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Evaluation of glycemic abnormalities in children and adolescents with β-thalassemia major

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Abstract

Background: The quality of life of B-thalassemia major (β-TM) patients has improved with the use of frequent blood transfusions. However, this leads to chronic iron overload with its sequelae, as prediabetes and diabetes mellitus. This study aimed to assess insulin resistance and glucose abnormalities in a sample of B-thalassemia major patients in Benha, Egypt.

Results: This case-control study included 40 B-thalassemia major patients on regular blood transfusion and iron chelation. Their ages ranged from 8 to 16 years, and 30 normal age and sex-matched controls. Thorough clinical examination was performed including weight (kg), height (m), body mass index (BMI) (kg/m^2), and liver and spleen size. Laboratory investigations were done in the form of complete blood count, liver enzymes, serum ferritin, fasting plasma insulin, and fasting, and 2 h postprandial plasma glucose. Insulin resistance (IR) was calculated using the Homeostasis Model Assessment of insulin resistance (HOMA-IR) index. Insulin resistance was found in 27.5% of thalassemic patients; 18.2% of them had diabetes, 72.7% were prediabetics (with impaired fasting glycemia), and 9.1% had normal fasting and 2 h postprandial plasma glucose level. Insulin resistance increased significantly with increased blood transfusion duration, serum ferritin, liver enzymes, fasting plasma insulin, fasting plasma glucose, and 2 h postprandial plasma glucose (ROC). The curve analysis showed that the duration of blood transfusion, serum ferritin, fasting plasma insulin, fasting, and 2 h postprandial plasma glucose could significantly predict insulin resistance at a certain cut-off point.

Conclusion: Our data show that HOMA-IR can be used to detect insulin resistance in β-TM patients on long-term blood transfusions, especially patients with high serum ferritin and impaired liver enzymes.

Keywords: Glycemic abnormalities, Diabetes, Insulin resistance, Thalassemia major, B-Thalassemia

Background

B-Thalassemia major (β-TM) patients' life span and quality are highly dependent on regular blood transfusion, which comes with the cost of iron overload [1]. Despite advances in iron-chelating agents, iron overload remains a significant challenge in managing β-TM patients [2]. Diabetes mellitus (DM) is one of the important endocrinal disorders that happen due to iron overload. The precise mechanism of iron-induced diabetes is still unknown, but these three mechanisms are most likely to occur: insulin deficiency, insulin resistance (IR), and liver dysfunction. Evidence suggests that the most crucial factor in the pathogenesis of the disease's clinical complications is oxidative stress (caused by iron accumulation) [3]. Both IR and impaired insulin secretion lead to impaired glucose tolerance and type 2 diabetes mellitus (T2DM) [4].

It is said that iron excess and its related oxidative stress can mediate pancreatic islet cell apoptosis

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resulting in reduced insulin secretory capacity [5]. Islet cells are also very susceptible to oxidative damage due to an almost exclusive dependence on mitochondrial glucose metabolism to secrete glucose-induced insulin and have a flawed system of antioxidant defense [6]. Recently, McClain and colleagues have demonstrated a high prevalence of irregular homeostasis of glucose in patients with hemochromatosis as well as impaired insulin secretion and insulin resistance [7].

In several pathophysiological states, IR broadly occurs. Several researchers have indicated that IR is already present in diabetic patients before blood glucose irregularities. Hyperinsulinemia and IGT, in other words, are both T2DM reserve forces. Even in subjects with normal glucose tolerance [8], hyperinsulinemia and IR are dangerous. Homeostasis Model Assessment (HOMA), which involves the measurement of only fasting plasma insulin and fasting plasma glucose, is the easiest and most widely used marker in clinical practice to measure IR [9].

Aim of the study

We aimed in this study to evaluate IR and glucose abnormalities in a sample of β-TM patients in Benha, Egypt.

