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Correlation between Iron Overload and Glycemic Abnormalities among Thalassemia Patients Attending Suez Canal University Hematology Outpatient - Clinic

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Abstract

Background: **Thalassemia is one of the commonest hemoglobinopathies in the world. Frequent blood transfusions are recommended for transfusion-dependent thalassemia. The human body lacks a physiological mechanism to eliminate excess iron load following a blood transfusion. Excess iron accumulates particularly in the liver, heart, and endocrine organs. Diabetes mellitus is one of the endocrine complications. Three main processes—insulin resistance, insulin insufficiency, and hepatic dysfunction—are thought to be involved in its development.** ***Aim:*** **early detection of glycemic abnormalities in patients with thalassemia to prevent its complications and start early and proper management.** ***Subjects and Methods:*** **This was an analytical cross-sectional study conducted over 67 patients attending the hematology outpatient clinic of Suez Canal University Hospital, Ismailia, Egypt, in the period between March 1 and June 10, 2022. Additionally, the patients included were all thalassemic patients of both sexes aged more than 12 years old with exclusion of type 1 Diabetes Mellitus patients and chronic liver disease patients.** ***Results:*** **Our study demonstrated that 19.4% were diabetic and 35.8% were prediabetic among thalassemia patients according to fasting glucose. On the other hand, regarding assessment of insulin resistance using homeostatic model assessment (HOMA-IR), 3 % of our study sample was within the border line range and 14.9% has HOMA IR more than 2.** ***Conclusion:*** **Our study concluded that iron overload is considered a risk factor for developing glycemic abnormalities in thalassemia patients which is most probably caused by inadequate chelation that led to hemosiderosis of the pancreas and other organs.**

Keywords: Hemoglobinopathies, Insulin resistance, Excess iron, Transfusion-dependent

Introduction

One of the most prevalent monogenic disorders in humans is thalassemia. They are found at a high gene frequency across populations of Mediterranean area [(1)]. Nowadays, thalassemias are categorized into transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) according to severity of clinical phenotype, and assessment of their requirement of regular blood transfusion to survive or not [(2)].

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Patients with TDT require routine blood transfusions to avoid complications like chronic anemia and bone deformities. Iron overload can be attributable to frequent blood transfusions, or the outcome of increased intestinal iron absorption signaled by ineffective erythropoiesis. Our bodies do not have a physiological mechanism to get rid of the excess iron load from regular transfusion which leads to various complications [3]. Diabetes mellitus (DM) is considered one of the commonest endocrine complications [4].

At the level of the liver, Insulin resistance (IR) develops as a result of (hepatic iron load and liver impaired function), as it may interfere with insulin's ability to decrease hepatic glucose uptake, and at the level of the muscle as well, where iron deposits may lower glucose uptake [5].

Pancreatic iron accumulation starts in early childhood among patients who lack sufficient iron chelation. By getting older, persistent IR combined with lower insulin levels (from worsening beta-cell function) leads to glucose intolerance, which can progress to frank DM. [5]. Additionally, pancreatic cells have increased divalent metal transporter expression which enhances iron deposition in these cells, followed by cell death, pancreatic volume reduction, fat replacement and pancreatic dysfunction [6].

Besides iron overload, further factors that account for organ damage include chronic hypoxia as a result of anemia, which can amplify the toxic effects of iron deposits in endocrine glands and various organs. Furthermore, viral infections and individual vulnerability to iron overload are involved contribute to endocrine complications [7].

The prevalence of DM in β-thalassemia varies from 9.7% to 29% and the whole prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) is 17.2% and 12.4% respectively in the patients of TDT. Accordingly, the earlier to detect glucose dysregulation (GD), the better prevention outcome [8].

In the present study, we determine the frequency of glycemic abnormalities i.e. DM and IR in patients attending Hematology outpatient clinic of Suez Canal University Hospitals. The objective of this study was to assess the relation between iron overload and glycemic abnormalities in thalassemic patients and to detect factors affecting glycemic abnormalities among them.

Patients and methods

study Populations, area and data collection:

Analytical cross-sectional study conducted over 67 thalassemia patients of either sexes aged more than 12 years old attending Hematology outpatient clinic of Suez Canal University Hospital. Exclusion criteria include Type 1 DM patients, chronic liver disease patients and patients with other hematological disorders. A structured interview-based questionnaire was used. Data collected from each patient included: socio demographic data, prediabetic and diabetes history, thalassemia history including age of onset of first blood transfusion, frequency of blood transfusion, iron chelation agents and compliance, history of splenectomy.

Collection and storage of samples:

Blood Samples: All patients were asked to fast for 8 hours then Seven ml of blood sample were collected from each patient as follows:

• 2 ml of the blood sample were collected in a sterile EDTA tube to measure glycosylated hemoglobin (HbA1C).
• 5ml of the blood sample were collected in a sterile plain tube and the serum was separated by centrifugation at 3,000 rpm for 5 minutes. Then, the serum was collected in Eppendorf tubes to measure: fasting plasma glucose, fasting insulin, ferritin, iron.

