemic patients with sickle cell disease. *Hemoglobin* 2017;41:6-11.
63. Smiley D, Dagogo-Jack S, Umpierrez G. Therapy insight: metabolic and endocrine disorders in sickle cell disease. *Nat*

- Clin Pract Endocrinol Metab 2008;4:102–9.
64. Mandese V, Bigi E, Bruzzi P, et al. Endocrine and metabolic complications in children and adolescents with Sickle Cell Disease: an Italian cohort study. *BMC Pediatr* 2019;19(1):56.
65. Alsultan AI, Seif MA, Amin TT, Naboli M, Alsuliman AM. Relationship between oxidative stress, ferritin and insulin resistance in sickle cell disease. *Eur Rev Med Pharmacol Sci* 2010;14:527–38.
66. Al Harbi M, Khandekar R, Kozak I, Schatz P. Association between sickle cell trait and the prevalence and severity of diabetic retinopathy. *PloS One* 2016;11:e0159215.
67. Zhou J, Han J, Nutescu EA, et al. Similar burden of type 2 diabetes among adult patients with sickle cell disease relative to African Americans in the U.S. population: a six-year population-based cohort analysis. *Br J Haematol* 2019;185:116–27.
68. Diaw M, Pialoux V, Martin C, et al. Sickle cell trait worsens oxidative stress, abnormal blood rheology, and vascular dysfunction in type 2 diabetes. *Diabetes Care* 2015;38:2120–7.
69. Badawy SM, Payne AB. Association between clinical outcomes and metformin use in adults with sickle cell disease and diabetes mellitus. *Blood Adv* 2019;3:3297–306.
70. Gordon D K, Hussain M, Kumar P, Khan S, Khan S. The Sickle Effect: The Silent Titan Affecting Glycated Hemoglobin Reliability. *Cureus* 2020;12(8): e9685.
71. Reid HL, Famodu AA, Photiades DP, Osamo ON. Glycosylated haemoglobin HbA1c and HbS1c in non-diabetic Nigerians. *Trop Geogr Med* 1992;44:126–30.
72. Schnedl WJ, Trinker M, Lipp RW. HbA1c determination in patients with hemoglobinopathies. *Diabetes Care* 1999;22:368–9.
73. Kosecki SM, Rodgers PT, Adams MB. Glycemic monitoring in diabetics with sickle cell plus beta-thalassemia hemoglobinopathy. *Ann Pharmacother* 2005;39:1557–60.
74. Lacy ME, Wellenius GA, Sumner AE, et al. Association of Sickle Cell Trait With Hemoglobin A1c in African Americans. *JAMA* 2017;317:507–15.
75. Koduri PR. Iron in sickle cell disease: a review why less is better. *Am J Hematol.* 2003;73:59–63.
76. Lucania G, Vitrano A, Filosa A, Maggio A. Chelation treatment in sickle-cell-anaemia: much ado about nothing? *Br J Haematol.* 2011;154:545–55.

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