Methods

Subjects

This case-control study was conducted on 40 children and adolescents with β-TM (27 males and 13 females), aged between 8 and 16 years and 30 normal, age and sex-matched controls. The diagnosis of the patients was confirmed by Hb electrophoresis. They were regularly transfused at the hematology units of the Pediatric Departments, at Benha University Hospitals and Benha Children's Hospital. Informed consent was taken before conducting the study from parents of both cases and controls.

This research was approved by the ethical committee, Faculty of Medicine, Benha University.

Patients suffering from any acute illness, liver disease, or those previously diagnosed with DM were excluded from this study.

Methods

All cases were subjected to detailed history taking regarding blood transfusion duration and the chelation therapy details. Then, clinical examination including measurement of weight (kg), height (m), body mass index (BMI) (kg/m^2), and liver and spleen size was performed for all the subjects. Laboratory investigations were done for all the subjects, including complete blood picture (CBC) (performed by Sysmex XS-8001 cell counter), liver enzymes; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (performed by Biosystem A 15 autoanalyzer), and serum ferritin (performed by AIA 15 fluorescence, chemiluminescent immunoassay system, TOSOH Corporation, Tokyo, JAPAN). Moreover, fasting plasma glucose was obtained after 8 h of fasting (3 ml of venous blood (done by Glucose TR, SPINREACT), and at the same time, fasting plasma insulin level was collected (measured by DRG® Insulin ELISA, USA (EIA-2935)), then after taking a meal, 2 h postprandial plasma glucose (2 h pp plasma glucose) was obtained (2 ml of venous blood (done by Glucose TR, SPINREACT)).

DM and prediabetes diagnosis is based on the American Diabetes Association criteria [10]:

-Prediabetes (impaired fasting glycemia (IFG)) was diagnosed if fasting plasma glucose was 100-125 mg/dL (5.6-6.9 mmol/L).

-Diabetes was diagnosed if fasting plasma glucose was > 126 mg/dL (11.1 mmol/L).

Evaluation of the IR index was done using the Homeostasis Model Assessment (HOMA-IR) = (fasting plasma glucose (mmol/L) X fasting plasma insulin (μu/mL))/ 22.5). HOMA-IR value of ≥ 2.7 was considered to be an indicator of IR [11].

Statistical methods

The collected data were tabulated and analyzed using SPSS version 16 software (SpssInc, Chicago, ILL Company). Categorical data were presented as numbers and percentages, chi-square (χ^2) and Fisher's exact tests were used to analyze them. Quantitative data were tested for normality using the Shapiro-Wilks test, assuming normality at $P > 0.05$. Normally distributed variables were expressed as mean ± standard deviation and analyzed by St. "t" for two independent groups. Simultaneously, nonparametric data were presented as a median and interquartile range (IQR) and analyzed by Mann Whitney U test (Z_{MWU}) test. Spearman's correlation coefficient (rho) was used to assess the correlation between nonparametric variables. Receiver operator characteristic curve (ROC) curves were constructed to detect the studied parameters' cut-off values to early diagnose IR among β-TM patients. P value ≤ 0.05 was considered significant(s), $P > 0.05$ was non-significant (NS), $P \leq 0.001$ is highly significant (HS) [12].

Results

The patient group included forty thalassemic patients with a mean age of 11 ± 2.86 ys (range, 8-16 years); 67.5% were males (27 patients), and 32.5% were females (13 patients). The control group consisted of thirty healthy subjects with a mean age of 10.8 ± 2.49 years (range, 8-16 years); 60.0% were males (18 patients), and 40% were females (12 patients), with no statistically

significant difference between the two groups (P = 0.51) (Table 1).

All patients were on iron chelating therapy (34 patients were on Desferasirox, four patients were on Deferiprone, and two patients were on combined therapy (deferasirox and deferoxamine)). Two of our patients were splenectomized.

Thalassemic patients had significantly higher serum ferritin, ALT, fasting, 2 h pp plasma glucose levels, and HOMA-IR than controls (Table 1).

