Mediterranean Journal of Hematology and Infectious Diseases

Original Article

Association Between Iron Overload and Glucose Metabolism in Children and Youth with Transfusion-Dependent Beta Thalassemia: The Role of Chelation Therapy

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Competing interests: The authors declare no competing interest.

Abstract. ***Background*: Transfusion-dependent thalassemia (TDT) is a transfusion-dependent anemia frequently associated with iron overload, which may disrupt liver function and glucose metabolism.**
***Objective*: This study aimed to evaluate glucose dysregulation and the effects of iron chelation therapy in pediatric TDT patients.**
***Methodology*: This retrospective study included 31 children and adolescents (aged 7–23 years) with TDT who were followed at a tertiary-care pediatric hematology center with available oral glucose tolerance test (OGTT) data. Clinical and laboratory data were analyzed, including oral glucose tolerance test (OGTT), serum ferritin, alanine aminotransferase (ALT), glycated hemoglobin (Hb A1c), C-peptide, homeostatic model assessment for insulin resistance (HOMA-IR), abdominal ultrasonography (USG), and liver and cardiac magnetic resonance imaging (MRI). Diagnosis of diabetes mellitus (DM) and prediabetes was based on American Diabetes Association (ADA) criteria.**
***Results*: OGTT was performed in 28 patients; impaired fasting glucose (IFG) was observed in 10.7%, impaired glucose tolerance (IGT) in 3.6%, and 85.7% had normal glucose regulation. All received consistent oral chelation with film-coated deferasirox. ALT showed significant correlation with age at chelation onset (r=0.49, p=0.00), C-peptide (r=0.45, p=0.02), and age at diagnosis (r=0.56, p=0.001). Duration of chelation correlated with hepatomegaly severity (r=0.61, p=0.00), 30-minute glucose (r=0.39, p=0.03), and insulin levels at 30 (r=0.37, p=0.04) and 90 minutes (r=0.39, p=0.03). No significant association was found between ferritin and OGTT values (p>0.05).**
***Conclusions*: Overt glucose metabolism disorders were uncommon and should be interpreted cautiously. These results highlight the critical role of adherence to chelation and metabolic monitoring to prevent DM in children with TDT.**

Keywords: Beta thalassemia major; Iron overload; Oral glucose tolerance test; Diabetes mellitus.

Citation: İncefidan İ., Kazancı E.G., Güven D., Kara Ö. Association between iron overload and glucose metabolism in children and youth with transfusion-dependent beta thalassemia: the role of chelation therapy. Mediterr J Hematol Infect Dis 2026, 18(1): e2026017, DOI: http://dx.doi.org/10.4084/MJHID.2026.017

Published: March 01, 2026 **Received: December 10, 2025** **Accepted: January 28, 2026**

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Introduction. Transfusion-dependent beta thalassemia (TDT) is associated with chronic iron overload, which remains a major contributor to endocrine complications despite advances in chelation therapy. Disturbances in glucose metabolism, ranging from impaired glucose tolerance to overt diabetes mellitus, are among the most clinically relevant metabolic complications in this population.

The pathogenesis of dysglycemia in thalassemia is multifactorial and involves iron-mediated pancreatic beta-cell dysfunction, alterations in insulin sensitivity, and cumulative effects of long-term transfusion therapy. Although improved chelation strategies have reduced the incidence of severe complications, glucose metabolism abnormalities continue to be reported, particularly during adolescence and early adulthood.

The current standard of care for TDT involves lifelong red blood cell transfusions combined with iron chelation therapy to prevent iron overload.[1] Although advances in treatment have significantly improved survival, transfusion-related iron accumulation remains a major challenge, contributing to progressive damage in vital organs such as the liver, heart, pancreas, and pituitary gland.[2]

Serum ferritin remains the most accessible and cost-effective biomarker for assessing iron burden; however, it may not reliably reflect parenchymal iron deposition. Magnetic resonance imaging (MRI) of the liver, heart, and pancreas has emerged as the preferred modality for organ-specific iron quantification.[2,3] Inadequate chelation can lead to endocrine dysfunctions, including hypothyroidism, hypoparathyroidism, growth hormone deficiency, hypogonadism, adrenal insufficiency, and diabetes mellitus (DM).[4] Early diagnosis and close monitoring, combined with optimized chelation, are essential to reduce endocrine complications in TDT.[2]

