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# THE FREQUENCY AND CLINICAL SPECTRUM OF GLUCOSE DYSREGULATION IN BETA THALASSEMIA

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**ABSTRACT**
**Objective:** To determine the frequency and clinical spectrum of glucose dysregulation in patients with beta thalassemia and to evaluate its association with clinical and transfusion-related factors.
**Study Design:** Descriptive cross-sectional study.
**Place and Duration of Study:** Department of Pediatric Endocrinology and Diabetes, University of Child Health Sciences, The Children's Hospital, Lahore, from January 2026 to June 2026.
**Methodology:** A total of 50 patients with confirmed beta thalassemia, aged 10 years or above and receiving regular blood transfusions for at least five years, were included. Demographic and clinical characteristics, transfusion history, chelation therapy, anthropometric measurements, serum ferritin, fasting plasma glucose, oral glucose tolerance test values, and HbA1c were recorded. Data were analysed using SPSS version 25.0.
**Results:** The mean age of the patients was 13.14 ± 1.47 years, and 28 (56.0%) were males. Glucose dysregulation was identified in 15 (30.0%) patients. Impaired fasting glucose was present in 5 (10.0%), impaired glucose tolerance in 4 (8.0%), diabetes mellitus in 3 (6.0%), and indeterminate glucose abnormality in 3 (6.0%) patients. Median serum ferritin was significantly higher in patients with glucose dysregulation than in those with normal glucose regulation, 5275 versus 4514 ng/mL (p=0.031). Median annual transfusion frequency was also higher in the dysregulation group, 18 versus 14 transfusions per year (p=0.009).
**Conclusion:** Glucose dysregulation was present in nearly one-third of patients with beta thalassemia and ranged from impaired fasting glucose and impaired glucose tolerance to overt diabetes mellitus.

**KEYWORDS:** Beta thalassemia, Glucose dysregulation, Impaired fasting glucose, Impaired glucose tolerance, Diabetes mellitus

## INTRODUCTION

Beta thalassemia is an inherited haemoglobinopathy which results from the partial or complete absence of the synthesis of the beta chain of haemoglobin. In beta thalassemia major, red blood cell transfusion is essential for life to keep the haemoglobin level within normal range and to prevent ineffective erythropoiesis [1]. Transfusion therapy has significantly improved survival; however, repeated transfusion therapy will lead to increasing total body iron stores. Iron overload becomes a significant source of chronic endocrine problems in these individuals when transferrin's iron binding capacity is exceeded and the excess iron is deposited in such organs as the liver, heart, pituitary gland, and pancreas. Beta thalassemia is a serious health issue in Pakistan, with a prevalence of 5–8% carriers and about 5,000 beta thalassemia children being born annually [2].

Impaired fasting glucose, impaired glucose tolerance and diabetes mellitus constitute a spectrum of glucose dysregulation, which is an important endocrine complication of beta thalassemia. It tends to develop slowly and can start as a child or adolescent before you notice that you have clinical diabetes. Iron deposits in the pancreatic beta cells may affect insulin synthesis and secretion, and the liver deposition of iron and underlying chronic inflammatory and metabolic disorders may lead to insulin resistance [3]. As the pancreas progresses to injury, compensatory hyperinsulinaemia can then lead to diminished insulin secretion and diabetes. This has led to

disturbances in glucose homeostasis being associated with disease duration, transfusion burden, poor adherence to iron chelation and elevated serum ferritin [4].

