e-ISSN: 0975-9506, p-ISSN: 2961-6093

Available online on www.ijpqa.com doi: 10.25258/ijpqa.16.6.38

International Journal of Pharmaceutical Quality Assurance 2025; 16(6); 212-223

Original Research Article

Study on Association of Serum Ferritin Level with Growth, Thyroid Profile, and Oral Glucose Tolerance Test in the β Thalassemia Major Children in Pediatric Department of DMCH, Laheriasarai

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Received: 25-03-2025 / Revised: 23-04-2025 / Accepted: 26-05-2025

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Conflict of interest: Nil

Abstract:

Background: β-thalassemia major is a common inherited blood disorder requiring regular blood transfusions, which often lead to iron overload. This iron accumulation, measured by serum ferritin, can damage vital organs, especially endocrine glands, potentially leading to growth retardation, hypothyroidism, and glucose intolerance.

Aim: To assess the association between serum ferritin levels and growth parameters, thyroid function, and oral glucose tolerance in children with β-thalassemia major.

Materials and Methods: This cross-sectional study included 100 β-thalassemia major patients (<12 years) attending the Pediatric Department at DMCH, Laheriasarai. Anthropometry, thyroid profile (TSH, fT4), OGTT, and serum ferritin were evaluated. Data were analyzed using SPSS v25 with appropriate statistical tests ($p<0.05$ considered significant).

Results: A significant inverse correlation was found between serum ferritin and fT4 ($R = -0.27$), and a positive correlation with TSH ($R = 0.41$), indicating hypothyroidism in 12% of patients—most notably when ferritin >2000 ng/mL. Growth retardation was more prevalent in males (54.2% underweight), and short stature was associated with higher ferritin levels (median: 2934 ng/mL vs. 1343 ng/mL; $p<0.001$). Additionally, patients with abnormal OGTT (7%) had significantly elevated ferritin (median: 3090 ng/mL; $p<0.001$).

Conclusion: Elevated serum ferritin in β-thalassemia major is strongly linked to hypothyroidism, impaired growth (especially in males), and glucose intolerance. Routine monitoring and individualized chelation therapy may help prevent long-term endocrine complications.

Keywords: β-Thalassemia Major, Serum Ferritin, Hypothyroidism, Growth Retardation, Glucose Intolerance.

Introduction

β-thalassemia major is one of the most common inherited hemoglobinopathies worldwide, especially prevalent in South Asia, the Mediterranean region, and parts of the Middle East. It is characterized by absent or severely reduced synthesis of β-globin chains, resulting in ineffective erythropoiesis and chronic hemolytic anemia. Children diagnosed with β-thalassemia major typically require regular blood transfusions beginning early in life to maintain adequate hemoglobin levels and support normal growth and development. [1-4]

However, chronic transfusion therapy leads to progressive iron overload, as the human body lacks a physiologic mechanism for active iron excretion. The excess iron is primarily deposited in vital organs such as the heart, liver, and endocrine glands, causing tissue damage and dysfunction. Serum ferritin, an acute-phase reactant and iron storage protein, is widely used as a surrogate marker to estimate body iron burden. Persistently elevated serum ferritin levels have been associated with various complications in thalassemia patients, including growth failure, hypothyroidism, and glucose metabolism disorders. [2,5]

Growth retardation is a well-recognized complication in β-thalassemia major, often multifactorial in origin—ranging from chronic anemia, iron overload, endocrine dysfunction, to inadequate chelation. Similarly, iron deposition in the thyroid and pancreas can lead to subclinical or overt hypothy-

roidism and glucose intolerance or diabetes mellitus, respectively. The early identification of these complications is crucial to minimize long-term morbidity and improve quality of life. [6-9]

Despite the growing burden of β-thalassemia major in resource-limited settings like Bihar, limited data is available on the association between serum ferritin levels and endocrine complications among children in this region. This study was conducted to evaluate the relationship between serum ferritin levels and parameters such as growth status, thyroid function, and glucose tolerance in β-thalassemia major children attending the Pediatric Department at Darbhanga Medical College & Hospital (DMCH), Laheriasarai.

Materials and Methods

Study Design: This cross-sectional observational study was carried out to evaluate the serum ferritin concentrations association with growth parameters, thyroid profile, and oral glucose tolerance in children diagnosed with β-thalassemia major. This study was approved by the Institutional Ethics Committee (IEC). Parental or guardian consent was obtained in written form before participation, assent was also obtained from children when applicable.

Study Setting and Duration: This study was performed at the Department of Pediatrics, at a DMCH Laheriasarai. The period of the study spanned over 12 months (from Jan 2023 to Dec 2023).

Study Population: The study population included pediatric individuals with confirmed β-thalassemia major who were under frequent blood transfusions and attending the thalassemia clinic or pediatric outpatient department for follow-up.

Inclusion Criteria

1. Patients that have confirmed β-thalassemia major.
2. Age below 12 years.

Exclusion Criteria

1. Patients having acute illness
2. Patients with hormonal therapy
3. Family history of hypothyroidism
4. Not on medication known to cause glucose intolerance.

