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Relationship between pancreatic iron overload, glucose metabolism and cardiac complications in sickle cell disease: An Italian multicentre study

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Abstract

Objectives: Evidence about the cross-talk between iron, glucose metabolism, and cardiac disease is increasing. We aimed to explore the link of pancreatic iron by Magnetic Resonance Imaging (MRI) with glucose metabolism and cardiac complications (CC) in sickle cell disease (SCD) patients.

Methods: We considered 70 SCD patients consecutively enrolled in the Extension-Myocardial Iron Overload in Thalassemia Network. Iron overload was quantified by R2* technique and biventricular function by cine images. Macroscopic myocardial fibrosis was evaluated by late gadolinium enhancement technique. Glucose metabolism was assessed by the oral glucose tolerance test.

Results: Patients with an altered glucose metabolism showed a significantly higher pancreas R2* than patients with normal glucose metabolism. Pancreatic siderosis emerged as a risk factor for the development of metabolic alterations (OddsRatio 8.25, 95%confidence intervals 1.51–45.1; $p = .015$). Global pancreas R2* values were directly correlated with mean serum ferritin levels and liver iron concentration. Global pancreas R2* was not significantly associated with global heart R2* and macroscopic

myocardial fibrosis. Patients with history of CC showed a significantly higher global pancreas R2* than patients with no CC.

Conclusions: Our findings support the evaluation of pancreatic R2* by MRI in SCD patients to prevent the development of metabolic and cardiac disorders.

KEYWORDS
glucose metabolism, heart, iron, pancreas, sickle cell disease

1 | INTRODUCTION

Sickle cell disease (SCD) is a group of inherited red blood cell disorders, due to a single-point mutation on the β-globin subunit of haemoglobin (Hb) that causes sickle-shaped erythrocytes. The HbS mutation can be inherited in homozygosis or in heterozygosis with other β-globin qualitative or quantitative defects.[1] It is characterised by a chronic severe haemolytic anaemia, endothelial dysfunction and vaso-occlusive crisis that promote acute complications and chronic multi-organ damage.[2,3] In the last decades, the continuous improvement in the care and treatment of patients with SCD has driven a significant increase in life expectancy. However, the reduction of mortality has led to an increased risk of long-term complications, as metabolic alterations and iron overload.[4,5]

There is conflicting evidence about the epidemiology of diabetes mellitus among patients with SCD. Past studies suggested a relatively low prevalence, possibly due to the small sample sizes and to the shortened life expectancy associated with SCD.[6] A recent large study conducted on over 7000 U.S. SCD patients revealed a standardised prevalence of diabetes of 15.7%, with a modest increase from 2009 to 2014.[7]

A possible complication induced by chronic transfusions and haemolysis in SCD patients is iron overload.[5] This condition can contribute to long-term progressive damage to the endocrine system, leading to the onset of insulin resistance, impaired glucose tolerance (IGT) and subsequently overt diabetes.[8] Increasing evidence is showing that there is a cross-talk between iron metabolism and diabetes. Previous studies in thalassemia major (TM) patients showed that iron accumulates within β-cells and that the severity and duration of iron overload are determinant for the onset of IGT and its progression to diabetes. However, the relationship between iron metabolism and diabetes is extremely complex and not yet fully elucidated. Various mechanisms underlying this cross-talk have been proposed, like insulin deficiency, insulin resistance, hepatic dysfunction, and oxidative stress.[9–11]

R2-star (R2*) or its reciprocal T2* Magnetic Resonance Imaging (MRI) is the technique of choice for the non-invasive and reproducible quantification of organ-specific iron overload (IO).[12,13] R2* and T2* quantitative MRI of hepatic and cardiac iron has been extensively studied, while reports on the use of this technique on pancreas and its clinical correlations are still few. Among TM patients pancreatic iron was found significantly correlated to cardiac iron, cardiac complications and diabetes.[14] A profound link between pancreatic iron and heart disease exists, as in TM patients diabetes was associated with an increased risk of heart failure (HF), hyperkinetic arrhythmias and myocardial fibrosis, independently by the levels of cardiac iron.[15] It has been shown that transfused SCD patients have lower cardiac and pancreatic iron loading than chronically-transfused TM patients having similar liver iron levels.[16] To the best of our knowledge, no studies evaluated the association between pancreatic R2* and glucose metabolism or cardiac disease among SCD patients.