Thalassemia is the most common inherited hemoglobinopathy in the world. In the case of B-thalassemia major (TM), because of the risks associated with transplantation of hematopoietic stem cell, a regular, lifelong transfusion program may be beneficial to maintain development and growth and optimise quality of life [5]. Pakistan has the highest prevalence of thalassemia among the countries in the world. Due to iron overload, beta thalassemia major patients have various complications in their lives throughout, which include behavioural and neurotic disorders, endocrinopathies, cardiovascular disorders, liver disease, gonadal dysfunction, growth failure and delayed puberty. The amount of iron in each unit of packed cells is approximately 200 mg, which means that a patient receiving 25 units each year would receive around 5 g per year [6]. Multiple studies have shown that glucose-related disturbances in patients with β-thalassemia major (β-TM) are common complications, particularly in inadequately iron-chelated patients, and less frequently in well-transfused and efficiently chelated patients [7]. Glucose dysregulation in beta-thalassemia is a broad range of clinical conditions including impaired fasting glucose, impaired glucose tolerance and diabetes mellitus [8]. In the pancreas, there is iron overload-induced cytotoxicity as an important mechanism in the pathogenesis of diabetes in thalassemia major. This sheds light on the complex relationship between iron metabolism and pancreatic function [9]. The prevalence of GD is found to be variable depending on studies, as it is affected by genotype, transfusion frequency, compliance to iron chelation, and age [10]. Although the importance of endocrine dysfunction in thalassemia, especially glucose abnormalities, has been increasingly recognised, there is very limited local information available about the actual incidence, progression and patterns of these complications in the various populations [11]. Given the high level of diabetes mellitus (DM) among subjects with β-TM, it is advisable to screen for detection of GD as early as possible. There are several studies that have examined strategies that use clinical and diagnostic information to identify those with high risk of GD. However, screening practices vary, with many centres not yet following the recommendation of periodic OGTT in all β-TM patients starting from the age of 10 years [12].

**Objective**

To estimate the prevalence and clinical manifestations of glucose intolerance in patients with beta thalassemia.

## METHODOLOGY

This Descriptive, cross-sectional study was conducted at the Department of Pediatrics Endocrinology and Diabetes, University of Child Health Sciences, The Children Hospital, Lahore from January 2026 to June 2026. The study group consisted of 50 patients with a definite diagnosis of beta thalassemia receiving regular blood transfusion. The sample size was determined with the help of the sample size calculator developed by WHO for estimation of a population proportion with a 95% confidence level, anticipated frequency of glucose dysregulation is 5%, and margin of error is 5%. The number of patients planned was 51 but 50 patients had complete data, and these were used in the final analysis. Consec sampling technique was used, which is a non-probability sampling. Patients who met the eligibility criteria were enrolled until the appropriate number of patients were reached during the study period. Both males and females were included if they had a confirmed diagnosis of beta thalassaemia, age 10 years or older, received regular transfusion therapy for at least 5 years, and gave informed consent or assent (where applicable) with their parents/guardians. Patients with a known diagnosis of type 1 diabetes mellitus or those who were taking medications that are known to influence glucose metabolism (systemic corticosteroid) were excluded as were patients with other coexisting endocrine disorders that are known to influence glucose metabolism (hypothyroidism, Cushing syndrome).

**Data Collection Procedure**

After approval from the Institutional Review Board and obtaining informed consent, 50 patients fulfilling the eligibility criteria who presented to the Department of Pediatric Endocrinology and Diabetes during the study period were enrolled. A structured proforma was used to collect data. The demographic and clinical data recorded were age, sex, age at diagnosis, duration and frequency of blood transfusion, type and duration of iron chelation therapy, history of splenectomy, and family history of diabetes mellitus. Anthropometric measurements, such as weight and height, were taken following standardised procedures, and body mass index (BMI) was calculated as weight (kg) divided by height ($m^2$). Biochemical tests used were fasting plasma glucose, glycated haemoglobin, serum ferritin, and oral glucose tolerance test. A standard oral glucose load of 1.75 g/kg body weight (up to 75 g) was given after an overnight fast. The plasma glucose level was assessed at 0 minutes, at 2-hour post OGTT and at other times. Serum ferritin was used as a measure of iron overload. Where available and clinically relevant, additional investigations were noted such as liver function tests, and serum insulin levels. A proforma for recording the data collected during the study was used. A glucose regulation status classification was done based on the predefined criteria from the study protocol: Normal glucose regulation, IFG, IGT, DM, and Indeterminate glucose abnormality.

**Data Analysis**

All 50 patients' data were entered and analyzed in IBM SPSS Statistics version 25.0. Data on the quantitative variables were summarized as mean with standard deviation for normally distributed quantitative data and as median and interquartile ranges for non-normally distributed quantitative data. Frequencies and percentages were provided for categorical variables. Fisher's exact test or the chi-square test was used to examine the association between categorical variables. Independent-samples t test or Mann–Whitney U test was used to compare

continuous variables between patients with normal glucose regulation and those with glucose dysregulation. The factors associated with glucose dysregulation were obtained by binary logistic regression, which included serum ferritin level, transfusion frequency, duration of chelation therapy, age and BMI. A p-value <0.05 was considered statistically significant.