Sample Size: The study included 100 children who fulfilled the eligibility criteria. The sample size was estimated based on previous prevalence studies and using standard statistical methods with appropriate confidence intervals.

The calculation of sample size for the current observational cross-sectional study based on endocrine complications frequency (including growth retardation, thyroid dysfunction, and glucose intolerance) in children with β-thalassemia major as reported in previous studies. Literature suggests that approximately 30–40% of β-thalassemia major children experience at least one endocrine abnormality due to iron overload.

Use the following formula for estimating the sample size for proportion:

$$n = \frac{Z^2 \times p \times (1-p)}{d^2}$$

Where:

n = required sample size

Z = Z-value (standard normal deviate) at 95% confidence = 1.96

p = expected prevalence (assumed as 0.35 or 35% based on previous studies)

d = allowable margin of error (taken as 10% or 0.10)

Therefore, the minimum required sample size was approximately 88 participants.

To account for possible dropouts or incomplete data, a 10% buffer was added, bringing the final sample size to:

$$n = 88 + (10\% \text{ of } 88) = 88 + 8.8 \approx 97$$

Thus, 100 children with β-thalassemia major constituted the study cohort to ensure adequate statistical power and representativeness.

Data Collection Tools and Procedure: After obtaining informed consent, each participant underwent detailed clinical evaluation including history-taking and complete physical examination. Data was collected using a structured proforma including:

Demographic Details

- Age, sex, and socioeconomic status
- Age at diagnosis and age at first transfusion

Anthropometric Measurements

- Growth parameters were assessed by measuring standing height and weight, with values referenced to WHO child growth standards for percentile determination.
- BMI was calculated.

Laboratory Investigations

Following a standardized 8-hour overnight fast, venous blood was drawn for:

- **Serum Ferritin** – estimated using chemiluminescent immunoassay
- **Thyroid Profile** – TSH, Free T3, and Free T4

- **OGTT** – using standard 1.75 g/kg body weight of glucose (maximum 75 g); blood glucose measured at 0 and 2 hours
- **CBC**
- **Liver and Renal Function Tests** (if needed, to rule out hepatic or renal involvement)

Statistical Analysis: The collected data was entered into Microsoft Excel and analyzed using SPSS software-25. Descriptive statistics such as mean/median, standard deviation/IQR, and percentage were used. Comparative test were performed using t-test/Mann-Whitney U test. Correlation between serum ferritin and growth parameters, thyroid profile, and OGTT results was assessed using Pearson's or Spearman's correlation coefficient. A p-value of <0.05 was considered statistically significant.

Results

Demographic Characteristics: A total of 100 individuals participated in this study. The age distribution illustrated in the figure 1 revealed that the largest proportion of participants (25%) belonged to the 2–3.9 years age group (n = 25), followed by the 6 –7.9 years group (21%, n = 21), the 4–5.9 years group (20%, n = 20), the 10–12 years group (18%, n = 18), and finally the 8–9.9 years group (16%, n = 16). This distribution shows a fairly even representation of participants belonging to different groups.

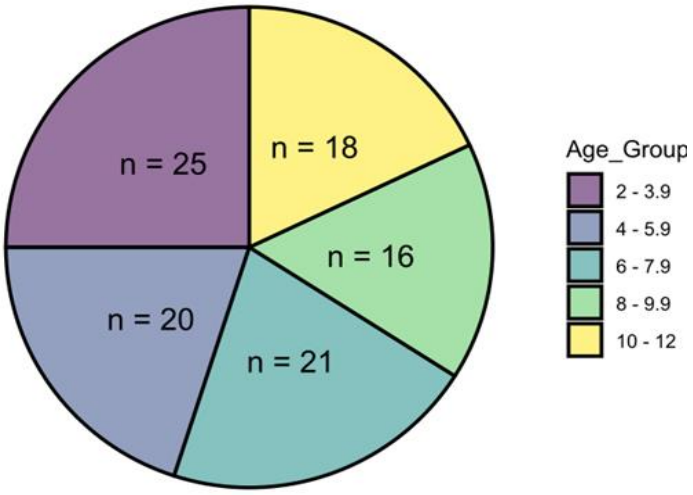

Figure 1: Pie Chart showing the distribution of the sample across age groups.

The overall gender distribution was balanced, with 48 males (48%) and 52 females (52%) (Figure 2). However, further stratification by age group showed distinct gender differences (Table 1). In the 2–3.9 years group, females outnumbered males (15 vs. 10), while males were more prevalent in the 4–5.9 years group (13 vs. 7). The 6–7.9 years group had a slight female predominance (12 vs. 9), whereas the 8–9.9 years group exhibited a pronounced female majority (12 vs. 4). Conversely, in the 10–12 years group, males were more represented (12 vs. 6).

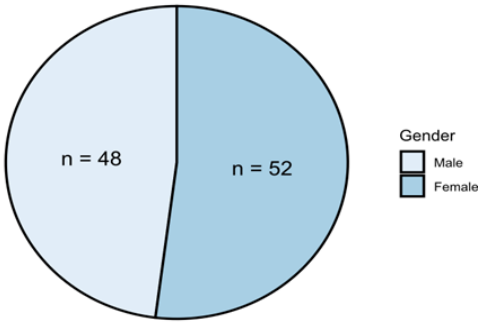

Figure 2: Pie chart showing distribution of sample according to gender.