The aim of this multicentre study was to systematically explore the link of pancreatic iron with glucose metabolism and cardiac disease in SCD patients.

2 | METHODS

2.1 | Study population

The E-MIOT (Extension-Myocardial Iron Overload in Thalassemia) project is an Italian Network comprised of 11 MRI sites and 66 thalassaemia centres, with the aim of investigating the link of pancreatic iron quantified by MRI with glucose metabolism and cardiac complications in patients with haemoglobinopathies. MRI exams are performed using homogeneous, standardised and validated procedures for the heart, the liver and the pancreas.[17–19] Clinical and instrumental data are collected in a web-based centralised database by all the E-MIOT centres.

We considered seventy patients with SCD (37.6 ± 15.1 years, 34 females), consecutively enrolled in the project at basal from October 2015 to January 2021. The subtype of SCD was sickle cell anaemia (HbSS) for 30% of patients and sickle β-thalassaemia (Sβ-thal) for 70% of patients. A total of 54 (77.1%) SCD patients were regularly transfused (RT), receiving regular blood transfusions or regular exchange transfusions (≥4/year) for at least 1 year, while patients who received no or sporadic blood/exchange transfusions were considered non-regularly transfused (NRT). Considering the patients with HbSS, 52.6% were Caucasian, 42.1% Black, and 5.3% mixed-race.

The study complied with the Declaration of Helsinki and was approved by the ethics committees of all the Italian MRI sites involved in the study. Informed consent was obtained from all patients for being included in the study.

2.2 | MRI

MRI exams were performed on 1.5 T scanners of three main vendors (GE Healthcare, Siemens Healthineers, and Philips Healthcare). An phased-array receiver surface coil was used for signal reception.

For iron overload assessment the R2* multiecho technique was used. Its reproducibility and transferability among centres had been previously demonstrated.[17–19] Five or more axial slices covering the whole abdomen and including the whole pancreas were obtained.[20] For the liver, a single mid-transverse slice was acquired,[21] and for the heart, three parallel short-axis views (basal, medium and apical) of the left ventricle (LV) were obtained.[17,22] Analysis of R2* images was performed using a custom-written, previously validated software (HIPPOMIOT®).[23] Three small regions of interest (ROI) were manually drawn over pancreatic head, body and tail encompassing parenchymal tissue and taking care to avoid large blood vessels or ducts and areas involved in susceptibility artifacts from gastric or colic intraluminal gas.[24] Global R2* pancreatic value was calculated as the mean of R2* values from the three ROI. Hepatic R2* values were obtained in a circular ROI[25] chosen in a homogeneous area of parenchyma without blood vessels and were converted into liver iron concentration (LIC) using the Wood's calibration curve.[26,27] Cardiac R2* value was obtained for all the 16 segments of the LV, according to the standard American Heart Association (AHA)/American College of Cardiology (ACC) model.[28] Global heart R2* value was obtained by averaging all segmental values.

For the study of cardiac function, steady-state free precession cines were acquired in sequential 8 mm short-axis slices from the atrio-ventricular ring to the apex. Images were analysed in a standard way[29] using MASS® software (Medis). The inter-centre variability for the quantification of cardiac function has been previously reported.[30]

To detect the presence of macroscopic myocardial fibrosis, late gadolinium enhancement (LGE) short-axis images were acquired 10–18 min after Gadobutrol (Gadovist®; Bayer Schering Pharma) intravenous administration at the standard dose of 0.2 mmoL/kg.[31,32,33]

LGE images were not acquired in patients with a glomerular filtration rate < 30 ml/min/1.73m^2, age < 10 years, and in patients who refused.