A total of 27.5% of the thalassemic patients (11 patients) had IR, while none of the controls group had IR. Patients with IR included two patients with DM (18.2%), eight patients with high fasting plasma glucose (72.7%), and one patient with regular fasting and 2 h pp plasma glucose levels (no glycemic abnormality) (9.1%).

Patients with IR had a significantly longer duration of blood transfusions, higher serum ferritin, ALT, fasting plasma insulin, fasting, and 2 h pp plasma glucose than those with no IR (Table 2).

HOMA-IR showed a significant positive correlation with blood transfusion duration, ALT, serum ferritin (Fig. 1), fasting plasma glucose, and 2 h pp plasma glucose, and a highly significant positive correlation between HOMA-IR and fasting plasma insulin. There was a significant positive correlation between serum ferritin and fasting plasma insulin, fasting, 2 h pp plasma glucose levels, HOMA-IR, and ALT level. There was a significant positive correlation between fasting plasma insulin and serum ferritin and fasting and 2 h pp plasma glucose. There was a significant positive correlation between fasting plasma glucose and duration of blood transfusions and serum ferritin and a highly significant positive correlation with the 2 h pp plasma glucose. There was a significant positive correlation between the 2 h pp plasma glucose and serum ferritin (Table 3).

ROC curve analysis showed that the duration of blood transfusions (mean, 10.2 years), serum ferritin (mean, 3173 ng/ml), fasting insulin, fasting, and 2 h pp plasma glucose can significantly predict IR at the shown cut-off values (Table 4) (Fig. 2).

Discussion

Regular and frequent blood transfusions usage in patients with β-TM has improved patients' lifespan and quality of life. However, it contributes to chronic iron overload, sometimes causing endocrine issues, mainly DMD [13].

In our study, 27.5% of the thalassemic patients (11 patients) had IR. Patients with IR included two patients with DM (18.2%), eight patients with high fasting plasma glucose (72.7%), and one patient with regular fasting and 2 h pp plasma glucose levels (no glycemic abnormality) (9.1%).

Patients with IR had a significantly longer duration of blood transfusions and higher serum ferritin, ALT, fasting plasma insulin, fasting, and 2 h pp plasma glucose compared with those with no IR.

This study showed that fasting plasma glucose and 2 h pp plasma glucose were significantly higher in thalassemic patients than the control group (P = 0,002 and P < 0.001, respectively), similar to the study of Metwally and El-Said [14]. Moreover, IR was significantly higher in patients than in controls (P = 0.015). This is consistent

Table 1 Comparison between patient and control groups

Variable		Patients (N = 40)			Controls (N = 30)			St. "t"	P
		Mean	± SD	Range	Mean	± SD	Range		
Age (years)		11.0	2.86	8-16	10.8	2.49	8-16	0.31	0.75
Sex (no., %)	Male	27 (67.5%)			18 (60%)			χ^2 (0.42)	0.51
	Female	13 (32.5%)			12 (40%)				
BMI (kg/m^2)		20.1	5.47	13.6-40.4	19.6	2.98	15.4-24.8	0.43	0.66 (NS)
Hb%		8.49	1.15	6.3-10.0	10.68	1.34	8.4-13.0	7.34	< 0.001 (HS)
ALT (U/L)		55.5	15.4	35-96	48.3	4.22	41-59	2.47	0.016 (S)
AST (U/L)		51.8	12.3	35-95	43.9	5.0	34-53	3.31	0.002 (S)
S ferritin (ng/ml)		2808.1	1344.0	1103-6989	20	3.0	30-18	4.05	< 0.001 (HS)
Fasting plasma glucose (mg/dl)		104.7	21.0	70-151	90.4	11.9	74-108	3.1	0.002 (S)
Fasting plasma insulin (μU/ml)		10.9	14.8	2.62-74.9	8.0	7.1	2.98-43.7	0.99	0.32
2 h pp plasma glucose (mg/dl)		157.0	32.2	99-225	114.5	10.5	95-130	St. "t" = 6.94	< 0.001 (HS)
HOMA-IR%		3.21	4.77	0.66-27.9	1.51	0.49	0.55-2.39	2.43	0.015 (S)
IR (no., %)	No	29 (72.5%)			30 (100%)				0.002 (S)
	Yes	11 (27.5%)			0 (0%)				