Table 1: Gender distribution by age group showing number and percentage composition within each section.

Age group (Years)	Male; n (%)	Female; n (%)
2 - 3.9	10 (40)	15 (60)
4 - 5.9	13 (65)	7 (35)
6 - 7.9	9 (43)	12 (57)
8 - 9.9	4 (25)	12 (75)
10 - 12	12 (67)	6 (33)

Biochemical and Metabolic Profile: Table 2 summarises the biochemical and metabolic profile of the study population. The median serum ferritin level was 1457.0 ng/mL (IQR: 1092.5–1846.8; range: 458–3935), with all participants (100%) exhibiting high ferritin levels. The histogram illustrates the distribution of serum ferritin levels across the study population (Figure 3). The median ferritin level (red line) was observed at 1457 ng/mL.

Table 2: Biochemical and metabolic profile in Thalassemia patients

Variables	Median [IQR] / n (%)	Range
Iron Metabolism		
Ferritin	1457.0 [1092.5 - 1846.8]	458 - 3935
Ferritin Status (High/Low)	100 / 0	-
Thyroid Function		
fT4	1.5 [1.1 - 1.9]	0.5 - 2.1
fT4 Status (Normal/Low)	94 / 6	-
TSH	2.95 [2.10 - 3.93]	0.40 - 10.00
TSH Status (Normal/High)	88 / 12	-
Thyroid Function Status (Eu/Hypo)	88 / 12	-
Normal Thyroid Function (Yes/No)	88 / 12	-
Glucose Metabolism		
OGT (Abnormal/Normal)	7 / 93	-

Thyroid function analysis showed a median fT4 level of 1.5 ng/dL (IQR: 1.1–1.9; range: 0.5–2.1), with 6% of participants below the reference range. TSH levels had a median of 2.95 µIU/mL (IQR: 2.10–3.93; range: 0.40–10.00), with 12% of participants displaying elevated values. Collectively, 88% of the cohort maintained euthyroid status, while 12% met the criteria for hypothyroidism.

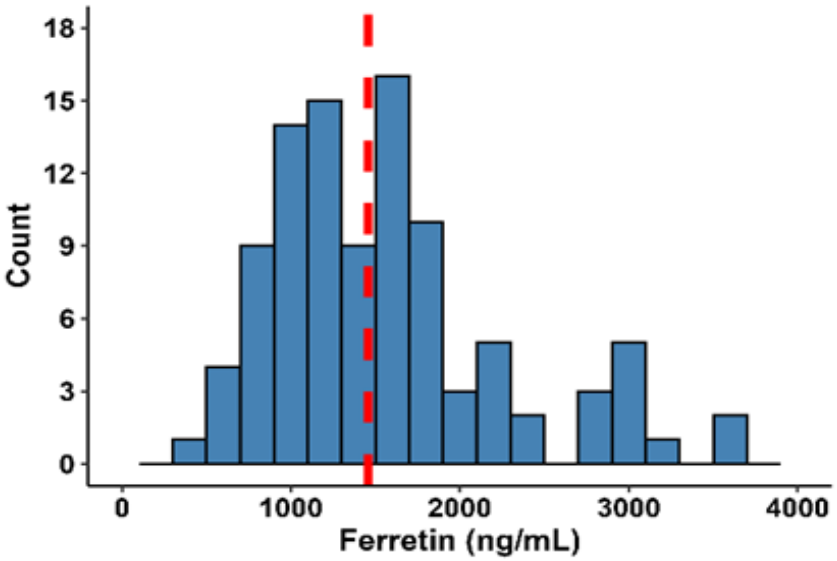

Figure 3: Distribution of serum ferritin levels in the study population (n = 100). The histogram shows frequency counts of ferritin measurements (ng/mL), with the red vertical line indicating the median value (1457 ng/mL).