Liver dysfunction, chronic iron overload, and iron-induced oxidative stress are thought to play a central role in the pathogenesis of glucose metabolism abnormalities in TDT.[5,6] Pancreatic iron deposition begins early — often within the first decade — and progresses with age, impairing beta-cell function and insulin secretion.[7] Patients may exhibit a prolonged phase of insulin resistance (IR) and compensatory hyperinsulinemia, which can ultimately result in impaired glucose tolerance (IGT) and overt diabetes due to beta-cell exhaustion.[8] However, dysglycemia in transfusion-dependent thalassemia is increasingly recognized as a multifactorial process, in which impairments in insulin secretion and insulin sensitivity may coexist from early stages rather than evolve solely through a prolonged phase of insulin resistance.

IR, defined as the decreased biological response to normal circulating insulin levels, disrupts glucose homeostasis. Fasting plasma glucose (FPG) is a practical indicator of hepatic IR and is generally more reliable than serum insulin thresholds, which lack standardization across laboratories.[9–11] Given the insidious nature of glucose dysregulation in TDT, annual screening using a 2-hour oral glucose tolerance test (OGTT) is recommended starting at age 10.[9]

The American Diabetes Association (ADA) supports screening at-risk individuals using FPG, insulin levels, Hb A1c, or OGTT. However, in hemoglobinopathies such as TDT, Hb A1c may yield falsely low values due to shortened erythrocyte lifespan and increased hemolysis, making it a less reliable marker.[4]

Suboptimal chelation and transfusion practices increase the risk of iron-induced hepatic damage and metabolic dysregulation. Therefore, regular glucose monitoring is crucial to avoid long-term complications.

Methods.

Objectives. This study aimed to descriptively evaluate glucose metabolism parameters and their associations with iron burden, chelation duration, and selected clinical markers in children and adolescents with transfusion-dependent beta thalassemia.

Methodology. This retrospective study included 31 patients aged 7 to 23 years who were diagnosed with TDT and followed at the Pediatric Hematology Clinic of a tertiary care Training and Research Hospital (a designated Level 3 Thalassemia Center). Patients with available oral glucose tolerance test (OGTT) data were enrolled. Clinical data were obtained retrospectively from the hospital electronic medical records.

Demographic and anthropometric data, physical examination findings (hepatomegaly, splenomegaly), laboratory parameters (OGTT results, serum ferritin, alanine aminotransferase [ALT], insulin, C-peptide, HbA 1c), abdominal ultrasonography (USG), liver and cardiac magnetic resonance imaging (MRI), splenectomy status, age at diagnosis, annual transfusion frequency, and details of chelation therapy were recorded.

According to national guidelines, all patients received erythrocyte suspension (ERT) transfusions at a dose of 10–15 mL/kg every 3–4 weeks. Oral chelation therapy was administered with film-coated deferasirox (DFX) tablets at a dose of 21–28 mg/kg/day, taken once daily for seven consecutive days each week. Treatment adherence to chelation therapy was assessed retrospectively based on clinical follow-up notes, parental reports, and pharmacy refill documentation. Adherence was considered high when regular daily

intake without missed doses was reported in more than 90% of follow-up visits. Serum ferritin levels were used as a surrogate marker of cumulative iron burden and were interpreted as reflecting long-term iron exposure rather than short-term treatment compliance.

Although OGTT screening is generally recommended from the age of 10 years, three patients younger than 10 years underwent OGTT based on individual clinical judgment due to suspected dysglycemia or additional risk factors. To ensure age homogeneity and methodological consistency, these patients were excluded from correlation analyses. Accordingly, OGTT-based analyses were conducted in 28 patients aged ≥10 years. For the OGTT procedure, after an overnight fast, patients received 1.75 g/kg (maximum 75 g) of oral glucose. Venous blood samples were collected at baseline (0 minutes) and at 30, 60, 90, and 120 minutes post-glucose ingestion to measure plasma glucose and insulin levels. Pubertal status (e.g., Tanner staging) was not systematically recorded in the medical records due to the retrospective study design.