2.3 | Assessment of glucose metabolism

Baseline blood assessments of glucose and insulin were performed in all patients, who were required to fast overnight (at least 12 h). Patients without known diabetes had an oral glucose tolerance test (OGTT) for the assessment of the disturbances of glucose metabolism, within 3 months from the MRI study at the reference thalassaemia centre. Patients were given 1.75 g/Kg (maximum dose of 75 g) glucose solution, and glucose and insulin were measured at 60 and 120 min. To assess insulin resistance in patients not already diagnosed with diabetes we used the HOMA of insulin resistance (HOMA-IR), computed as the product of fasting glucose and insulin levels divided by 22.5.[34] As a measure of β-cell function, the HOMA of β-cell function (HOMA-B) index was used, and it was calculated as the product of 360 and fasting insulin level divided by the value of fasting glucose concentration minus 63.[35]

2.4 | Diagnostic criteria

A fasting plasma glucose (FPG) <100 mg/dl and 2-h glucose <140 mg/gl were considered indicative of normal glucose tolerance. The presence of FPG levels between 100 mg/dl and 126 mg/dl indicated a diagnosis of impaired fasting glucose (IFG). IGT was defined as 2-h plasma glucose between 140 and 200 mg/dl, with a FPG < 126 mg/dl. Diabetes was diagnosed with a FPG ≥126 mg/dl or 2-h plasma glucose ≥200 mg/dl during an OGTT or a random plasma glucose ≥200 mg/dl with classic symptoms of hyperglycaemia or hyperglycaemic crisis.[36]

We considered 38 Hz (T2* = 26 ms) as the highest threshold of normal global R2* pancreatic value, as previously demonstrated.[20] A MRI LIC ≥3 mg/g/dw was considered indicative of significant hepatic iron load.[37] A R2* measurement of 50 Hz (T2* = 20 ms) was taken as 'conservative' normal value for segmental and global heart R2* values.[23]

HF was diagnosed by clinicians based on symptoms, signs and instrumental findings according to the ESC guidelines.[38] Pulmonary hypertension (PH) was diagnosed if the trans-tricuspid velocity jet was greater than 3.2 m/s.[39] Arrhythmias were diagnosed if documented by ECG or 24-h Holter ECG if requiring specific medications. Arrhythmias were classified according to the AHA/ACC guidelines.[40]

The term 'cardiac complications' included globally HF, arrhythmias, and PH.

2.5 | Statistical analysis

All data were analysed using SPSS version 13.0. Continuous variables were reported as mean ± standard deviation and categorical variables were expressed as frequencies and percentages. The continuous parameters were checked for normal distribution using the Kolmogorov–Smirnov test.

Between-groups comparisons were made by independent-samples t-test (two groups) for continuous variables with normal distribution and with Mann–Whitney U test for continuous variables with non-normal distribution. χ^2 testing was performed for non-continuous variables. Correlation analysis was performed by using Pearson's or Spearman's tests.

Odds ratios (OR) and 95% confidence intervals (CI) were calculated by using logistic regression.

For determination of the best pancreas R2* cutoff for discriminating the presence of an altered glucose metabolism, the maximum sum of sensitivity and specificity was calculated from receiver operating characteristic (ROC) curve analysis.

For each test, statistical significance was considered for $p < .05$.

3 | RESULTS

3.1 | Demographics

The two SCD subtypes, HbSS and Sβ-thal patients, were comparable for age, sex and haematochemical parameters, while Sβ-thal patients were more frequently splenectomised (57.1% vs. 23.8%; $p = .01$). Global pancreas R2* was not significantly different between the two groups (HbSS 44.6 ± 36.7 Hz, Sβ-thal 42.0 ± 30.9 Hz; $p = .84$) and the frequency of patients with altered glucose metabolism was comparable (HbSS 15%, Sβ-thal 10.4%; $p = .59$).

Table 1 presents the comparison between RT and NRT patients. The RT group had significantly lower HbS and HbF levels and was more frequently chelated, while the two groups were comparable for age, sex, global pancreatic and cardiac R2*, and LIC.