**RESULTS**

A total of 50 patients were included in the study; the mean age was 13.14 ± 1.47 years. There were 28 (56.0%) males and 22 (44.0%) females. Twenty-three (46.0%) patients were residents of Lahore, while 27 (54.0%) lived outside Lahore. The median age at diagnosis was 9.0 months (IQR 7.0–10.0). Mean weight, height, and calculated BMI were 37.06 ± 6.52 kg, 136.56 ± 8.51 cm, and 20.04 ± 4.08 kg/m², respectively. All 50 (100.0%) patients were receiving chelation therapy, with 49 (98.0%) on oral therapy and 1 (2.0%) receiving intravenous therapy.

**Table 1. Demographic and clinical characteristics of children with thalassemia major (N = 50)**

| Variable | Overall, N = 50 |
|---|---|
| Age, years | 13.14 ± 1.47 |
| Male | 28 (56.0%) |
| Female | 22 (44.0%) |
| Lahore residence | 23 (46.0%) |
| Residence outside Lahore | 27 (54.0%) |
| Age at diagnosis, months | 9.0 (7.0–10.0) |
| Weight, kg | 37.06 ± 6.52 |
| Height, cm | 136.56 ± 8.51 |
| Calculated BMI, kg/m² | 20.04 ± 4.08 |
| Receiving chelation therapy | 50 (100.0%) |
| Oral chelation therapy | 49 (98.0%) |
| Intravenous chelation therapy | 1 (2.0%) |
| Duration of chelation therapy, years | 5.54 ± 1.44 |
| Serum ferritin, ng/mL | 4666 (2762–5866) |
| Blood transfusions/year | 16.5 (12.0–20.0) |
| Positive family history of diabetes | 1 (2.0%) |
| Previous splenectomy | 14 (28.0%) |

Normal glucose regulation was observed in 35 (70.0%) patients, while 15 (30.0%) had some form of glucose dysregulation. Impaired fasting glucose was present in 5 (10.0%) patients, impaired glucose tolerance in 4 (8.0%), diabetes mellitus in 3 (6.0%), and an indeterminate glucose abnormality in 3 (6.0%).

**Table 2. Frequency of glucose dysregulation among children with thalassemia major (N = 50)**

| Glucose regulation status | n (%) |
|---|---|
| Normal glucose regulation | 35 (70.0%) |
| Impaired fasting glucose | 5 (10.0%) |
| Impaired glucose tolerance | 4 (8.0%) |
| Diabetes mellitus | 3 (6.0%) |
| Indeterminate glucose abnormality | 3 (6.0%) |
| Any glucose dysregulation | 15 (30.0%) |

The mean age was almost identical between patients with normal glucose regulation and those with glucose dysregulation, 13.14 ± 1.47 versus 13.13 ± 1.49 years (p=0.993). Male sex was observed in 20 (57.1%) versus 8 (53.3%) patients (p=1.000), while Lahore residence was reported in 17 (48.6%) versus 6 (40.0%) patients (p=0.758). Median age at diagnosis was 9.0 months in both groups, with IQRs of 7.5–11.5 and 7.0–9.0 months, respectively (p=0.282). Mean chelation duration was 5.80 ± 1.35 versus 4.93 ± 1.51 years (p=0.067), and BMI was 20.41 ± 3.73 versus 19.20 ± 4.85 kg/m² (p=0.400).