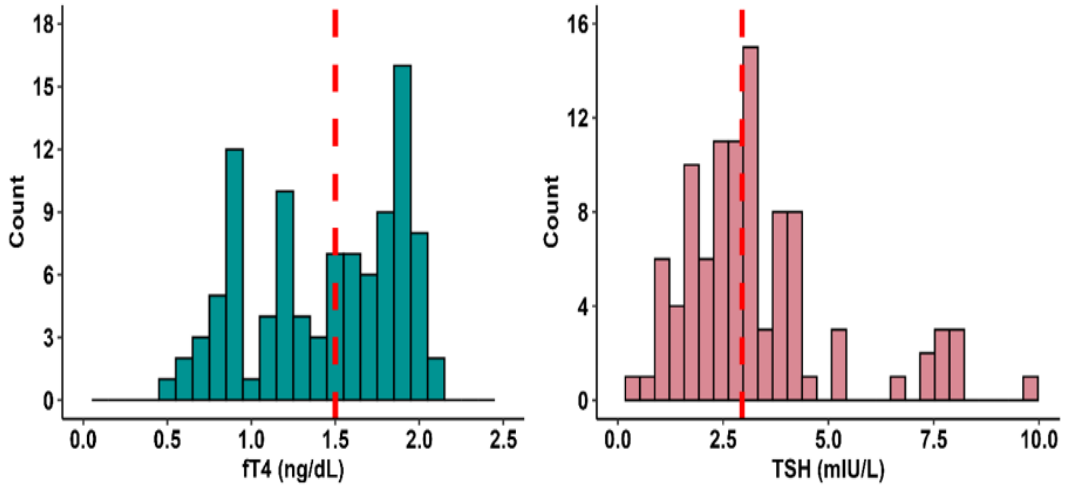

Figure 2: Distribution of thyroid function biomarkers in the study population (n = 100). Left panel: fT4 levels (ng/dL) showing a left-skewed distribution with a median of 1.5 ng/dL. Right panel: TSH levels (mIU/L) demonstrating a right-skewed distribution with a median of 2.95 mIU/L (IQR: 2.10-3.93). The red vertical lines in each panel indicate median values.

The distributions of fT4 and TSH are presented in Figure 4 fT4 levels (median: 1.5 ng/dL, IQR: 1.1-1.9) demonstrated a skewed distribution, with the majority of values falling within the normal physiological range (0.8-1.8 ng/dL).

Notably, 6% of participants exhibited subnormal fT4 concentrations (<0.7 ng/dL), consistent with potential hypothyroidism. TSH levels (median: 2.95 mIU/L, IQR: 2.10-3.93) showed right skewness, with 12% of values exceeding the upper reference limit (4.0 mIU/L). The co-occurrence of elevated TSH with low fT4 confirmed overt hypothyroidism. Evaluation of glucose metabolism via OGTT identified abnormalities in 7% of participants, contrasting with 93% who demonstrated normal glucose tolerance.

Association between serum ferritin and thyroid dysfunction: A correlation analysis was employed to assess the association between serum ferritin and thyroid dysfunction in the thalassemia patients (Figure 5). Serum ferritin levels were significantly correlated with thyroid function parameters. A negative correlation was observed between ferritin and fT4 levels ($R = -0.27$, $p = 0.0074$), signifying that greater ferritin concentrations were linked with lower fT4 concentrations. On the other hand, ferritin showed a positive correlation with TSH levels ($R = 0.41$, $p = 2.3 \times 10^{-5}$), suggesting that elevated ferritin levels were linked to increased TSH concentrations. These findings indicate a potential association between iron overload and thyroid dysfunction.

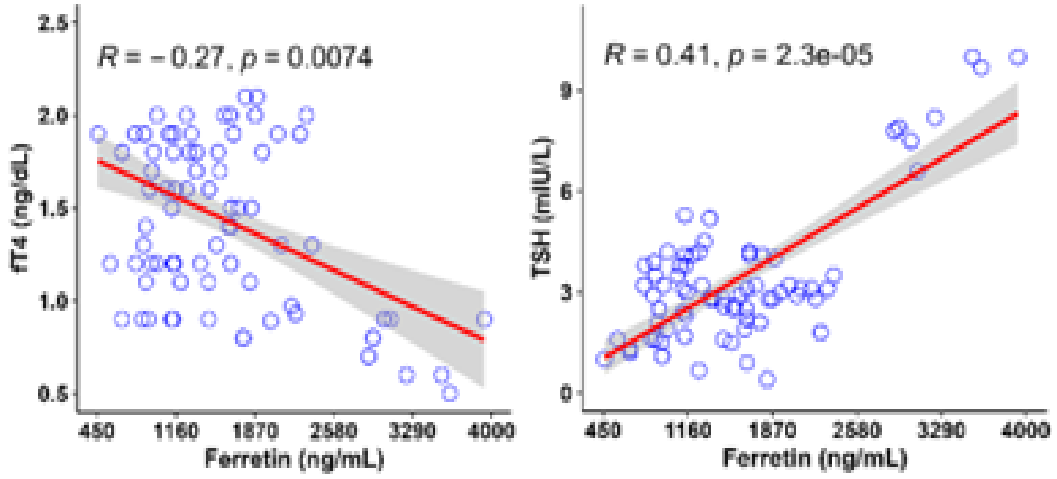

Figure 5: Correlation between serum ferritin and thyroid function markers. Left: Ferritin vs. fT4. Right: Ferritin vs. TSH. Red lines indicate linear regression, with shaded areas showing 95% confidence intervals. Spearman's correlation was used.

The patients were segregated into three distinct groups on the basis of the ferritin levels to determine the dose-dependent relationship between iron overload and thyroid dysfunction: First group (< 1000 ng/mL), second group (1000 – 2000 ng/mL) and the third group (> 2000 ng/mL) as shown in Table 3.

Table 3: Thyroid function across different ferritin categories. The Kruskal-Wallis test was used to assess statistical significance.