3.2 | Pancreatic iron and clinical correlates

The mean global pancreas R2* was 42.8 ± 32.5 Hz and 23 (32.9%) patients showed a pathological pancreas R2*. Frequency of pancreatic IO was comparable between males and females (33.3% vs. 32.4%, respectively; $p = .93$), and patients with a pathological global pancreas R2* were not significantly older (41.9 ± 15.9 years vs. 35.5 ± 14.3 years; $p = .10$).

Splenectomised patients (N = 33) showed a significantly higher frequency of pancreatic IO than patients with the spleen (45.5% vs. 21.6%; $p = .034$).

Table 2 presents the comparison between patients who had been receiving the same chelation therapy for >1 year and non-chelated patients. Pancreatic IO was significantly more frequent among chelated patients, and mean global pancreas R2* was higher with a *p*-value close to the statistical significance. Moreover, chelated patients showed a significantly higher frequency of liver IO and higher LIC and ferritin values, when compared with the non-chelated group, which was less frequently transfusion-dependent. Comparing patients treated for >1 year with desferrioxamine (DFO), deferiprone (DFP) and deferasirox (DFX; $N = 11$, $N = 5$, $N = 21$, respectively), we did not find significant differences in global pancreatic R2*, cardiac R2*, and LIC values.

3.3 | Pancreatic iron and glucose metabolism

A total of 8 (11.8%) patients showed an altered glucose metabolism, in particular 5 (7.4%) patients showed IFG, 1 (1.5%) IGT, and 2 (2.9%) diabetes.

Patients with an altered glucose metabolism showed significantly higher pancreas R2* values than patients with a normal OGTT (Figure 1A) and the frequency of pancreatic IO was significantly higher among patients with altered glucose metabolism than in patients with normal glucose metabolism (Figure 1B). Patients with pancreatic IO showed a risk of metabolic alterations eight times higher than patients with no pathological pancreas R2* (OR 8.25, 95%CI 1.51–45.1; $p = .015$). At ROC curve analysis, a global pancreas R2* > 44.6 Hz predicted the presence of an altered glucose metabolism with a sensitivity of 75.0% and a specificity of 85.0% ($p = .023$). The area under the curve was 0.77 (95% CI: 0.66–0.87; Figure 1C).

In patients without DM, no association was found between pancreatic R2* values and glucose levels evaluated during the OGTT, fasting plasma insulin, HOMA-IR index and HOMA-B index.

Ferritin values and LIC were comparable in patients with and without an altered glucose metabolism.

TABLE 1 Comparison between RT and NRT SCD patients

	NRT ($N = 16$)	RT ($N = 54$)	*p*-value
Sβ-thal, *N* (%)	11 (68.8)	38 (70.4)	.90
Age (years)	35.4 ± 11.8	38.3 ± 15.9	.50
Female sex, *N* (%)	7 (43.8)	27 (50.0)	.66
Serum haemoglobin (g/dl)	9.5 ± 1.1	9.5 ± 0.8	.10
Hb S (%)	59.4 ± 13.3	42.1 ± 15.3	**<.0001**
Hb F (%)	18.2 ± 11.0	8.4 ± 6.5	**.003**
Splenectomy, *N* (%)	8 (50.0)	25 (46.3)	.79
Chelated, *N* (%)	6 (37.5)	44/52 (84.6)	**<.0001**
Serum ferritin (ng/ml)	772.3 ± 896.8	1151.2 ± 973.7	.15
MRI LIC (mg/g dw)	5.6 ± 8.3	6.0 ± 7.1	.98
Hepatic IO, *N* (%)	6 (37.5)	26 (48.1)	.45
Global heart R2* (Hz)	24.5 ± 2.7	25.6 ± 3.8	.28
At least 1 segment with R2* > 50 Hz, *N* (%)	1 (6.2)	9 (16.7)	.30
Global pancreas R2* (Hz)	33.6 ± 9.7	45.5 ± 36.2	.45
Pancreatic IO, *N* (%)	3 (18.8)	20 (37.0)	.17

Bold indicates significant *p*-values.