St. "t" Student "*t*" test, *S* Significant, *HS* highly significant, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *HOMA-IR* Homeostasis Model Assessment of insulin resistance index, *IR* insulin resistance

Table 2 Comparison between thalassemic patients with and without IR according to different variables

	No IR (*N* = 29)			IR (*N* = 11)			St. "*t*"	*P*
	Mean	± SD	Range	Mean	± SD	Range		
Age (years)	10.8	2.44	8-16	12.5	3.09	8-16	1.82	0.076
BMI (kg/m^2)	19.6	4.69	13.6-30.6	21.4	7.25	16.3-40.4	0.94	0.35 (NS)
Liver span	8.75	3.98	5-19	10.00	4.07	5-15	0.76	0.44 (NS)
Spleen size	3.32	2.38	0-7	4.30	3.78	0-10	0.68	0.49 (NS)
Duration of bl transfusion (years)	9.38	2.50	6-15	12.55	2.75	7.9-15.6	3.47	=0.001 (HS)
Hb%	8.43	1.18	6.3-10.0	8.62	1.11	6.5-10.0	0.45	0.65 (NS)
ALT(U/L)	52.0	13.5	35-93	64.7	17.1	37.5-96	2.46	0.018 (S)
AST(U/L)	49.7	8.54	35-65	57.4	18.47	36.2-95	1.83	0.075
Serum ferritin (ng/ml)	2447.2	1044.4	1103-5426	3759.7	1617.7	1234-6989	2.63	0.008 (S)
Fasting plasma glucose	98.4	18.94	70-125	121.5	17.40	88-151	3.17	0.002 (S)
2 h pp plasma glucose	146.4	26.8	99-199	184.7	29.3	144-225	3.02	0.003 (S)
Fasting plasma insulin	7.06	3.69	2.62-20.66	21.34	25.64	3.34-74.9	2.67	0.008 (S)

St. "t" Student *t* test, *IR* insulin resistance, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

with that reported in a study on Chinese children with β-TM, where IR was significantly higher in patients than controls [15]. In this study, 5% of thalassemic patients had fasting plasma glucose in the range of the provisional diagnosis of diabetes. This is similar to the Egyptian study conducted by Metwalley and El-Saied, who reported that the incidence of diabetes was 5% among studied β-TM cases [14]. This is also nearly similar to a recent study that found that the prevalence of DM in β-TM patients was 6.54% [16].

The incidence of DM in our study was higher than the overall prevalence of diabetes in Chinese thalassemic children under 18 years, which was 2% [15]. Our results were also higher than the reported incidence in the study conducted by Bhat and Periasamy, where diabetes was not diagnosed in any of the β-TM patients included in their study [17].

Our study showed that there was a significant positive correlation between HOMA-IR in β-TM patients and duration of blood transfusion and serum ferritin, in agreement with the study of Hafez et al., who reported

