Original Article

Impaired Glucose Regulation Among Thalassemia Major Patients on Blood Transfusions with or without Proper Chelation Therapy

Transfusion and Chelation Status among Thalassemia

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ABSTRACT

Objective: To evaluate transfusion and chelation status among thalassemia patients, determine the prevalence of hyperglycemia, and assess whether adherence to chelation therapy is associated with differences in hyperglycemia severity.

Study Design: Descriptive cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Pathology (Hematology) in collaboration with the Department of Pediatrics, Pakistan Railways Hospital (PRH), and the Thalassemia Center, Rawalpindi from September 2023 to September 2024.

Methods: A total of 137 patients with thalassemia major were assessed. Patients were categorized into three management groups: well transfused and adequately chelated (12.4%), well transfused but inadequately chelated (29.9%), and irregularly transfused with inadequate chelation (57.7%). Glycemic status was classified as normal, impaired glucose regulation, or diabetes mellitus.

Results: Among the 137 patients, 55.5% had normal glucose levels, 32.8% had impaired glucose regulation, and 11.7% were diabetic. Diabetes showed a significant association with irregular transfusion and inadequate chelation ($p < 0.001$). Of the diabetic patients, 78.5% were irregularly transfused and inadequately chelated, while 21.5% were well transfused but inadequately chelated. Importantly, none of the well transfused and adequately chelated patients were diabetic.

Conclusion: Effective transfusion schedules combined with adequate chelation therapy appear protective against the development of diabetes in thalassemia major. Poor adherence to transfusion and chelation regimens is strongly linked with hyperglycemia and diabetes, underscoring the need for strengthened patient education, monitoring, and early intervention strategies to prevent iron-related endocrine complications.

Key Words: Impaired Glucose, Thalassemia Major, Blood Transfusions, Chelation Therapy

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INTRODUCTION

Thalassemia major is a severe hereditary blood disorder characterized by the body's inability to produce adequate hemoglobin, demanding regular blood transfusions for survival[1]. These transfusions, while lifesaving, introduce significant complications, one of the most critical being iron overload[2].

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The excess iron deposited in various organs, including the liver, heart, and endocrine glands, can lead to many health issues[3]. Among these, impaired glucose regulation stands out as a significant concern due to its potential to evolve into diabetes mellitus, further complicating the clinical management of thalassemia patients[4]. Impaired glucose regulation in thalassemia major patients is a multifaceted issue, primarily rooted in the pathophysiological impact of iron overload on pancreatic beta cells. These cells, which play a crucial role in insulin production, are particularly vulnerable to the toxic effects of excessive iron deposition[5]. The pancreas, particularly its beta cells, is one of the primary targets of iron-induced damage. Beta cells produce insulin, a hormone crucial for regulating blood glucose levels. Iron overload in thalassemia patients leads to the accumulation of iron in these cells, which triggers oxidative stress[6]. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these harmful byproducts. Excessive ROS can damage cellular structures, including lipids, proteins, and DNA[7]. Several studies have shown that iron overload disrupts mitochondrial function in beta cells, leading to decreased ATP production. ATP is essential for insulin secretion, and its reduction directly impacts the beta cells' ability to produce and release insulin in response to glucose. Additionally, oxidative stress can activate pathways that lead to beta-cell apoptosis (programmed cell death), further reducing the number of functional insulin-producing cells[8]. The initial manifestation of this damage is often impaired glucose tolerance (IGT), a condition characterized by higher-than-normal blood glucose levels after eating but not high enough to be classified as diabetes. IGT represents an intermediate stage in the spectrum of glucose dysregulation. If left unmanaged, it can progress to diabetes mellitus. Diabetes mellitus in thalassemia major patients typically presents as type 2 diabetes, characterized by both insulin resistance and beta-cell dysfunction[9]. The transition from IGT to diabetes mellitus involves multiple factors. Chronic iron overload continuously stresses the beta cells, diminishing their insulin-producing capacity over time. As the beta-cell mass and function decline, the body becomes less able to maintain normal glucose homeostasis. Concurrently, iron overload can induce insulin resistance in peripheral tissues such as the liver, muscle, and adipose tissue. Insulin resistance further exacerbates hyperglycemia and increases the demand on already compromised beta cells, accelerating their dysfunction[10]. Iron overload also affects other endocrine functions that indirectly impact glucose metabolism[11]. Iron deposition in the liver can impair hepatic insulin clearance, leading to hyperinsulinemia and subsequent insulin resistance. Furthermore, iron-induced damage to the hypothalamic-pituitary axis can result in hormonal imbalances, such as hypogonadism, which are known to exacerbate insulin resistance[12]. Certain genetic polymorphisms in genes involved in glucose metabolism and insulin signaling pathways may increase the susceptibility of TM patients to diabetes. Identifying these genetic markers could help stratify patients based on risk and tailor preventive and therapeutic strategies accordingly[13]. The function of cardiometabolic characteristics and α-thalassemia-related erythrocyte indicators in diabetes susceptibility are elucidated by establishing causal linkages.