Insulin resistance score (HOMA-IR) was calculated using the formula: fasting plasma glucose (mmol/l) times fasting serum insulin (mU/l) divided by 22.5. Low HOMA-IR score reflects high insulin sensitivity, while high HOMA-IR score suggests low insulin sensitivity (insulin resistance) [9].

The biochemical assessment:

The colorimetric assays used to measure the tests followed a standardized protocol. Analysis was performed using a semi-automated clinical chemistry analyzer, specifically the Micro lab 300-ELITechGroup spectrophotometer.

Results

Patients' ages ranged from 12 to 40 years old. Females were more predominant (67.2%) than males (32.8%). Most of the cases (65%) didn't have a family history of diabetes. The average age of frequency of transfusion and age of starting iron chelation was about 37.3 days and 8.4 years respectively. Regarding compliance on iron chelation therapy only 34.3% of patients were compliant. The results showed that 50.7% of patients had done splenectomy. About 44.8% of the cases had normal fasting glucose (lower than 100 mg/dl), while 35.8% had fasting glucose that ranged from 100 to 125 mg/dl and only 19.4% had fasting glucose more than 126 mg/dl (table 1). Most of the studied cases about 82.1 % had normal HOMA IR, while 3 % was within the borderline range (2) and 14.9% had HOMA IR more than 2 (table 2).

Table 1.Distribution of the studied cases according to Fasting glucose (n= 67)

Fasting glucose (mg/dl)	No.	%
Normal (<100)	30	44.8
Pre diabetes (100 – 125)	24	35.8
Diabetes (>126)	13	19.4
Min. – Max.	62.0 – 656.0	
Mean ± SD.	128.70 ± 97.55	
Median (IQR)	101.0(88.50 – 121.0)	

Table 2. Distribution of the studied cases according to HOMA IR (n= 67)

HOMA IR	No.	%
Normal (≤1.9)	55	82.1
Border line (2)	2	3.0
>2	10	14.9
Min. – Max.	0.19 – 5.70	
Mean ± SD.	1.31 ± 1.19	
Median (IQR)	1.0(0.50 – 1.55)	

Regarding iron overload, 46.3% of patients had serum ferritin between 1500 and 2500 (ng/ml) and 20.9% of patients had serum ferritin more than 4000 (ng/ml) (table 3). The results showed direct relationship between serum ferritin and HbA1c, HOMA-IR and fasting insulin and HOMA-IR and fasting glucose with (p<0.001) for each (table 4). There was also significant correlation between frequency of blood transfusion and HbA1c, serum ferritin and fasting insulin with (p=0.002), (p<0.001) and (p=0.008) respectively. Also, between Age of first transfusion and HOMA IR with (p=0.049) (table 5).

Table 3. Distribution of the studied cases according to Serum ferritin (n= 67)

Serum ferritin (ng/ml)	No.	%
1500 – 2500	31	46.3
2501 – 4000	22	32.8
4001 – 5500	10	14.9
5501 – 7000	4	6.0
Min. – Max.	860.0 – 8600.0	
Mean ± SD.	2982.16 ± 1582.50	
Median (IQR)	2545.0(2142.5 – 3793.50)	

Table 4. Correlation between different laboratory parameters

		HbA1c	Serum ferritin	Serum iron	Fasting insulin	Fasting glucose	HOMA IR
HbA1c	rs		0.719	0.241	0.193	0.279	0.250
	p		<0.001*	0.049*	0.117	0.022*	0.041*
Serum ferritin	rs			0.427	0.331	0.163	0.250
	p			<0.001*	0.006*	0.187	0.041*
Serum iron	rs				0.282	0.091	0.231
	p				0.021*	0.462	0.061
Fasting insulin	rs					0.101	0.759
	p					0.417	<0.001*
Fasting glucose	rs						0.442
	p						<0.001*
HOMA IR	rs						.
	p						

rs: Spearman coefficient

: Statistically significant at p ≤ 0.05

Table 5. Correlation between thalassethalassemia-relatedund data and laboratory parameters							
		HbA1c	Serum ferritin	Serum iron	Fasting insulin	Fasting glucose	HOMA IR
Age of diagnosis (years)	r_s	-0.184	-0.016	-0.149	-0.228	0.155	-0.189
	p	0.136	0.898	0.230	0.063	0.210	0.126
Age of first transfusion (years)	r_s	-0.233	-0.114	-0.169	-0.234	0.000	-0.240
	p	0.057	0.358	0.172	0.056	0.997	0.049*
Frequency of transfusion (days)	r_s	-0.365	-0.506	-0.136	-0.322	0.001	-0.206
	p	0.002*	<0.001*	0.272	0.008*	0.993	0.094
Age of iron chelaion (years)	r_s	0.054	0.009	-0.039	-0.150	-0.012	-0.149
	p	0.664	0.942	0.753	0.225	0.924	0.227

rs: Spearman coefficient
***: Statistically significant at p ≤ 0.05*

Discussion:

Long-term extravascular hemolysis in thalassemia causes a rise in intestinal iron absorption and a reduction of iron bioavailability. Iron overload and a rise in the number of iron ions could result from this condition in conjunction with prolonged repeated blood transfusions [(10)]. In thalassemic individuals, DM continues to be a significant cause of morbidity and mortality [(11)].