TABLE 2 Comparison between SCD patients who had been receiving the same chelation therapy for >1 year and non-chelated SCD patients

	Non chelated ($N = 16$)	Chelated ($N = 40$)	p-value
Age (years)	37.0 ± 12.9	39.7 ± 13.7	.49
Female sex, *N* (%)	7 (43.8)	22 (55.0)	.45
Serum haemoglobin (g/dl)	10.0 ± 1.0	9.3 ± 0.7	**.004**
Hb S (%)	56.0 ± 14.2	42.3 ± 16.8	**.010**
Hb F (%)	14.4 ± 12.8	8.7 ± 6.3	.27
Splenectomy, *N* (%)	6 (37.5)	22 (55.0)	.24
Serum ferritin (ng/ml)	359.6 ± 256.3	1312.2 ± 1035.3	**.001**
RT, *N* (%)	8 (50)	36 (90)	**.001**
MRI LIC (mg/g dw)	2.9 ± 3.5	7.8 ± 8.8	**.010**
Hepatic IO, *N* (%)	4 (25.0)	22 (55.0)	**.042**
Global heart R2* (Hz)	25.9 ± 3.7	25.2 ± 3.2	.46
At least 1 segment with R2* > 50 Hz, *N* (%)	3 (18.8)	4 (10.0)	.37
Global pancreas R2* (Hz)	30.4 ± 6.8	50.4 ± 40.9	.053
Pancreatic IO, *N* (%)	2 (12.5)	17 (42.5)	**.032**

Bold indicates significant p-values.

3.4 | Pancreatic iron and serum ferritin

Mean serum ferritin levels in the last 12 months were 1058.0 ± 962.6 ng/ml. A weak correlation was found between global pancreas R2* values and mean serum ferritin levels ($R = 0.259$; $p = .038$).

3.5 | Pancreatic iron and MRI findings

Mean LIC was 5.9 ± 7.3 mg/g dw, and 32 (45.7%) patients showed hepatic IO. Figure 2A describes the significant positive correlation that was found between global pancreas R2* and MRI LIC values. Moreover, patients with hepatic IO showed a mean global pancreas R2* significantly higher than patients with no pathological LIC (Figure 2B).

All patients had a normal global cardiac R2*, the mean value was 25.4 ± 3.6 Hz. No association was found between global pancreas R2* and global cardiac R2* values.

Based on the segmental approach, we identified two groups of patients: the group with no MIO (all segments with R2* ≤ 50 Hz) made by 60 (65.7%) patients, and the group with a heterogeneous iron distribution (some segments with R2* ≤ 50 Hz and others with R2* > 50 Hz) with global heart R2* ≤ 50 Hz, composed by 10 (14.3%) patients. Mean global pancreas R2* was higher in patients with at least 1 segment with R2* > 50 Hz than in patients with no MIO, but the statistical significance was not reached (60.2 ± 52.2 Hz vs. 39.9 ± 27.5 Hz respectively, $p = .13$). Among patients with pancreas IO the frequency of patients with at least 1 segment with R2* > 50 Hz was double than in patients with no pancreas IO, despite not statistically different (21.7% vs. 10.6%, $p = .21$).

LV and right ventricular (RV) end-diastolic volume indexes and ejection fractions and LV mass index were not correlated with global pancreatic R2* values.

The contrast medium was administered in 28 (40.0%) patients. Among them, LGE was detected in 11 (39.3%) patients. Global pancreas R2* values were comparable in patients without and with myocardial fibrosis.

3.6 | Pancreatic iron cardiac complications

Global pancreas R2* values were comparable in SCD patients with an active or eradicated HCV infection and in negative patients (41.7 ± 37.7 Hz vs. 43.5 ± 30.8 Hz; $p = .21$).

Six of 68 (8.8%) patients had history of at least 1 cardiac complication: 4 supraventricular arrythmias, 2 HF + PH. Patients with history of cardiac complications showed significantly higher values of global pancreas R2* (72.1 ± 56.5 Hz vs 40.0 ± 29.0 Hz; $p = .02$) than patients with no cardiac complications (Figure 2C). Moreover, patients with cardiac complications showed a significantly higher frequency of glucose metabolism alterations than patients without cardiac complications (40% vs. 8.1%, $p = .025$).