METHODS

This was a descriptive cross-sectional study, conducted in the Department of Pathology (Hematology) in collaboration with the Department of Pediatrics, Pakistan Railways Hospital (PRH), and the Thalassemia Center, Rawalpindi from September 2023 to September 2024, following approval from the Institutional Review Committee of Riphah International University, Islamabad. A non-probability convenience sampling technique was used for patient recruitment. The sample size was calculated using a reported 9.0% prevalence of diabetes mellitus among thalassemia patients, a 95% confidence level, 80% study power, and a 5% margin of error. The estimated sample size was 125.8, which was adjusted to 137 participants to account for precision requirements.

Inclusion Criteria

- Diagnosed cases of thalassemia major
- Age 5–20 years
- Receiving regular blood transfusions for ≥1 year
- No known diagnosis of diabetes or glucose metabolism disorders
- Availability of complete medical records for at least one year

Exclusion Criteria

- Family history of diabetes mellitus
- Systemic illnesses including chronic liver, renal, or cardiovascular disease
- Severe psychiatric or cognitive impairment
- History of surgical procedures affecting glucose homeostasis

Data Collection

A total of 137 patients fulfilling the eligibility criteria were recruited from the pediatric outpatient clinics and inpatient wards of PRH and the Thalassemia Center. After obtaining informed consent, a structured proforma was used to record demographic information, clinical history, transfusion frequency, chelation therapy practices, and previous laboratory results. Blood samples were collected to measure hemoglobin concentration, serum ferritin, and fasting plasma glucose. Based on transfusion regularity and chelation adequacy, patients were classified into three groups: well transfused and adequately chelated, well transfused but inadequately chelated, and irregularly or inadequately transfused. Fasting glucose levels were categorized as normal, impaired fasting glucose, or diabetic using ADA guidelines.

Laboratory Procedures:

All laboratory analyses were conducted using standardized and validated equipment. Complete blood count was performed using the Mindray BC-5000 hematology analyzer after appropriate sample mixing and barcode verification. Serum ferritin was measured using a Rayto RT-6000 Microplate Reader following an ELISA-based protocol involving reagent preparation, incubation, washing, and absorbance measurement at 450 nm. Fasting plasma glucose was analyzed using the Selectra Pro M chemistry analyzer after calibration verification and quality control processing. All procedures adhered strictly to manufacturer instructions and departmental SOPs. Quality assurance measures were implemented throughout the analytical process to ensure accuracy and reproducibility. Samples were checked for hemolysis, clotting, proper volume, labeling accuracy, and correct timing of collection. SOPs were followed rigorously during sample handling, storage, and processing. Hematology cell controls, internal quality control sera, and analyzer-based validation checks were performed regularly. Only results meeting acceptable quality control standards were included in the final analysis.

Data Analysis

Data were analyzed using IBM SPSS version 23. Numerical variables were expressed as mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. Differences in mean values between two groups were assessed using the independent samples t-test, while comparisons across more than two groups employed one-way ANOVA. A p-value of less than 0.05 was considered statistically significant.

RESULTS

There was total 137 thalassemia patients were included in the study. Out of 137, there were 66 (48.2%) males and 71 (51.8%) females in the study. Age distribution showed that 40 (29.2%) participants belonged to 5-10 years of age group, followed by 43 (31.4%) and belonging to 11-15 and 16-20 years of age group, respectively. The mean age was calculated to be 13.16±4.5 years (age range 5 to 20). In terms of residential area, 75 (54.7%) participants were from rural area while 62 (45.3%) were from urban settings. Table 1.

Table 1: Socio-demographic characteristics (n=137)

Variables		Count (n)	%)age
Gender	Male	66	48.2%
	Female	71	51.8%
	Total	**137**	**100%**
Age Group	5-10 years	40	29.2%
	11-15 years	43	31.4%
	16-20 years	54	39.4%
	Total	**137**	**100%**
Area	Rural	75	54.7%
	Urban	62	45.3%
	Total	**137**	**100%**

Hemoglobin levels were highest in the well-transfused, adequately and inadequately chelated groups (10.8 ± 0.73 g/dL and 10.9 ± 0.86 g/dL), both tightly clustered around similar confidence intervals, while the irregularly transfused and inadequately chelated group demonstrated a much lower mean hemoglobin of 7.6 ± 0.95 g/dL, reflecting significant anemia. A similar trend appeared in the platelet counts: both well-transfused groups maintained higher platelet levels (136.3 ± 31.52 and 135.7 ± 27.32 $\times 10^9$/L), whereas irregular transfusion was associated with marked thrombocytopenia (77.4 ± 28.44 $\times 10^9$/L). Interestingly, WBC counts followed the opposite pattern, remaining lowest in adequately and inadequately chelated groups (8.3 ± 2.07 and 7.8 ± 1.94 $\times 10^9$/L) while rising sharply in the irregularly transfused group (11.7 ± 6.65 $\times 10^9$/L), suggesting inflammatory stress or recurrent infections in poorly managed patients. Table 2.