This Analytical cross-sectional study aimed at the early detection of Glycemic abnormalities in thalassemia patients to prevent its complications and start early and proper management with the main objective to assess the relation between iron overload and glycemic abnormalities in thalassemia patients.

This study involved 67 patients with the mean age of 22.04 years. Most of the patients were females 67.2% while males were 32.8%. In a similar study, Setoodeh analyzed data of 48 thalassemia patients and 33 controls in a case control study and thalassemia patients aged 21.8 ± 6.4 years among them 47.9% were females [(12)]. We suggest that the difference variations in the number of males and females is due to the different sample sizes

Our study demonstrates that only 34.3% of patients were compliant on iron chelating agents while 65.7% weren't compliant. Which goes in line with Metwalley, as 33.3% of thalassemia patients were on regular iron chelation [(13)].

This study found that the mean of HbA1c of the β-TM patients was 5.8 while serum iron mean was 164.21 and fasting insulin mean was 6.01. Supporting these observations, Setoodeh's research also identified elevated fasting blood sugar and increased insulin resistance in β-thalassemia major patients [(12)]. Which was consistent with the findings expressed by previous study [(14), (15)].

This study demonstrated that 19.4% were diabetic and 35.8% were prediabetic among thalassemia patients according to fasting glucose. Consistent to our results, Diab et al showed that 18.2% had diabetes among patients with thalassemia [(16)]. Additionally, Zhang et al agreed that prevalence of diabetes among beta thalassemia patients was 14.4% and prediabetic patients made up over one-third of the total. [(17)]. In Soliman study, they demonstrated that the prevalence of

glycemic abnormalities in adolescents and young adults who had β-TM using oral glucose tolerance test was 25% [18]. Controversy, in a study including 57 transfusion-dependent -TM patients from Sun Yat-sen Memorial Hospital, it was discovered that 24% of them had impaired fasting glucose and only 7% had been diagnosed with diabetes mellitus [19].

Previous research revealed that the distinct diabetes mechanisms in people with beta TM were connected to insulin resistance and abnormalities in insulin production [20], [21]. Other research has discovered that iron overload-induced insulin secretion abnormalities and pancreatic beta cell damage may be intimately related to the pathophysiology of diabetes. The problems of diabetes were mostly attributed to malfunction of the pancreatic beta cells [19], [21]. Additionally, in patients with beta TM, growing older is a separate risk factor for DM, and the risk rises by 1.1 times for every year of age [22], [23].

The present study showed that the mean HOMA IR was 1.31 ± 1.19 and 14.9% of β-TM had HOMA IR >2. Meanwhile, Diab et al found that mean HOMA IR was 3.21± 4.77 and 27.5% had insulin resistance [16]. However, 3/14 (21.4%) showed insulin resistance state among thalassemia patients [18].

Hereditary hemochromatosis and TM patients frequently have chronic iron overload. Studies on these patients revealed that beta cell malfunction followed by insulin resistance resulted in glucose dysregulation [24]. Insulin resistance, pancreatic beta cell death, and insulin insufficiency were all caused by iron excess [25].

This study agreed that mean serum ferritin was 2982.16 ± 1582.50 among thalassemia patients, 46.3% of patients had serum ferritin between 1500 and 2500 and 20.9% of patients had serum ferritin more than 4000. In the same line Setoodeh found that mean serum ferritin was 2717 ± 3411 ng/ml in β-TM patients compared to 75 ± 74 ng/ml among controls. Moreover, 31.2% had serum ferritin between 1000- 2500 ng/ml, and 29.2% had serum ferritin more than 2500 ng/ml [12].

In the current study there was a weak positive correlation between serum ferritin and HOMA IR and HbA1C. Consistent with our findings, Setoodeh and colleagues agreed that ferritin was notably correlated with HOMA IR ($r = 0.311$, $p = 0.032$) and insulin ($r = 0.304$, $p = 0.036$) [12]. Consistently, Diab et al found that serum ferritin was positively correlated with HOMA IR [16] (M. Diab et al., 2021). Which goes in line with results from a study by Metwalley, as they agreed that ferritin and HOMA IR showed a positive correlation [13]. These results were agreed that there was positive correlation between HOMA IR and fasting glucose. In agreement, Diab et al demonstrated that HOMA IR was significantly correlated with fasting glucose and fasting insulin [16].

These results showed that glycemic irregularities in our β-TM patients were mostly caused by inadequate chelation (as 65.7% of our patients were not compliant on iron chelators), which led to hemosiderosis of the pancreas and other organs.

Recommendations:

Glycemic indices and serum ferritin levels should be early checked even in children and young people with β-TM who are receiving long-term transfusions to diagnose DM early.

More educational programs to raise

awareness about the importance of iron chelating agents, the hazards of iron overload and starting early management plans.

Future studies should be directed to evaluate the role of iron overload on glucose level through larger and follow up studies.

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