**Table 3. Comparison of demographic and clinical characteristics according to glucose regulation status**

| Variable | Normal glucose regulation (n = 35) | Glucose dysregulation (n = 15) | p-value |
|---|---|---|---|
| Age, years | 13.14 ± 1.47 | 13.13 ± 1.49 | 0.993 |
| Male sex | 20 (57.1%) | 8 (53.3%) | 1.000 |
| Lahore residence | 17 (48.6%) | 6 (40.0%) | 0.758 |
| Age at diagnosis, months | 9.0 (7.5–11.5) | 9.0 (7.0–9.0) | 0.282 |
| Duration of chelation, years | 5.80 ± 1.35 | 4.93 ± 1.51 | 0.067 |
| Calculated BMI, kg/m² | 20.41 ± 3.73 | 19.20 ± 4.85 | 0.400 |
| Serum ferritin, ng/mL | 4514 (2559–5449) | 5275 (3774–6225) | 0.031 |
| Blood transfusions/year | 14.0 (10.0–19.0) | 18.0 (16.5–22.5) | 0.009 |

| Variable | Normal glucose regulation (n = 35) | Glucose dysregulation (n = 15) | p-value |
|---|---|---|---|
| Previous splenectomy | 14 (40.0%) | 0 (0.0%) | 0.004 |

*Chi-square test was used for categorical variables. A p-value <0.05 was considered statistically significant.*

Patients with glucose dysregulation had significantly higher median fasting glucose levels than those with normal glucose regulation, 120.0 mg/dL (IQR 96.5–131.5) versus 84.0 mg/dL (IQR 77.0–91.0; p<0.001). Mean 30-minute OGTT glucose was also higher, 166.40 ± 14.22 versus 159.03 ± 10.85 mg/dL, although this difference was not statistically significant (p=0.087). Median 60-minute OGTT glucose was 176.0 mg/dL (IQR 156.0–212.0) versus 140.0 mg/dL (IQR 135.0–147.5; p<0.001), while median 2-hour OGTT glucose was 170.0 mg/dL (IQR 137.0–186.5) versus 115.0 mg/dL (IQR 97.5–125.5; p<0.001).

**Table 4. Comparison of glycemic parameters according to glucose regulation status**

| Glycemic parameter | Normal glucose regulation (n = 35) | Glucose dysregulation (n = 15) | p-value |
|---|---|---|---|
| Fasting blood glucose, mg/dL | 84.0 (77.0–91.0) | 120.0 (96.5–131.5) | <0.001 |
| 30-minute OGTT glucose, mg/dL | 159.03 ± 10.85 | 166.40 ± 14.22 | 0.087 |
| 60-minute OGTT glucose, mg/dL | 140.0 (135.0–147.5) | 176.0 (156.0–212.0) | <0.001 |
| 2-hour OGTT glucose, mg/dL | 115.0 (97.5–125.5) | 170.0 (137.0–186.5) | <0.001 |
| HbA1c, % | 5.4 (5.1–5.8) | 6.2 (6.0–6.8) | <0.001 |

*Independent-samples t-test or Mann–Whitney U test was applied according to data distribution. OGTT = oral glucose tolerance test; HbA1c = glycated hemoglobin.*

On univariable logistic regression, age was not associated with glucose dysregulation (OR 1.00, 95% CI 0.66–1.51; p=0.993). Longer chelation duration showed a borderline inverse association (OR 0.62, 95% CI 0.38–1.01; p=0.057), while BMI was also not significantly associated (OR 0.93, 95% CI 0.79–1.08; p=0.340). Each 1000 ng/mL increase in serum ferritin was associated with higher odds of glucose dysregulation (OR 1.52, 95% CI 1.00–2.30; p=0.048), and each additional transfusion per year increased the odds by 23% (OR 1.23, 95% CI 1.05–1.43; p=0.010).

**Table 5. Logistic regression analysis of factors associated with glucose dysregulation**

| Variable | Crude OR (95% CI) | p-value | p-value |
|---|---|---|---|
| Age, per 1-year increase | 1.00 (0.66–1.51) | 0.993 | — |
| Duration of chelation, per 1-year increase | 0.62 (0.38–1.01) | 0.057 | — |
| Calculated BMI, per 1 kg/m² increase | 0.93 (0.79–1.08) | 0.340 | — |
| Serum ferritin, per 1000 ng/mL increase | 1.52 (1.00–2.30) | 0.048 | 0.172 |
| Blood transfusions, per additional transfusion/year | 1.23 (1.05–1.43) | 0.010 | 0.024 |

Median ferritin was 4514 ng/mL in the normal group, 3721 ng/mL in impaired fasting glucose, 6224.5 ng/mL in impaired glucose tolerance, 6796 ng/mL in diabetes mellitus, and 4992 ng/mL in the indeterminate group. Corresponding median transfusion frequencies were 14, 18, 20, 22, and 17 transfusions/year, respectively. Median fasting glucose values were 84, 122, 90, 146, and 101 mg/dL, while median 30-minute OGTT values were 159, 164, 153, 174, and 179 mg/dL. Median 60-minute OGTT values were 140, 142, 176, 210, and 248 mg/dL, and median 2-hour OGTT values were 115, 120, 184, 271, and 170 mg/dL, respectively.