4 | DISCUSSION

Chronic transfusion therapy is increasingly used in patients with SCD to prevent the risk of stroke,[41] with iron burden as a possible consequence. Moreover, the frequency of long-term complications as endocrine and metabolic alterations is increasing due to the reduction of mortality and ageing of patients.[4,7] While cardiac and hepatic iron overload have been extensively studied, there are still few studies

about pancreatic iron, especially in patients with SCD, and none has evaluated the association between pancreas R2* and glucose metabolism or cardiac disease among SCD patients.

In the present study, we systematically explored the link of pancreatic iron with glucose metabolism and cardiac disease in a cohort of 70 SCD patients.

A pathological global pancreas R2* was found in 32.9% of patients, a prevalence consistent with previous studies.[5,16] Global pancreas R2* was not significantly different between the two SCD subtypes and between RT and NRT patients, but as expected, among RT patients the frequency of pancreatic IO was slightly higher than in NRT. The observed difference was likely attenuated by the fact that RT patients were more frequently chelated. As observed in studies focused on TM patients,[14,42] the frequency of pancreatic siderosis was higher among splenectomised patients than in patients with the spleen. This could be explained by the spleen's ability to act as a non-toxic iron depot and by the consequent increase in extrahepatic iron caused by surgical splenectomy.[43]

A higher pancreatic and hepatic siderosis was found among chelated patients, which were also more frequently treated with a regular transfusion regimen. This finding probably reflects the current clinical practice about the tendency to intensively treat patients with the more severe phenotype.