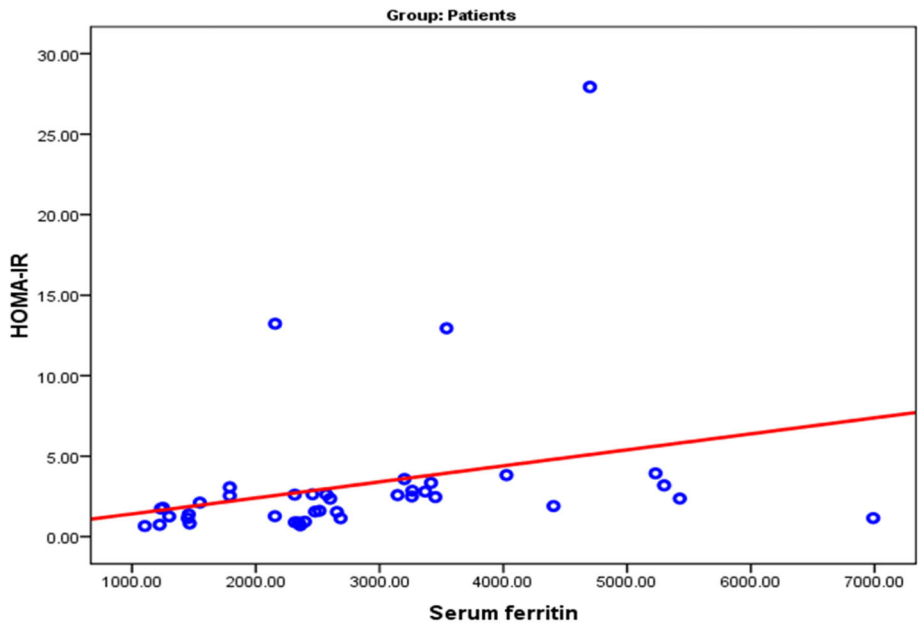

Fig. 1 Scatter graph showing significant positive correlation between HOMA-IR and serum ferritin

Table 3 Correlations between serum glycemic parameters and various parameters in the patient group

With	Serum ferretin (*n* = 40)		Fasting plasma glucose (*n* = 40)		Fasting insulin (*n* = 40)		2 h pp plasma glucose (*n* = 40)		HOMA-IR (*n* = 40)	
	Rho	*P*	Rho	*P*	Rho	*P*	Rho	*P*	Rho	*P*
Age	0.375	0.017 (S)	0.169	0.29	0.069	0.67	0.029	0.86	0.291	0.068
Duration of blood transfusion	0.181	0.26	0.361	0.022 (S)	0.192	0.23	0.252	0.11	0.481	0.002 (S)
BMI (kg/m^2)	0.206	0.20	0.018	0.91	−0.064	0.69	0.096	0.55	0.005	0.97
Liver size	0.008	0.96	0.157	0.33	−0.088	0.59	0.046	0.78	0.031	0.85
Spleen size	0.293	0.075	0.071	0.67	−0.023	0.89	0.033	0.84	−0.051	0.76
Hb	0.019	0.91	0.147	0.36	0.166	0.31	0.244	0.13	0.146	0.37
ALT	0.519	=0.001 (HS)	0.225	0.16	0.149	0.35	0.200	0.21	0.391	0.013 (S)
AST	0.251	0.12	0.120	0.46	0.02	0.90	0.156	0.34	0.124	0.44
Serum ferritin			0.361	0.022 (S)	0.425	0.006 (S)	0.393	0.012 (S)	0.396	0.012 (S)
Fasting plasma glucose	0.361	0.022 (S)			0.315	0.048 (S)			0.473	0.002 (S)
Fasting plasma insulin	0.425	0.006 (S)							0.707	< 0.001 (HS)
2 h pp plasma glucose	0.393	0.012 (S)	0.837	< 0.001 (HS)	0.347	0.028 (S)			0.383	0.015 (S)
HOMA-IR	0.396	0.012 (S)								

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *HOMA-IR* Homeostasis Model Assessment of insulin resistance index

that there was a positive correlation between serum ferritin and HOMA IR [18], and in agreement with Bhat and Periasamy, who found that there was a progressive increase in IR with the increase in the number of units transfused and age [17]. Also, in agreement with Ansari et al., who found that the association between serum ferritin values and HOMA-IR index value was highly statistically significant ($P < 0.001$) [19].