Table No. 2: Comparison of laboratory parameters among study groups

Parameter	Group	n	Mean ± SD	95% CI (Lower–Upper)
Hemoglobin (g/dL)	Well transfused / adequately chelated	17	10.8 ± 0.73	10.4–11.2
	Well transfused / inadequately chelated	41	10.9 ± 0.86	10.6–11.1
	Irregularly transfused / chelated	79	7.6 ± 0.95	7.4–7.8
	Total	**137**	**9.0 ± 1.82**	**8.7–9.3**
WBCs ($\times 10^9$/L)	Well transfused / adequately chelated	17	8.3 ± 2.07	7.3–9.4
	Well transfused / inadequately chelated	41	7.8 ± 1.94	7.2–8.5
	Irregularly transfused / chelated	79	11.7 ± 6.65	10.3–13.2
	Total	**137**	**10.2 ± 5.51**	**9.2–11.1**
Platelets ($\times 10^9$/L)	Well transfused / adequately chelated	17	136.3 ± 31.52	120.1–152.5
	Well transfused / inadequately chelated	41	135.7 ± 27.32	127.1–144.3
	Irregularly transfused / chelated	79	77.4 ± 28.44	71.0–83.8
	Total	**137**	**102.2 ± 40.51**	**95.3–109.0**

Adequately chelated patients showed the lowest iron burden, with a mean ferritin of 832.3 ± 165.4 µg/L (95% CI: 747.2–917.3), aligning with adequate chelation efficacy. In contrast, ferritin rose dramatically in both inadequately chelated groups: 1583.7 ± 383.5 µg/L in the well-transfused but poorly chelated group and 1615.6 ± 560.4 µg/L in the irregularly transfused and inadequately chelated group. Their confidence intervals overlapped substantially, indicating consistently high iron overload regardless of transfusion regularity when chelation was poor. Table 3.

Normal glucose levels were slightly more frequent in females (33.6%) than males (27.0%), while impaired glucose was comparable between genders (15.3% in males vs. 13.9% in females). Diabetes was present in 5.8% of males and 4.4% of females, again demonstrating no major gender-based differences. Out of 137 patients, 83 had normal glucose, 40 showed impaired glucose tolerance, and 14 were diabetic, indicating that more than one-third of the cohort had some form of dysglycemia.

Table No. 3. Comparison of Mean Ferritin Levels Between the Three Study Groups (n = 137)

Group	n	Mean ± SD (µg/L)	95% CI (Lower–Upper)
Well transfused / adequately chelated	17	832.3 ± 165.4	747.2–917.3
Well transfused / inadequately chelated	41	1583.7 ± 383.5	1462.7–1704.8
Irregularly transfused / inadequately chelated	79	1615.6 ± 560.4	1490.0–1741.1
Total	**137**	**1508.8 ± 540.5**	**1417.5–1600.2**

Table No. 4. Distribution of Blood Glucose Levels by Gender (n = 137)

Gender	Normal	Impaired Glucose	Diabetes	Total (n)
Male	37 (27.0%)	21 (15.3%)	8 (5.8%)	66
Female	46 (33.6%)	19 (13.9%)	6 (4.4%)	71
Total	**83**	**40**	**14**	**137**

Table 5. Comparison of Glucose Levels with Transfusion and Chelation Status (n = 137)

Status	Normal	Impaired Glucose	Diabetes	Total (n)
Well transfused / adequately chelated	16 (94.1%)	1 (5.9%)	0 (0.0%)	17
Well transfused / inadequately chelated	23 (56.1%)	13 (31.7%)	5 (12.2%)	41
Irregularly transfused / inadequately chelated	37 (46.8%)	31 (39.2%)	11 (13.9%)	79
Total	**76 (55.5%)**	**45 (32.8%)**	**16 (11.7%)**	**137**

The well-transfused and adequately chelated group had overwhelmingly normal glucose levels (94.1%) with almost no impaired glucose (5.9%) and no diabetes at all. In contrast, glucose abnormalities increased sharply when chelation was inadequate. In the well-transfused but inadequately chelated group, only 56.1% remained normoglycemic, while 31.7% had impaired glucose and 12.2% developed diabetes. The poorest outcomes were seen in the irregularly transfused and inadequately chelated group: normal glucose dropped to 46.8%, impaired glucose rose to 39.2%, and diabetes reached the highest frequency (13.9%). Table 5.