	Ferritin category			
Variable	**<1000**	**1000 - 2000**	**> 2000**	**P Value**
fT4	1.65 [1.20 - 1.86]	1.60 [1.20 - 1.90]	0.9 [0.7 - 1.3]	< 0.001
TSH	2.0 [1.3 - 3.2]	2.80 [2.35 - 3.80]	7.5 [3.1 - 7.9]	<0.001

Higher serum ferritin concentrations were significantly linked with thyroid dysfunction, as determined by the Kruskal-Wallis test ($p < 0.001$).

Patients with ferritin >2000 ng/mL had the lowest median fT4 levels (0.9 [0.7–1.3] ng/dL) and the highest median TSH levels (7.5 [3.1–7.9] mIU/L).

To determine the inter-group differences, a post hoc analysis Dunns test was performed with Bonferroni correction and the result of the analysis in illustrated in figure 6. fT4 levels were significantly lower in the >2000 ng/mL ferritin group compared to the <1000 ng/mL ($p < 0.01$) and 1000–2000 ng/mL ($p < 0.001$) groups, with no significant difference between the <1000 and 1000–2000 ng/mL groups. TSH levels were significantly higher in the >2000 ng/mL group than in the <1000 ng/mL ($p < 0.01$) and 1000–2000 ng/mL ($p < 0.001$) groups, with no significant difference between the latter two. These trends are illustrated in Figure 6, with significant pairwise comparisons marked accordingly.

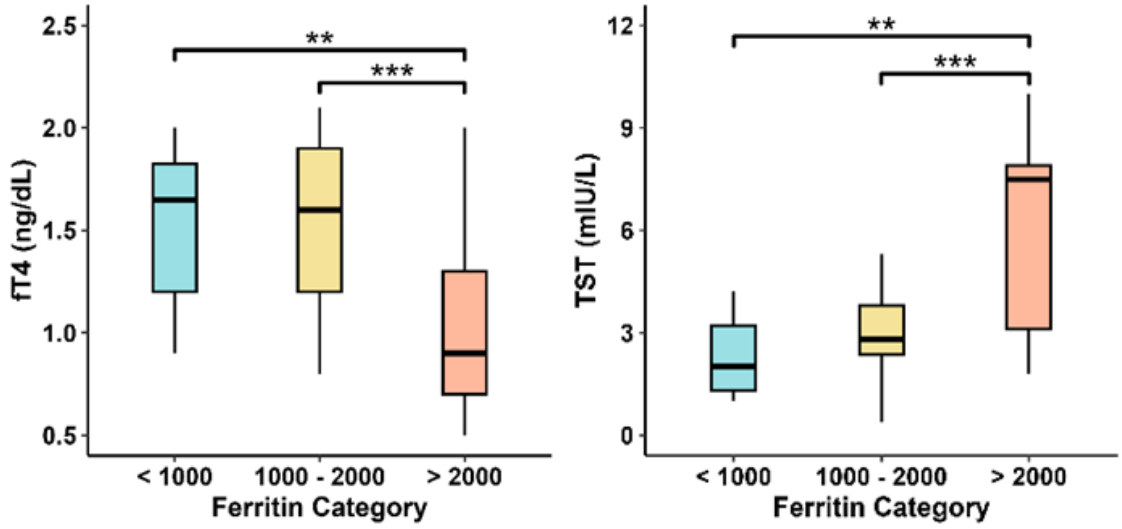

Figure 6: Box plots illustrating the relationship between thyroid function parameters across three ferritin categories in thalassemia patients. Left - fT4 levels and Right – TSH levels. ($p < 0.01$) and *** ($p < 0.001$)**

Robust regression analyses revealed consistent significant relationships between blood ferritin concentrations and thyroid function markers in the thalassemia patients (Table 4).

Table 4: Robust regression analyses of thyroid function markers.

Model	Predictor	β (per 1000 ng/mL)	t(df)	P value	95% CI
fT4 Unadjusted	Ferritin	−0.3	−4.97(98)	<0.001	[−0.4, −0.2]
fT4 Adjusted*	Ferritin	−0.5	−4.53(96)	<0.001	[−0.7, −0.3]
TSH Unadjusted	Ferritin	2.1	11.02(98)	<0.001	[1.7, 2.5]
TSH Adjusted*	Ferritin	2.9	7.48(96)	<0.001	[2.1, 3.7]

***Models adjusted for age and gender. β coefficients represent change in thyroid marker per 1000 ng/mL ferritin increase. CI = confidence interval.**

Unadjusted models demonstrated that each 1000 ng/mL increase in ferritin was associated with a 0.3-unit decrease in fT4 ($\beta = -0.0003$ per ng/mL, $t(98) = -4.97$, $p < 0.001$) and a 2.1-unit increase in

TSH (β = 0.0021 per ng/mL, t(98) = 11.02, p < 0.001). After adjustment for age and gender, these associations strengthened further: ferritin maintained an independent negative correlation with fT4 (β = −0.0005 per ng/mL, t(96) = −4.53, p < 0.001) and positive correlation with TSH (β = 0.0029 per ng/mL, t(96) = 7.48, p < 0.001), confirming iron overload as a robust predictor of thyroid dysfunction (Table 4).