In this study, HOMA-IR significantly increased with the increase in ALT level. This is similar to a study done by Liang et al., which reported a significant positive correlation between HOMA-IR, the gold standard marker of IR, and age, serum ferritin, and ALT levels, suggesting that the degree of iron overload and hepatic dysfunction were responsible for the IR [15]. This study demonstrated a significant positive correlation between serum ferritin and fasting plasma insulin, fasting plasma glucose and 2 h pp plasma glucose, and HOMA-IR. This was similar to the study, which reported that the ferritin level was positively correlated with the fasting plasma glucose and 2 h pp plasma glucose [20]. This study showed a highly significant positive correlation between serum ferritin in thalassemic patients and ALT level ($P = 0.001$). This was in agreement with Ezzat et al., who found a significant positive correlation between serum ferritin and liver enzymes; AST ($r = 0.978$, P ˂0.001), and ALT ($r = 0.98$, P ˂ 0.001) [21]. In our study, 11 patients had IR, two of them had DM, eight patients had IFG, and one patient did not have any glycemic abnormality, suggesting that IR precedes the glycemic abnormalities (prediabetes and DM). This was similar to the study of Soliman et al., who reported that three of their adolescents with B-TM showed IR state, one of them had DM, one had prediabetes, and the third one did not have any glycemic abnormality [20]. This state of IR may overwork the beta-cell function and, in addition to iron toxicity, leads to prediabetes and DM later.

In our study, there was a significant increase in DM, and prediabetes with the increase of the duration of blood transfusion, ALT, 2 h pp plasma glucose, and HOMA-IR than those with no glycemic abnormality, and there was a highly significant increase in serum ferritin of DM and IFG (prediabetic) than those with no glycemic abnormality.

The only patient in our study who had IR with no glycemic abnormality had the youngest age, the least duration of blood transfusion, and the least serum ferritin. This might show that IR precedes prediabetes and DM, which may develop after that with age progression and increased blood transfusion duration. This highlights the

Table 4 ROC curve analysis for the performance of glucose parameters in early diagnosis of IR

Variable	Sensitivity	Specificity	PPV	NPV	AUC	95% CI	*P*
Fasting plasma g ≥ 115.5 mg/dl	81.8%	79.3%	60%	92%	0.828	0.68-0.98	0.002 (S)
2 h pp plasma glucose ≥ 162.5 mg/dl	81.8%	62.1%	45%	90%	0.812	0.66-0.96	0.003 (S)
Fasting insulin ≥ 9.13μU/ml	81.8%	72.4%	52.9%	91.3%	0.776	0.58-0.96	0.008 (S)

PPV positive predictive value, *NPV* negative predictive value, *AUC* area under the curve, *CI* confidence interval