DISCUSSION

Thalassemia major is a hereditary blood disorder that requires lifelong blood transfusions for patient survival. The excess iron gets deposited in various body organs if chelation therapy following blood transfusions is not properly done and the iron overload then causes malfunctioning of involved body organs. Liver and pancreas are one of the main organs that gets effected by iron deposition leading to blood glucose imbalance. Therefore, it is important to identify this problem in thalassemia major patients, timely addressing a prevalent complication that significantly impacts patient outcomes. The purpose of this study was to determine the blood transfusion and chelation status in thalassemia patients reporting to our center, to assess the presence of hyperglycemia among them and to explore if severity of hyperglycemia vary between thalassemia major patients who receive proper chelation therapy versus those who do not adhere to or have inadequate chelation therapy. In this study, data was analyzed from 137 thalassemia patients, and categorized them according to the transfusion and chelation status. There were only 12.4% (17/137) thalassemia patients found to be well transfused and adequately chelated and 29.9% (41/137) were well transfused but inadequately chelated. While on the other hand, majority of the thalassemia patients, 57.7% (79/137) were found to have been irregularly transfused and inadequately chelated. Similarly, the blood glycemic status was also explored in terms of normal blood glucose, impaired glucose and diabetes, and it was compared against different groups made as per transfusion and chelation status. Among included thalassemia patients, where 11.7% (16/137) were found to be diabetic, followed by 32.8% (45/137) with impaired blood glucose levels and remaining majority of 55.5% (76/137) were found to have normal blood glucose levels. Comparing the transfusion status and diabetes among included thalassemia patients it was reported that diabetes was significantly associated with irregular transfusion and inadequate chelation. Among 14 diabetic patients, 11 (78.5%) had irregular transfusion and inadequate chelation, while 5 (21.5%) had regular transfusion and inadequate chelation

($p<0.001$)[14]. None of the well transfused and adequately chelated thalassemia patient was found to be diabetic in this study. This type of grouping and comparison was not reported in any other study previously in the literature, focus was mainly on prevalence of blood metabolic and endocrine disorders among thalassemia major patients[15-17].

In literature, various studies reported prevalence of diabetes and endocrine disorders as discussed here. A study conducted in Pakistan included 120 thalassemia major patients, where 60% patients were female and mean age was 21.6±8.23 (Ahmad et al, 2022). Similarly, in our study females (51.8%) were more in number as compared to males, and 39.5% patients belonged to age group of 16-20 years. In study by Ahmed et al, frequency of diabetes was reported to be 9.0% among thalassemia major patients, while in our study the prevalence of diabetes was 11.7%[18]. Ahmed et al reported that diabetes was found to be more common among males as compared to females (66.7% vs 33.3%), similarly patients belonging of age group of more than 25 years, having ferritin levels more than 6000 ng/ml and longer blood transfusion duration also had high prevalence of diabetes. In our study similar results were found where diabetes was more common among males as compared to females (11.2% vs 9.0%). The authors concluded that nine percent of significant thalassemia patients had diabetes, with men making up the majority of cases. We think this is related to being older, having a higher mean ferritin level over the course of five years, and receiving more blood transfusions[19].

This study has several limitations that should be considered when interpreting the findings. The cross-sectional design restricts the ability to establish causal relationships between transfusion chelation status, iron overload, and glucose abnormalities. Data were collected from a single center, which may limit generalizability to broader thalassemia populations with different treatment protocols or resource availability. Laboratory values were taken at a single time point, so fluctuations in hemoglobin, ferritin, and glucose levels over time could not be assessed. Self-reported adherence to chelation therapy may also introduce recall or reporting bias.

CONCLUSION

The study highlights the critical role of proper transfusion and chelation therapy in thalassemia major patients to prevent complications such as hyperglycemia and diabetes. A significant proportion of thalassemia patients were found to have irregular transfusion and inadequate chelation, which is strongly associated with an increased risk of developing diabetes. Conversely, patients who were well transfused and adequately chelated showed no signs of diabetes, underscoring the importance of adherence to chelation therapy. Early identification and management of glycemic abnormalities are essential to improving the overall outcomes and quality of life of thalassemia major patients.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Rahmat Javed, Ayesha Nayyar, Sana Saleem Rana
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Agreement to accountable for all aspects of work:	All the above authors

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