**Table 6. Clinical and glycemic profile according to type of glucose regulation abnormality (N = 50)**

| Variable | Normal (n = 35) | Impaired fasting glucose (n = 5) | Impaired glucose tolerance (n = 4) | Diabetes mellitus (n = 3) | Indeterminate (n = 3) |
|---|---|---|---|---|---|
| Serum ferritin, ng/mL | 4514 (2559–5449) | 3721 (3674–6170) | 6224.5 (5622.5–6364.5) | 6796 (6035.5–6889.5) | 4992 (3409–5119.5) |
| Blood transfusions/year | 14 (10–19) | 18 (18–19) | 20 (16–24) | 22 (17.5–23) | 17 (17–20) |
| Fasting glucose, mg/dL | 84 (77–91) | 122 (121–124) | 90 (85.5–94) | 146 (145.5–150.5) | 101 (98.5–102.5) |
| 30-min OGTT glucose, mg/dL | 159 (152.5–166) | 164 (155–164) | 153 (148–160.5) | 174 (163–184) | 179 (178.5–182) |

| Variable | Normal (n = 35) | Impaired fasting glucose (n = 5) | Impaired glucose tolerance (n = 4) | Diabetes mellitus (n = 3) | Indeterminate (n = 3) |
|---|---|---|---|---|---|
| 60-min OGTT glucose, mg/dL | 140 (135–147.5) | 142 (140–154) | 176 (175.5–176.3) | 210 (190–244.5) | 248 (231–261.5) |
| 2-hour OGTT glucose, mg/dL | 115 (97.5–125.5) | 120 (120–135) | 184 (176.3–185.3) | 271 (246–296.5) | 170 (161.5–173.5) |
| HbA1c, % | 5.4 (5.1–5.9) | 6.3 (5.8–6.5) | 6.1 (6.0–6.2) | 8.6 (7.9–9.2) | 6.2 (5.9–6.2) |

**DISCUSSION**

The current study aimed to assess the prevalence and clinical spectrum of glucose intolerance in 50 beta thalassemia patients on regular transfusion who were followed for 2 years. The present study investigated the prevalence and nature of glucose intolerance among 50 patients with beta thalassemia on regular transfusion for 2 years. The overall frequency of glucose dysregulation was 30.0% (15 patients). Eleven percent had impaired fasting glucose, eight percent had impaired glucose tolerance, six percent had diabetes mellitus, and six percent had an indeterminate glucose abnormality. These results indicate that glucose metabolism was disturbed relatively frequently in this population, and not exclusively in diabetes. Poor glycemic control is evident in many patients with impaired fasting glucose and impaired glucose tolerance, indicating that abnormalities in glucose metabolism may occur insidiously before the onset of clinically developed diabetes. The frequency in the present study was like that of other studies, which reported an overall frequency of glucose abnormalities in transfusion-dependent beta thalassemia, but with a wide range in different populations [13]. Previous studies have reported diabetes mellitus in about 3–7% of patients, and impaired fasting glucose and impaired glucose tolerance were more common in general. Variation among studies could be due to age of the patient, disease duration, transfusion requirements, level of iron chelation, criteria for diagnosis, and the approach to glucose testing. The relatively young mean age of 13.14 years in this study is relevant as it shows that identification of glucose dysregulation can occur during adolescence, not just when patients are older with long duration of thalassemia [14].