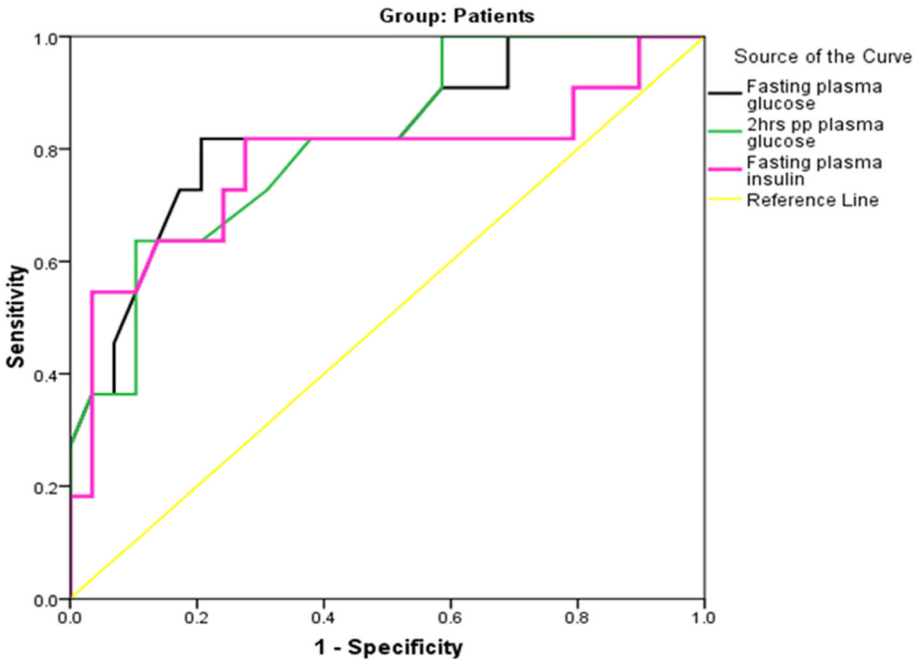

Fig. 2 ROC curve for the performance of glucose parameters in early diagnosis of insulin resistance

importance of good observation and close monitoring of glycemic parameters of these patients. However, to confirm our results, this requires more extensive longitudinal studies rather than cross-sectional studies. This was in agreement with Metwally and El-Saied. They found that fasting and 2 h pp glucose, fasting insulin, HOMA-IR, ALT, and serum ferritin levels showed a significant increase in thalassemic patients with DM and prediabetes than patients with standard glucose tolerance [14].

In this study, there was no significant difference between patients with IR and those with no IR regarding liver span and spleen size; this was in agreement with Bhat and Periasamy, who found that the size of the liver and spleen did not correlate with any of the parameters like IR, age, ferritin, number of transfusions or glycemic indices, like fasting glucose and fasting insulin [17].

ROC curve analysis in our study showed that the duration of blood transfusion at a cut-off value ≥ 10.2 years and serum ferritin at a cut-off value ≥ 3173 ng/dl could significantly predict IR, with a sensitivity of 63.6% and 81.8% and a specificity of 69% and 82.8%, respectively. Also, ROC curve analysis showed that fasting plasma glucose at a cut-off value ≥ 115.5 mg/dl, 2 h pp glucose at a cut-off value ≥ 162.5 mg/dl, and fasting plasma insulin at a cut off value ≥ 9.13 could significantly predict IR, with a sensitivity of 81.8% and a specificity of 79.3%, 62.15%, and 72.4%, respectively. This was in disagreement with Ghergherehchi and Habibzadeh, where they found that only ALT could predict DM occurrence, unlike other variables such as serum ferritin or blood transfusion duration [22].

Conclusion

Our results show that HOMA-IR can be used to detect IR in (β-TM) patients on long-term transfusions, especially patients with high serum ferritin and liver enzymes (ALT).

Recommendation

Adolescents and children with β-TM on long-term transfusions should be periodically monitored with glycemic indices and serum ferritin levels for early detection of DM. More efficient therapeutic strategies that could ameliorate insulin resistance should be considered in treating transfusion-dependent thalassemic patients.

Abbreviations

β-TM: B-Thalassemia major; HOMA-IR: Homeostasis Model Assessment of insulin resistance index; IR: Insulin resistance; IFG: Impaired fasting glycemia; DM: Diabetes mellitus; T2DM: Type 2 diabetes mellitus; PP: Postprandial; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ROC curve: Receiver operator characteristic curve; HS: Highly significant; NS: Non-significant; CBC: Complete blood count

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Authors' contributions

All authors have read and approved the manuscript. AD: Writing this manuscript and collecting data. GA: Share in writing this manuscript and revising data. KE: Collecting data and revising data. EM: Laboratory step. EA: Writing this manuscript and collecting data

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Ethics approval and consent to participate
This research accepted by the Research Ethics Committee (REC) of the Faculty of Medicine, Benha University (chairman: Prof/ Nermeen Adly Mahmoud), Ethics committee reference number RC 1.11.2020.
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A written informed consent was obtained from each patient after explaining all steps of this study.

Consent for publication
All patients or their parents have been consented for taking their laboratory results for scientific researches

Competing interests
The authors declare no conflict of interest.

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