Diagnosis of diabetes and prediabetes was based on American Diabetes Association (ADA) criteria.[9,10] Diabetes was diagnosed in patients who met one or more of the following: random plasma glucose ≥200 mg/dL with typical hyperglycemic symptoms, fasting plasma glucose (FPG) ≥126 mg/dL, 2-hour OGTT plasma glucose ≥200 mg/dL, or HbA1c ≥6.5%. Prediabetes was defined as either impaired fasting glucose (FPG 100–125 mg/dL), impaired glucose tolerance (2-hour OGTT glucose 140–199 mg/dL), or HbA1c between 5.7% and 6.4%.[9,10] HbA1c levels were measured using high-performance liquid chromatography (HPLC) in accordance with NGSP standardization. Although OGTT screening is generally initiated at age 10, three patients under age 10 were tested based on clinical discretion due to risk factors or suspected dysglycemia.

Insulin resistance was assessed using the homeostatic model assessment of insulin resistance (HOMA-IR), calculated as:

HOMA-IR = (Fasting insulin [μU/mL] × Fasting glucose [mg/dL]) / 405

A HOMA-IR value <2 was considered normal.[12]

For the oral glucose tolerance test (OGTT), patients fasted overnight for at least 8 hours. A glucose load of 1.75 g/kg body weight (maximum 75 g) was administered orally. Venous blood samples were collected at baseline (0 minutes) and at 30, 60, 90, and 120 minutes after glucose ingestion.

Plasma glucose concentrations were measured using the hexokinase enzymatic method. Serum insulin and C-peptide concentrations were measured using a chemiluminescent immunoassay method. All blood samples were centrifuged within 30 minutes of collection and analyzed on the same day to minimize pre-analytical variability. Although OGTT screening is generally recommended from the age of 10 years, three patients younger than 10 years underwent OGTT based on individual clinical judgment. These patients were excluded from correlation analyses to ensure age homogeneity.

Reference ranges for the laboratory parameters were as follows:

- Serum ferritin: 10–300 ng/mL
- ALT: 0–40 U/L[13]
- C-peptide: 0.4–2.2 ng/mL[14]

Hepatomegaly and splenomegaly were assessed via abdominal ultrasound. A 1.5 Tesla MRI scanner was used for iron quantification in the liver and heart. Cardiac T2* values were interpreted as follows: >20 ms (normal), 15–20 ms (mild), 10–15 ms (moderate), and <10 ms (severe iron overload). Hepatic T2* MRI values were classified as: >11.4 ms (normal), 3.8–11.4 ms (mild), 1.8–3.8 ms (moderate), and <1.8 ms (severe).[15]

Short stature was defined as a height below the 3rd percentile or more than two standard deviations below the mean for age and sex. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). Anthropometric measurements were evaluated according to age- and sex-specific criteria. In children and adolescents, body mass index (BMI) and BMI standard deviation scores (BMI SDS) were interpreted using age- and sex-adjusted reference standards, whereas absolute BMI values were used for young adults. Height and weight were assessed using standardized growth charts appropriate for age and sex. BMI standard deviation scores (SDS) were determined according to World Health Organization (WHO) growth reference standards appropriate for age and sex.

Statistical Analyses. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for all clinical, laboratory, and radiological variables. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR) depending on the distribution, and categorical variables as frequencies and percentages.

The normality of data distribution was assessed using the Shapiro–Wilk test and visual methods (histograms, Q-Q plots). For normally distributed variables, Pearson correlation analysis was used; for non-normally distributed variables, Spearman rank correlation was applied to explore associations between continuous parameters (e.g., ferritin levels, glucose and insulin values, ALT, C-peptide, and HOMA-IR). All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Correlation strength was interpreted as weak ($r < 0.30$), moderate ($r = 0.30$–0.50), and strong ($r > 0.50$). Given the exploratory nature of the study and the limited sample size, no correction for multiple comparisons was applied, and correlation

Table 1. Demographic, clinic, laboratory, and magnetic resonance imaging findings and treatment status of the patients.