Patients with glucose dysregulation had significantly elevated serum ferritin levels when compared to patients with normal glucose regulation. The median level of ferritin was 5275 ng/mL in the dysregulated group and 4514 ng/mL in the normal group. This association between increased ferritin levels and glucose metabolism abnormalities was also observed in the past in patients with beta thalassemia. Chronic iron overload can lead to initial iron deposition and then to oxidative stress on the pancreatic beta-cells, ultimately leading to glucose intolerance. Liver iron deposits can also be a factor in insulin resistance. The present study found that ferritin was significantly correlated with glucose dysregulation in univariable analysis and had 52% higher odds of dysregulation for each increase of 1000 ng/mL of ferritin [15]. However, this correlation was no longer significant when transfusion frequency was included and thus may not be an independent factor contributing to the metabolic disturbance. There was a greater correlation between transfusion burden and glucose dysregulation. Patients with abnormal glucose metabolism had a median of 18 transfusions per year vs 14 transfusions per year in patients with normal glucose regulation. On univariable analysis, every extra annual transfusion increased the odds of glucose dysregulation by 23% and the relationship persisted after adjusting for ferritin. This is consistent with the biological link between repeated transfusion, progressive iron overload and endocrine dysfunction [16]. Previous studies also have indicated that an increase in the number of transfusion episodes and poor control of iron overload are linked to an increased risk of endocrine complications. The fact that transfusion frequency remained an independent variable in the present study indicates that transfusion burden might be a valuable parameter to consider in the identification of patients in need of more intensive metabolic monitoring [17].

There were also significant differences in the glycemic profile of the two groups. Patients with glucose dysregulation had significantly higher fasting plasma glucose, 60-minute OGTT glucose, 2-hour OGTT glucose, and HbA1c levels. The median fasting glucose, 2-hour OGTT glucose and median HbA1c was most significantly different in the specific subgroups with diabetes mellitus, with levels being 146 mg/dL, 271 mg/dL and 8.6%, respectively. They also had the highest median serum ferritin level and frequency of transfusion per year. The same was also true of patients with impaired glucose tolerance, who had relatively high levels of ferritin and transfusion burden. These results substantiate the belief that there is a metabolic continuum from early glucose intolerance to actual diabetes. The usefulness of the OGTT seems to be especially in the identification of abnormalities which would not be evident from fasting glucose levels. However, care must be taken when interpreting HbA1c levels in patients who are undergoing frequent blood transfusions as the reliability of HbA1c may be influenced by altered erythrocyte survival and transfused red blood cells [18]. One other finding that was surprising was the fact that no patients with glucose dysregulation had had a splenectomy, while 40.0% of those with normal glucose regulation had had a splenectomy. This difference was statistically significant but should not be interpreted to mean that splenectomy prevents glucose dysregulation [19]. However, a small number of patients (n=5) and the lack of patients with splenectomy in the dysregulation group in this study resulted in no cells and potentially an unstable association. No evidence from previous studies suggests that splenectomy protects against glucose abnormalities. Before any meaningful conclusions could be drawn from this observation, larger studies would be necessary.

## LIMITATIONS

There were several limitations of this study. This study could not establish a temporal or causal relationship between transfusion burden, iron overload and glucose dysregulation due to its cross-sectional design. The study sample size of 50 patients was relatively small, so generalizability was limited, and the reliability of the results of subgroup comparisons was reduced. Serum ferritin was used as a marker for iron overload, but may be affected by inflammatory, infectious and liver disease and does not accurately reflect total iron stores. Specific tests like MRI iron quantification to the liver or cardiac iron was not available. Chelator dose and cumulative transfusion exposure was limited and detailed information on chelation adherence was limited. HbA1c was also measured, but this could be influenced with frequent transfusion as a consequence of affecting red blood cell lifespan and recent transfusion. Evaluation of underlying mechanism of glucose dysregulation was limited by the absence of the routine availability of insulin levels and measures of insulin resistance.

## CONCLUSION

Conclusions: The study showed that the prevalence of glucose dysregulation among the patients with beta thalassemia is 30.0%, and it ranged from IFG to IGT to DM. The serum ferritin level was high in patients with glucose dysregulation and patients with glucose dysregulation had higher transfusion needs per year, and frequency of transfusion showed a strong relationship with glucose dysregulation even after adjusting for other variables. The need for continuous screening for glucose metabolism abnormalities in transfusion dependent beta thalassemia, especially for patients with a high transfusion burden and with iron overload, is evident, with the aim of identifying abnormalities as early as possible and preventing progression to overt diabetes.

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