Association between serum ferritin and growth: The analysis of weight-for-age distribution in thalassemia patients revealed notable differences between males and females (Table 5). Among the total cohort, 36% of patients fell below the 5th percentile for weight, indicating underweight status. However, this proportion varied significantly by sex, with 72% (n = 26) of the underweight being males (26 out of 36) compared to only 28% of females. Conversely, a substantially higher percentage of females (42 out of 52) maintained a weight at or above the 5th percentile, while less than half of male patients (22 out of 48) achieved this threshold. These findings suggest that male thalassemia patients are disproportionately affected by growth impairment, exhibiting more than twice the prevalence of underweight status compared to their female counterparts.]

Table 5: Weight-for-Age Distribution in Thalassemia Patients (N = 100).

Weight-for-Age Percentile	Total (n = 100)	Male (n = 48)	Female (n = 52)	P Value
< 5th percentile (Underweight)	36 (36%)	26 (72%)	10 (28%)	< 0.001
≥ 5th percentile (Normal weight)	64 (64%)	22 (34%)	42 (66%)	

The analysis of height distribution shown in table 6 among patients revealed that 7% (n=7) exhibited abnormal height status, while the majority (93%, n=93) maintained normal height. Among patients with abnormal height, the sex distribution was nearly equal (57% male [n=4] versus 43% female [n=3]), with no statistically significant sex difference observed (p=0.9).

Similarly, among patients with normal height, the sex distribution was balanced (47% male [n=44] versus 53% female [n=49]).

Table 6: Height distribution by sex among thalassemia patients

Height status	Total (n = 100)	Male (n = 48)	Female (n = 52)	P Value
Abnormal height	7 (7%)	4 (57%)	3 (43%)	0.9
Normal height	93 (93%)	44 (47%)	49 (53)	

Weight Status and Ferritin Levels in Thalassemia: The analysis of ferritin levels in thalassemia patients stratified by weight-for-age status revealed no statistically significant differences between underweight (<5th percentile) and normal-weight (≥5th percentile) groups overall (p = 0.41) (Table 7). However, sex-specific trends were observed. Among males, underweight patients exhibited lower median ferritin levels (1192.50 [922.50–1873.00] ng/mL) compared to normal-weight males (1678.00 [1342.00–2226.25] ng/mL), though this variation failed to attain statistical significance (p = 0.1). In contrast, underweight females had numerically higher median ferritin levels (1644.50 [1137.00–1923.25] ng/mL) than their normal-weight counterparts (1455.50 [1023.25–1738.00] ng/mL), but this disparity was also not significant (p = 0.4).

Table 7: Comparison of ferritin levels (median [IQR]) between underweight (<5th percentile) and normal-weight (≥5th percentile) participants, stratified by gender.

Group	Underweight (< 5th Percentile)	Normal Weight (> 5th Percentile)	P Value
Total	1265.50 [1062.75 - 1877.25]	1532.00 [1111.25 - 1795.00]	0.41
Male	1192.50 [922.50 - 1873.00]	1678.00 [1342.00 - 2226.25]	0.1
Female	1644.50 [1137.00 - 1923.25]	1455.50 [1023.25 - 1738.00]	0.4

Ferritin Concentrations Variation by Height Status: The analysis of ferritin levels between thalassemia patients with short stature (n=7) and those with normal height (n=93) showed a significant difference (p<0.001) (Table 8). Patients who were short for their target height demonstrated substantially higher median ferritin levels (2934.0 ng/mL, IQR: 2584.5-3430.0) compared to patients who achieved their normal target height (1343 ng/mL, IQR: 990-1765).

Table 8: Comparison of ferritin levels (median [IQR]) between Short height and normal height participants.

Group	Short for target Height	Normal for target height	P Value

Total	2934.0 [2584.5 - 3430.0]	1343 [990 – 1765]	< 0.001

Ferritin level and OGTT: The analysis revealed a significant link between ferritin concentrations and ipaired glucose tolerance in individuals diagnosed with thalassemia (Table 9). Patients with abnormal OGTT results (indicating prediabetes or diabetes) demonstrated markedly higher median ferritin levels (3090 ng/mL, IQR: 2895–3430) compared to those with normal glucose tolerance (1343 ng/mL, IQR: 990–1765). This difference was highly significant ($p < 0.001$), highlighting iron overload strongly associated with glucose metabolism dysregulation in this population.

Table 9: Comparison of serum ferritin levels (median [IQR], ng/mL) between thalassemia patients with normal and abnormal OGTT results. Mann-Whitney U test P Value < 0.001

Group	Normal OGTT (N = 93)	Abnormal OGTT (N = 7)	P Value
Ferritin (ng/mL)	1343 [990 - 1765]	3090 [2895 - 3430]	< 0.001

These findings suggest that elevated ferritin levels, reflecting increased iron burden, may underlie the progression of glucose intolerance and diabetes in thalassemia patients, likely through iron-mediated damage to pancreatic β-cells and/or insulin resistance.