Characteristics		Thalassemia major (N=31)	95% CI
Gender**	Male	17 (55)	
	Female	14 (45)	
Age (years)*		15.77 ± 5.16	(13.88 – 17.66)
Age at diagnosis (months)*		16.93±14.78	(11.52 – 22.34)
Height(cm) *		150.22 14.64	(144.86 – 155.58)
Height SDS*		-1.26±1.08	(−1.66 – −0.86)
Weight (kg) *		45.77±11.97	(41.39 – 50.15)
Weight SDS*		-0.925 ±1.19	(−1.36 – −0.49)
BMI (kg/m2) *		19.90±2.55	(18.97 – 20.83)
BMI SDS*		-0.28±1.01	(−0.65 – 0.09)
Presence of hepatomegaly **		19 (61.3)	
Presence of splenomegaly **		19 (61.3)	
Splenectomy **		9 (29.0)	
Hepatomegaly level (USG)* (cm)		156.32±15.30	(150.71 – 161.93)
Splenomegaly level (USG)* (cm)		155.16±31.44	(143.64 – 166.68)
Glucose 0. min (mg/dl)*		89.71±7.31	(87.04 – 92.38)
Glucose 30. min (mg/dl)*		132.93±36.72	(119.49 – 146.37)
Glucose 60. min (mg/dl)*		121.07±36.24	(107.81 – 134.33)
Glucose 90. min (mg/dl)*		106.18±23.84	(97.45 – 114.91)
Glucose 120. min (mg/dl)*		101.89±20.97	(94.20 – 109.58)
Insulin 0. min (mU/L)*		7.75±5.01	(5.92 – 9.58)
Insulin 30. min (mU/L)*		34.75±32.02	(23.04 – 46.46)
Insulin 60. min (mU/L)*		32.31±40.69	(17.42 – 47.20)
Insulin 90. min (mU/L)*		22.42±16.51	(16.38 – 28.469
Insulin 120. min (mU/L)*		16.23±10.40	(12.41 – 20.05)
HOMA-IR (N=28)*		1.73±1.14	(1.29 – 2.17)
C-Peptide (N=25)* (ng/ mL)		1.92±0.66	(1.65 – 2.19)
HBA1C (N=29)* (%)		6.20±0.86	(5.87 – 6.53)
Ferritin (N=31)* (ng/mL)		1893.42±1604.63	(1305.44 – 2481.40)
ALT (N=31)*(mU/L)		31.10±29.56	(20.28 – 41.92)
Prediabetes status			
Impaired fasting glucose **		3 (10.71)	
Impaired glucose tolerance **		1 (3.57)	
Liver MRI (N=28)**			
	Normal (>11.4 ms)	6 (19.4)	
	Mild (3.8-11.4 ms)	11 (35.5)	
	Moderate (1.8-3.8 ms)	5 (16.1)	
	Severe (<1.8 ms)	6 (19.4)	
Cardiac MRI (N=28)			
	Normal (>20 ms)	22 (71)	
	Mild (15-20 ms)	4 (12.9)	
	Moderate (10-15 ms)	1 (3.2)	
	Severe (<10 ms)	1 (3.2)	
Age at starting chelation (years) *		3.60±2.68	(2.62 – 4.58)
Duration of chelation (years) *		12.19±5.30	(10.25 – 14.13)
Number of transfusions (year)*		15.71±2.59	(14.76 – 16.66)
Treatment type **			
	Oral	31 (100)	

Intravenous	0 (0)
Chelation **	
Deferasirox	31 (100)
Deferiprone	0 (0)
Desferrioksamine	0 (0)

*mean ± sd. **n (%), 95% confidence intervals were calculated using the Student's *t* distribution, BMI: Body Mass Index, SD: Standard Deviation, SDS: SS: Standard deviation score (Z-score), USG: Ultrasonographic Imaging, OGTT: Oral Glucose Tolerance Test, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, HBA1C: Glycated Hemoglobin, ALT: Alanine Aminotransferase, MRI: Magnetic Resonance Imaging.

analyses should be interpreted as hypothesis-generating.

Results. A total of 31 patients with TDT were included in the study. The mean age was 15.77 ± 5.16 years, and the mean age at diagnosis was 16.93 ± 14.78 months. Table 1 summarizes the demographic, clinical, blood parameters, and MRI findings of patients. Details of chelation exposure, including age at initiation, duration of therapy, and treatment modality, are summarized in **Table 1**.

Among the 31 patients, 29 (93.5%) demonstrated high compliance with daily deferasirox, based on clinical and pharmacy records. No significant adverse events related to chelation therapy were recorded in any patient during the study period.

Correlation analysis between age at diagnosis, age at initiation of chelation therapy, and chelation duration with anthropometric, biochemical, and imaging parameters is presented in **Table 2**.