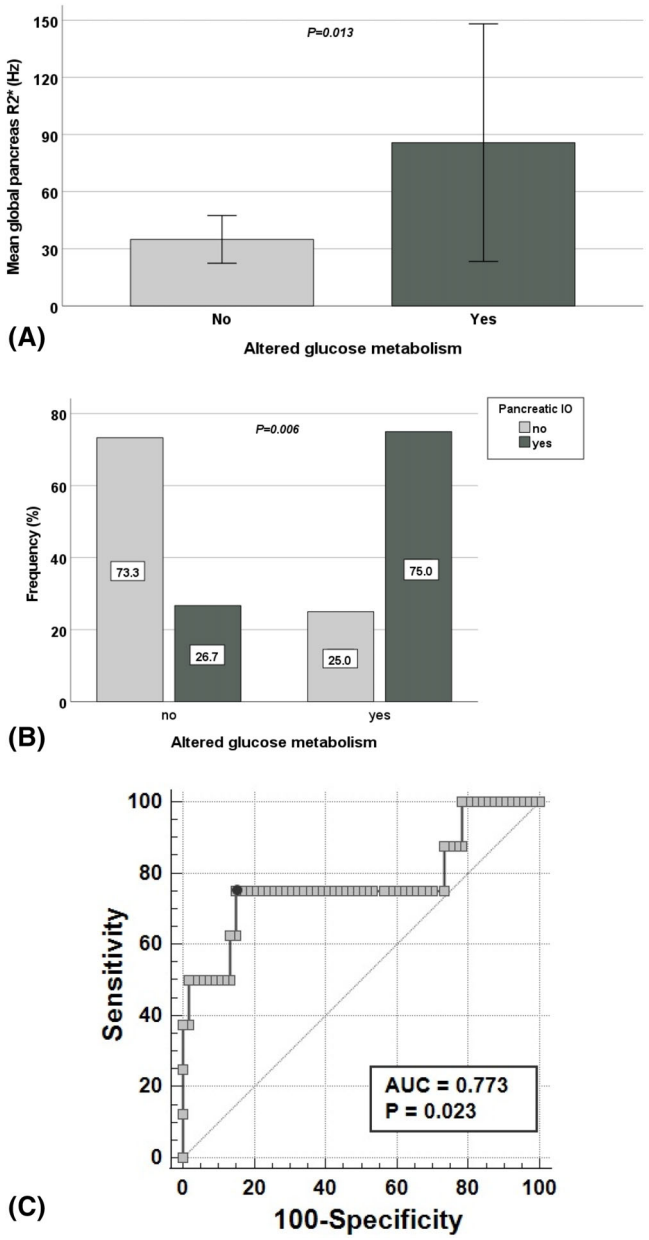

FIGURE 1 Pancreatic iron overload (IO) and glucose metabolism. Mean global pancreas R2* (A) and frequency of pancreatic IO (B) in patients with altered and non-altered glucose metabolism; (C) Receiver Operating Characteristic (ROC) curve analysis for the prediction of altered glucose metabolism by global pancreas R2*. Abbreviation: AUC, Area Under the Curve

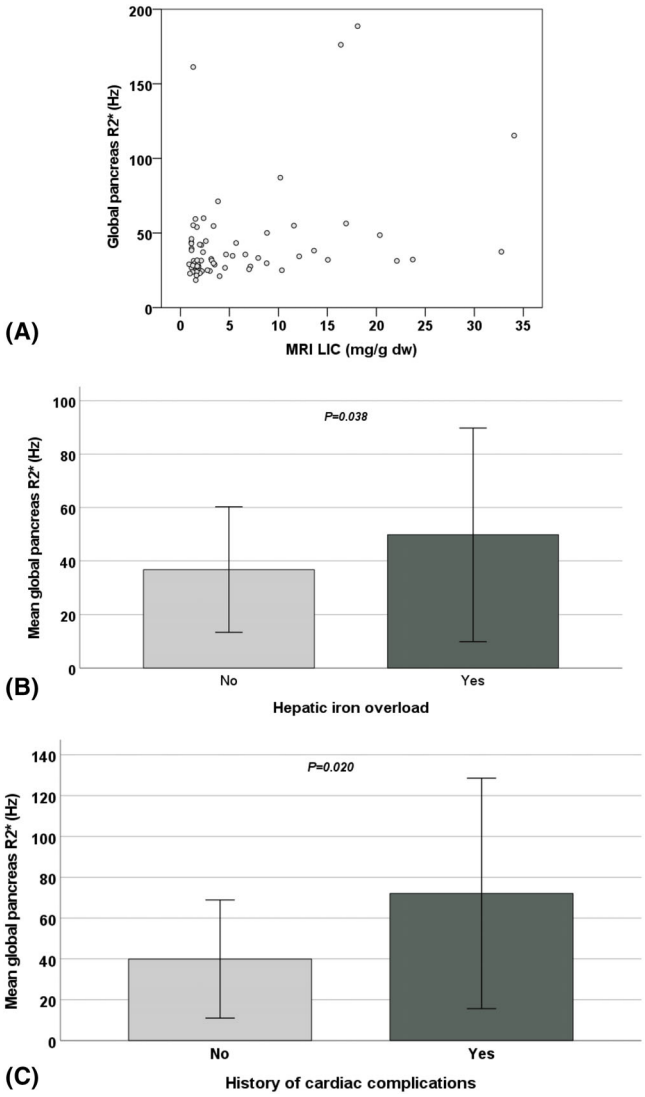

FIGURE 2 (A) Correlation between global pancreas R2* and liver iron overload (LIC); (B) Mean global pancreas R2* in patients with and without liver iron overload (IO). (C) Mean global pancreas R2* in patients with and without history of cardiac complications