Discussion

Thalassemia is an inherited hemoglobinopathy defined by impaired expression of hemoglobin, resulting in long-term anemia, ineffective red blood cell formation, and secondary complications such as iron overload.(49) Individuals diagnosed with thalassemia major often need regular blood transfusions, which lead to excessive iron build-up over time, while those with thalassemia intermedia, though less dependent on transfusion, may still develop iron overload because of the augmented absorption of gastrointestinal iron.(50) While the excess iron can accumulate across several vital organs, notably the heart and liver, the endocrine glands are mostly prone to the detrimental effect of iron. [10]

This study was aimed to explore the potential link between serum ferritin concentrations, a commonly used molecular indicator for iron status and a range of endocrine and metabolic derangements in 100 patients with thalassemia aged between 2 – 12 years. It specifically focused on examining the link between ferritin levels and thyroid dysfunction, exploring their association with growth impairment, and assessing the link between ferritin and glucose tolerance in this patient population.

Some previously reported data strongly suggest the iron-mediated endocrinopathy development in thalassemia patients, [11-13] while some studies were unable to observe a meaningful link between blood ferritin concentrations and endocrine complications. [14] Our findings highlight a significant iron-mediated thyroid axis disruption in thalassemia patients, suggesting a dose-dependent relationship. Elevated ferritin levels correlated negatively with fT4 ($R = -0.27$, $p = 0.007$), and positively with TSH levels ($R = 0.41$, $p = 2.3 \times 10^{-5}$), suggesting that elevated ferritin levels were linked to decreased fT4 levels and increased TSH concentrations. Individuals diagnosed with thalassemia having ferritin levels above 2000 ng/mL had notably lower fT4 levels and a higher TSH level in contrast to those exhibiting ferritin levels lesser than 2000 ng/mL. This result suggests a direct toxicity of excess iron on the thyroid cells. Our data corroborate previous observations of an inverse association between serum ferritin and fT4 concentrations [15] and a positive association with TSH levels. [16] However, the reported frequency and progression of thyroid dysregulation in individuals diagnosed with thalassemia have varied widely across different studies. [17] Chirici et al. (2013) recommended that ferritin concentrations might serve both as a predictive and prognostic molecular indicator for thyroid dysregulation in thalassemia-diagnosed individuals. [18]

Apart from this, age is also considered as a critical factor for the severity of endocrine disorder, and it is more prevalent in older people, but the data is inconsistent. For example, Salim et al. reported hypothyroidism more frequently in younger children (5 – 10 years), [19] whereas Akinci et al. reported a similar incidence of hypothyroidism in patients between 6 -12 years and 12 – 18 years. [25] All participants in this study were between 2 and 12 years of age. Out of 100 patients, 12 exhibited thyroid dysfunctions, including both males and females. These 12 participants had markedly elevated ferritin levels, with a median level of 3,034 ng/ml, far exceeding the normal paediatric range (12–150 ng/ml). These findings show a critical iron-mediated endocrine axis disruption in thalassemia. The observed prevalence of thyroid dysfunction (12%) aligns with existing literature, which reports endocrine complications in 3 - 27 % of thalassemia patients.

The coexistence of severe hyperferritinemia in all affected patients emphasizes the role of iron overload in this process, as ferritin levels above 2,500 ng/ml are strongly correlated with endocrine morbidity. Iron seems to deposit more heavily in the pituitary and thyroid glands, and in rare cases, even the hypothalamus, leading to more pronounced

disruptions in thyroid function than in other parts of the endocrine system. Research has shown that patients having ferritin levels under 1000 ng/mL have a 3.25 times lower risk of developing hypothyroidism in contrast with the levels over 2500 ng/mL. [20]

Growth retardation is a well-documented disorder in thalassemia, often attributed to chronic anemia, iron toxicity, and endocrine disruptions like deficiency of GH or hypogonadism. Chronic iron overload has detrimental effects on growth impairment. One of the earliest signs of iron overload is delayed puberty, such as missing the growth spurt or delayed menstruation, with some patients not menstruating until age 16 or later. This manifestation predominates in children having β-thalassemia major who receive frequent transfusions. Excess iron disrupts pituitary function, impairing the secretion of luteinising hormone and follicle-stimulating hormone, which are essential for activating the ovaries or testes. [21]

The present study revealed critical findings regarding growth patterns and excessive iron concentrations in individuals diagnosed with thalassemia. Apart from this, a pronounced sex disparity in weight-for-age distribution was observed, with male patients exhibiting a significantly higher prevalence of underweight status. The observation that 54.2% of males versus 19.2% of females fell below the 5th percentile for weight aligns with prior studies documenting male vulnerability in thalassemia-related growth failure.