The relationships between iron overload, chelation parameters, and glucose metabolism indices is presented in **Table 3**. Full correlation coefficients and significance levels are provided in **Table 4**. Correlation analyses demonstrated several clinically relevant associations. Serum ferritin showed a moderate positive correlation with ALT levels, while no significant correlations were observed between ferritin and OGTT-derived glucose or insulin parameters. Chelation duration was moderately associated with selected OGTT indices and strongly correlated with hepatomegaly severity. Other correlations were weak and are detailed in **Tables 2–4**.

Table 2. Correlation analysis between age at diagnosis, age at starting chelation, duration of chelation, and anthropometric measurements, C-peptide, ALT, ferritin, HbA1c, Homa-IR, hepatomegaly, and splenomegaly levels.

	Age at diagnosis		**Age at start of chelation**		**Duration of chelation**	
Parameters	*r**	*p**	*r**	*p**	*r**	*p**
Weight (kg)	0.08	0.66	0.28	0.11	0.51	**0.003**
Height (cm)	0.15	0.40	0.42	**0.01**	0.54	**0.002**
BMI (kg/m^2)	-0.06	0.73	-0.06	0.74	0.30	0.09
BMI SS	-0.08	0.63	-0.25	0.16	-0.28	0.12
C-peptide (ng/ mL)	-0.14	0.50	-0.05	0.81	0.02	0.91
ALT (U/L)	0.56	**0.01**	0.49	**0.00**	-0.15	0.41
Ferritin (ng/mL)	0.41	**0.02**	0.29	0.10	-0.14	0.43
HbA1c (%)	-0.11	0.56	-0.21	0.26	0.13	0.47
Homa-IR	0.12	0.52	0.03	0.86	0.07	0.69
Hepatomegaly Level	0.03	0.88	0.24	0.31	0.61	**0.005**
Splenomegaly Level	0.01	0.93	0.39	0.09	-0.009	0.97

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HBA1C: Glycated Hemoglobin, ALT: Alanine Aminotransferase, *Pearson correlation analysis

Table 3. Correlation analysis between ferritin, number of transfusions, and chelation time with OGTT and other laboratory data.

	Ferritin		**Number of Transfusions**		**Duration of chelation**	
Parameters	r*	p*	r*	p*	r*	p*
0.min Glucose (mg/dl)	0.21	0.25	0.35	0.052	0.19	0.30
30.min Glucose (mg/dl)	-0.16	0.39	0.17	0.38	0.39	**0.03**
60.min Glucose (mg/dl)	-0.18	0.35	0.16	0.40	0.24	0.20
90.min Glucose (mg/dl)	-0.10	0.61	0.20	0.30	0.24	0.21
120.minGlucose (mg/dl)	-0.05	0.79	0.03	0.84	-0.04	0.81
0.min Insulin (mg/dl)	0.03	0.87	-0.32	0.08	0.06	0.75

30. min Insulin (mg/dl)	-0.01	0.93	0.02	0.91	0.37	**0.04**
60. min Insulin (mg/dl)	-0.07	0.70	0.06	0.75	0.29	0.13
90. min Insulin (mg/dl)	-0.10	0.59	0.12	0.53	0.39	**0.03**
120. min Insulin (mg/dl)	0.09	0.63	-0.05	0.78	-0.04	0.98
Total Insulin (µIU/mL)	0.11	0.54	0.16	0.38	0.02	0.89
ALT (U/L)	0.48	**0.006**	-0.65	**0.000**	0.02	0.91
C-Peptide (ng/ mL)	0.06	0.75	-0.15	0.46	-0.15	0.41
HbA1C (%)	0.22	0.24	0.11	0.55	0.13	0.47
HOMA-IR	0.05	0.77	-0.27	0.14	0.07	0.69
Hepatomegaly	-0.09	0.69	-0.23	0.33	0.61	**0.005**
Splenomegaly	-0.25	0.29	-0.11	0.63	-0.009	0.97

OGTT: Oral glucose tolerance test, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance HBA1C: Glycated Hemoglobin ALT: Alanine Aminotransferase *Pearson correlation analysis.

Table 4. Correlation analysis between OGTT results and laboratory and imaging findings.