An altered glucose metabolism was found in 11.8% of patients. These patients had a higher pancreatic siderosis than patients with non-altered glucose metabolism. We found that patients with pancreatic IO have an eight-fold increased risk of having impaired glucose metabolism compared with patients without pancreatic iron. Moreover, we identified a pancreatic R2* cutoff value of 45 Hz for prediction of altered glucose metabolism, which may help to recognise the patients at high risk for glucose dysregulation. Our findings are in agreement with studies in TM patients.[14,44] Evidence about the toxic effect of transfusional iron overload on pancreatic β cells through inflammation and oxidative stress is increasing. Moreover, it has been reported that in SCD patients intravascular haemolysis contributes to organ damage by increasing oxidative stress due to unbound plasma iron and haeme.[45,46] To our knowledge, the only study that evaluated the relationship between iron stores and glucose metabolism was by Shah et al.[47] Their findings suggested that elevated iron stores, in terms of ferritin, were associated with glucose intolerance, even without the diagnosis of diabetes. Past studies showed that diabetes prevalence in SCD was lower than in TM patients and that diabetes approximately affected 2% of SCD patients,[6] similar to 2.9% reported in our study. In a more recent U.S. prospective study, diabetes prevalence in SCD patients reached 15.7% with a modest increase over the years,[7] indicating that many factors such as sample size, age of assessment, co-existing comorbid conditions can influence this finding. Moreover, the higher prevalence observed in the U.S. study could also reasonably be due to the generally more aggressive transfusion therapy regimen, resulting in more severe iron overload and endocrine complications. In non-diabetic SCD patients, pancreatic R2* values were unrelated to glucose and insulin levels, possibly because most patients had normal or only slightly altered values of these parameters.

In accordance with previous studies in patients with SCD,[16,48] we observed that pancreatic R2* was directly correlated with ferritin and LIC. No correlation was found between pancreatic and cardiac R2*, likely because all patients had no cardiac iron. In fact, it is known that haemosiderosis in SCD patients occurs primarily in the liver, later in the endocrine glands, and to a lesser extent in the heart.[6] In TM and TI patients, pancreatic and cardiac iron were directly related and normal values of pancreatic iron showed a negative predictive value of 100% for cardiac iron.[14,49] In a retrospective study with six SCD patients who developed cardiac iron, a direct relationship between pancreas and heart R2* was shown.[50] Thanks to the segmental approach, we found that the frequency of patients with at least 1 cardiac segment with R2* ≥ 50 Hz was double among patients with pancreatic IO than in patients with no pancreatic IO, despite the statistical significance was not reached. These data are in line with the earlier detection of pancreatic iron than cardiac iron in SCD patients. The lack of statistical significance could possibly be because SCD patients usually show a less severe pancreatic IO than TM[14] and the time between the detection of pancreatic iron and cardiac iron is higher in SCD than in TM patients.[16]

Finally, regarding the comparison of global pancreas R2* in patients with and without cardiac complications, we observed a significantly higher pancreatic siderosis in patients with history of cardiac complications. This finding confirms what is known from studies in TM patients, in which pancreatic iron is a strong predictor for cardiac complications.[14] It is known that the pathophysiology of cardiac complications in SCD is complex. As reported in studies on TM patients, multiple factors such as diabetes can play a role in the development of cardiac impairment, independently from myocardial iron overload.[15] Accordingly, in our study we found a correlation between the presence of cardiac complications and impaired glucose metabolism.

Nevertheless, prospective multicentre studies on larger groups of patients are needed to further explore the complex pancreas-heart link in SCD patients.

This study has some limitations. The first is the relatively small number of patients, which is comparable to the majority of other studies about rare anaemias as SCD. Larger prospective studies are needed to confirm our findings. The second limitation is that we used the HOMA-B index, which cannot give us information about the secretory response of b-cells to rising glucose concentrations, but only reflects fasting b-cell function. However, we are exploring to add a time point at 30 min after the load during the OGTT, so that we will be able to measure the insulinogenic index as a marker of b-cell function.[51] Furthermore, we had not sufficient information on the quantitative β-globin defect of Sβ-thal patients (β0 or β+ mutation), which could have been useful to better characterise the patient population.

In conclusion, this multicentre study firstly showed the significantly higher risk of altered glucose metabolism related to pancreatic siderosis in SCD patients. This finding supports the assessment of pancreatic R2* by MRI in SCD patients to prevent the development of metabolic disturbances. We are waiting for data from E-MIOT project to prospectively confirm the correlation between pancreatic R2* and cardiac iron overload and disease in SCD patients in a multicentre setting.

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CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from https://emiot.ftgm.it/, but restrictions apply to the availability of these data, which were used under license for the current study and therefore are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of F.C.

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