Regarding height distribution, only 7% of the thalassemia patients exhibited abnormal height status, with no significant sex-based differences observed. This finding contrasts with some earlier studies reporting an increased frequency of growth retardation in thalassemia major, particularly in patients with poor iron chelation therapy. The balanced sex distribution in both abnormal and normal height groups suggests that growth impairment in thalassemia is likely affected more by disease-related determinants like chronic anemia, iron overload, and endocrine dysfunction rather than sex-specific predispositions. [22]

A particularly striking observation in this study was the significantly elevated ferritin levels in thalassemia individuals exhibiting growth retardation relative to those achieving standard height. The median ferritin level in short-stature patients was more than double that of their normal-height counterparts, reinforcing the well-documented association between iron overload and growth failure in thalassemia. Sex steroids exert a crucial contribution in the pubertal growth spurt, but iron overload suppresses gonadotropin-releasing hormone (GnRH) secretion, resulting in hypogonadotropic hypogonadism. Consequently, delayed puberty and reduced sex hormone levels further stunt growth in adolescents with thalassemia. Males with thalassemia are particularly susceptible to growth failure due to hypogonadism, delayed puberty, and reduced testosterone levels, which delay peak growth velocity. Studies report that over 60% of male thalassemia patients experience delayed puberty, with some never achieving full sexual maturation. [23] Without a proper pubertal growth spurt, males often exhibit shorter final adult height compared to healthy individuals.

While females typically enter puberty earlier than males, thalassemia-related iron overload can prolong prepubertal growth, leading to shorter stature. Research advocates that females having thalassemia are shorter compared to males, possibly due to earlier growth plate fusion. Estrogen deficiency further contributes to poor bone mineralization and increased fracture risk. [24] Males are more prone to hypogonadism and reduced growth velocity, while females experience delayed menarche and estrogen deficiency, leading to shorter stature. Early iron chelation, hormonal therapy, and nutritional support are critical for optimising growth outcomes in thalassemia patients. Further research is needed to explore sex-specific treatment protocols and long-term growth monitoring.

Iron overload has been implicated in pancreatic beta-cell damage, leading to abnormal glucose homeostasis and an augmented progression to diabetes mellitus among individuals diagnosed with thalassemia. This study also aimed to evaluate whether high serum ferritin concentrations are linked with glucose intolerance as assessed by OGTT.

The analysis revealed a significant association between ferritin concentrations and abnormal OGTT in thalassemia patients, reinforcing the growing body of evidence linking iron overload to metabolic dysregulation. Patient's abnormal OGTT results (i.e., patients with prediabetes or diabetes) exhibited markedly higher median ferritin levels (3090 ng/mL) compared to those with normal glucose tolerance (1343 ng/mL), a difference that was highly statistically significant ($p < 0.001$). The development of abnormal glucose tolerance has been linked with high ferritin concentrations in previous studies. [25] The strong correlation identified in this investigation implies that iron overload may exert a crucial function in the pathogenesis of glucose intolerance and diabetes in thalassemia, likely through mechanisms involving pancreatic β-cell dysfunction and insulin resistance.

Excess iron has been implicated in the disruption of glucose homeostasis through multiple pathways. One proposed mechanism is the induction of oxidative stress, as iron catalyses ROS generation, resulting in cellular damage in insulin-sensitive tissues. The liver, a key organ in glucose regulation, is par-

ticularly vulnerable to iron-induced oxidative stress, which can impair hepatic insulin sensitivity and contribute to hyperglycemia. Additionally, iron overload may reduce peripheral glucose uptake in skeletal muscle by interfering with insulin signalling pathways, further exacerbating insulin resistance. [26] Studies in hemochromatosis patients confirm iron overload-mediated insulin resistance, extending to those with normal glucose tolerance. Similarly, investigations revealed a considerable frequency of glucose dysfunction in a relatively young and lean cohort with significant iron burden, suggesting that iron toxicity, rather than traditional risk factors such as obesity, may be a primary driver of metabolic abnormalities in these patients. [27]

However, despite the strong association observed in this study, some previous research has yielded conflicting results. A previous study on 26 thalassemic reported that about 50% of patients who received frequent blood transfusions had abnormal glucose tolerance, but found no correlation between number of transfusions and ferritin concentration. Instead, the authors proposed that genetic predisposition exerts a more substantial role in the advancement of glucose intolerance. [28] This discrepancy might be attributable to divergences in experimental design, study population attributes, or measurement techniques, such as variations in chelation therapy adherence, which can influence iron burden independently of transfusion frequency.

Additionally, the role of genetic factors in thalassemia-related diabetes cannot be overlooked. The HFE gene (which regulates iron absorption) mutations were linked to both iron overload and diabetes risk. [29] Furthermore, thalassemia itself may contribute to β-cell dysfunction due to chronic anemia and hypoxia, independent of iron toxicity. Thus, while iron overload appears to be a major contributor to glucose intolerance, it likely interacts with genetic and disease-specific factors to determine metabolic outcomes.

Conclusion

This study highlights the multifaceted impact of chronic iron overload on endocrine and metabolic functions in β-thalassemia patients. A dose-dependent relationship was observed between elevated serum ferritin and endocrine dysfunction, particularly hypothyroidism, evident by decreased fT4 and increased TSH beyond the 2000 ng/mL ferritin threshold. Growth impairment, especially in males, was linked to iron-induced hypogonadism, GH deficiency, and pituitary damage. Notably, ferritin levels were significantly higher in patients with glucose intolerance, implicating pancreatic iron toxicity in thalassemia-related diabetes. The study proposes ferritin as both a marker and mediator of these complications, advocating for early monitoring, individualized chelation, and sex-specific interventions to prevent irreversible damage and improve patient outcomes.

Acknowledgement: The authors thank the hospital staff and patients for supporting this study.

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