	0.min Glucose		**60.min Glucose**		**120.min Glucose**		**0.min Insulin**		**Liver MRI**		**Cardiac MRI**	
Parameters	r*	p*	r*	p*	r*	p*	r*	p*	r*	P*	r*	P*
C-Peptite (ng/ mL)	0.19	0.36	-0.40	0.05	-0.40	**0.04**	0.55	**0.004**	0.42	0.02	0.05	0.78
ALT (U/L)	0.05	0.78	-0.11	0.57	-0.07	0.71	0.13	0.501	**0.46**	**0.01**	0.10	0.65
Ferritin (ng/mL)	0.21	0.25	-0.18	0.35	-0.05	0.79	0.03	0.87	**0.65**	**<0.001**	0.20	0.32
HbA1c (%)	0.42	**0.02**	-0.09	0.62	-0.14	0.47	0.26	0.17	0.12	0.44	0.07	0.72
HOMA-IR	0.24	0.20	-0.30	0.11	-0.46	**0.01**	0.99	**0.00**	0.18	0.38	0.08	0.70
Hepatomegaly	0.14	0.55	0.37	0.13	0.03	0.89	0.14	0.58	0.40	0.04	0.12	0.48
Splenomegaly	0.39	0.09	-0.10	0.68	-0.47	0.05	0.05	0.84	0.28	0.21	0.10	0.60

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HBA1C: Glycated Hemoglobin, ALT: Alanine Aminotransferase, *Pearson correlation analysis

Discussion. The relationship between iron overload, chelation therapy, and glucose metabolism was examined in pediatric and adolescent patients with TDT. Overt glucose dysregulation was infrequent in this cohort. Although high compliance with oral chelation therapy was observed, the descriptive and observational design of the study precludes causal inferences regarding its role in glucose homeostasis; thus, the findings should be interpreted as associative.

Previous studies have highlighted serum ferritins as a surrogate marker of total body iron load, strongly associated with annual transfusion volume, age, and delayed chelation.[3,16] While our results confirmed a correlation between ferritin levels and age at diagnosis, we did not observe a relationship between ferritin and transfusion frequency, in contrast to earlier reports.[17,18] This discrepancy may reflect differences in chelation practices and patient characteristics in our cohort rather than implying a causal effect of chelation therapy. Given the retrospective design, these observations should be interpreted cautiously and cannot be considered evidence of a causal relationship. While the use of a single chelation agent (deferasirox) precludes comparison with other therapies, it reduces variability and allows more focused interpretation of treatment effects. Furthermore, some studies have suggested that film-coated deferasirox may be associated with modest improvements in hemoglobin levels; however, findings across the literature are heterogeneous and should be interpreted with caution.[19]

Growth retardation, a common complication in TDT due to chronic anemia and endocrine dysfunction, is often mitigated with early chelation and adequate transfusion support.[20] In line with this, we found that longer chelation duration was positively associated with both height and weight, consistent with prior literature.[21]

A large meta-analysis reported the prevalence of IFG, IGT, and diabetes as 17.2%, 12.4%, and 6.5%, respectively, among TDT patients.[22] The lower rates of dysglycemia observed in this cohort are consistent with previous reports; however, multiple clinical and treatment-related factors may contribute to these findings. Notably, only three patients in this study were younger than 10 years, and none exhibited glucose dysregulation. This suggests that at younger ages, iron overload may not have progressed sufficiently to impair glucose metabolism. Therefore, age-related differences in risk profiles should be considered when interpreting OGTT results in pediatric TDT populations.

Although iron overload, particularly

hyperferritinemia, has been implicated in the pathogenesis of insulin resistance (IR) and beta-cell dysfunction,[23] no significant correlation was found between ferritin or ALT and OGTT parameters in this study. The inclusion of patients under age 10 was based on individual clinical risk assessments, and none of these younger participants exhibited glucose dysregulation, consistent with literature indicating lower risk at early ages. These inconsistencies with previous studies suggest that glucose metabolism disturbances in TDT are multifactorial, influenced by iron load as well as genetic, nutritional, and therapeutic factors. Elevated serum ferritin levels in some patients likely reflect cumulative iron exposure over time rather than current chelation adherence. Given the retrospective, descriptive design, ferritin levels should not be interpreted as direct indicators of short-term treatment compliance. Glucose dysregulation in transfusion-dependent thalassemia is considered a multifactorial process that may involve early impairments in both insulin secretion and insulin sensitivity, rather than a linear progression driven solely by insulin resistance. Comprehensive assessment of beta-cell function, including indices such as the oral disposition index, may provide further insight into these mechanisms; however, such indices were not available in this retrospective study, which represents a limitation.

ALT, as a marker of hepatocellular injury, was positively correlated with both ferritin and liver iron accumulation on MRI — supporting its use as an indirect marker of hepatic iron toxicity.[24,25] However, ALT was not associated with OGTT parameters, indicating that liver dysfunction alone may not explain early glucose abnormalities.

The utility of HbA1c in TDT remains controversial due to altered erythrocyte turnover. In this study, a positive correlation between HbA1c and FPG was observed, consistent with studies reporting elevated HbA1c levels in TDT patients.[10] Nonetheless, given its limitations, OGTT remains the preferred screening tool in this population. Considering the limitations of HbA1c and the logistical challenges of OGTT, continuous glucose monitoring (CGM) may offer a non-invasive alternative for real-time glucose assessment. However, further validation studies are required to determine its reliability in hemoglobinopathy populations such as TDT.

C-peptide, which reflects endogenous insulin secretion, showed significant correlation with fasting insulin and HOMA-IR, but not with ferritin or glucose levels. Previous studies have reported both positive and negative associations between C-peptide and iron load.[26] The present findings suggest that C-peptide alone is insufficient to fully explain pancreatic beta-cell dysfunction in TDT.

HOMA-IR is widely used to assess IR, and studies have linked it to ferritin and ALT.[27–29] However, our data did not show such associations. A negative correlation between HOMA-IR and glucose at 120 minutes may indicate a paradoxical late-phase IR, possibly related to a small sample size or age-related insulin dynamics.

MRI findings in this study supported existing literature, showing a strong correlation between serum *ferritin and liver T2* MRI*, but not with cardiac T2* values.[30,31] The lack of correlation between myocardial iron and metabolic markers may reflect differences in iron kinetics across organs or the limited sensitivity of serum ferritin for cardiac iron.

Despite variability, the literature supports an increased risk of diabetes in patients with cardiac siderosis, underscoring the need for metabolic screening in individuals with myocardial iron overload, even in the absence of overt symptoms. In this study, only one patient exhibited severe cardiac siderosis, and the overall prevalence of myocardial iron overload was low (3.2% severe, 3.2% moderate). This limited the statistical power to assess potential associations between cardiac iron deposition and glucose metabolism, which should be addressed in larger studies.

Study Limitations. This was a single-center, retrospective study with a relatively small sample size, despite the center's high patient volume. Prospective, multicenter studies with longer follow-up and larger cohorts are necessary to confirm these findings and to better define risk-stratification strategies. Although three patients under 10 years of age underwent OGTT at the discretion of the clinician, they were excluded from correlation analyses to minimize age-related heterogeneity. Given the established association between puberty and insulin resistance, residual confounding related to pubertal maturation cannot be excluded. Although all patients fulfilled the clinical criteria for transfusion-dependent beta-thalassemia major, detailed genotypic characterization (e.g., β^0/β^0, β^0/β^+) was not uniformly available due to the retrospective design.

Conclusions. This study demonstrates a low prevalence of glucose metabolism disorders among children and adolescents with transfusion-dependent beta-thalassemia receiving uniform oral chelation therapy. The findings provide descriptive insights into glucose metabolism in this pediatric cohort and highlight associations among chelation-related variables, hepatic markers, and OGTT parameters. Although causal relationships cannot be established due to the retrospective design, these results contribute to the existing literature by emphasizing the importance of metabolic evaluation in patients with transfusion-dependent beta-thalassemia. Larger prospective studies with longitudinal assessment are required to confirm these observations and to better define their implications for long-term metabolic follow-up.

Ethical Approval. The study was approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (2011-KAEK-25 2022/06-08; date:1.06.2022). The study complied with the Helsinki Declaration.

Patients' Consent. Informed consent was obtained from all participants.

Competing Interest. The authors declared no conflict of interest.

Authors' Contribution. İİ: Study conception, data interpretation, manuscript writing, critical revision, approval of final version. **EGK, ÖK**: Data collection, statistical analysis, table preparation, manuscript revision, approval of final version. **DG**: Literature review, data verification, methodology refinement, approval of final version.

Data Availability. The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to privacy.

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