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Iron Overload and Endocrine Dysfunction in Adults with Transfusion-Dependent Beta-Thalassemia and Growth Retardation: A Correlational Study

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Abstract

Background & Objective: Iron overload remains a significant concern in patients with transfusion-dependent beta-thalassemia (TDT). The purpose of this study was to characterize iron load and endocrine profile of adult transfusion-dependent beta thalassemia patients and to evaluate their correlation with growth retardation. **Methods:** A cross-sectional study was carried out at PIMS Hospital, Islamabad, involving 62 patients with either homozygous or HbE beta-thalassemia who receiving regular blood transfusions. Serum ferritin (SF) and transferrin saturation (TS) were used to assessed iron overload, while endocrine functioning was evaluated through measurements of thyroid-stimulating hormone-sensitive (TSHs) and free thyroxine (FT4) and insulin-like growth factor-1 (IGF-1). Data was analyzed using SPSS v26.0 and R v4.3.1, which included chi-square test, Pearson correlation, and multivariable regression to explore associations between iron indices and endocrine dysfunction. **Results:** Serum ferritin demonstrated significant negative correlations with FT4 ($r = -0.348$, $p = 0.005$) and IGF-1 ($r = -0.302$, $p = 0.015$). MRI T2* pancreas values correlated positively with FT4 ($r = 0.268$, $p = 0.037$) and IGF-1 ($r = 0.312$, $p = 0.015$). Patients with ferritin >5,000 ng/mL exhibited a higher prevalence of low IGF-1 levels (89.2% vs. 64.0%, $p = 0.018$). No significant gender-based differences were observed in endocrine parameters. **Conclusion:** Pancreatic iron burden and elevated serum ferritin were significantly associated with impaired thyroid and growth axis function, highlighting the value of integrating MRI T2* and biochemical markers for early endocrine risk stratification in adult TDT patients.

Keywords: transfusion-dependent Beta-thalassemia; iron overload; serum ferritin; endocrine dysfunction; insulin-like growth factor one (IGF-1); thyroid function (TSHs; FT4); growth retardation

1. Introduction

Beta-thalassemia is a hereditary hemoglobinopathy characterized by impaired synthesis of beta-globin chains, leading to chronic anemia and requiring lifelong transfusion support in its severe form transfusion-dependent thalassemia (TDT). Globally, beta-thalassemia affects approximately 1.5% of the population, with over 60,000 symptomatic births annually [1]. In developed countries, advances in transfusion protocols, iron chelation therapy, and endocrine monitoring have significantly improved survival and reduced complications. Despite this, endocrine dysfunction remains prevalent, with studies reporting that up to 50% of adequately transfused TDT patients develop endocrine abnormalities such as hypothyroidism, hypogonadism, and growth hormone axis impairment [2].

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In South Asia, the burden of beta-thalassemia is disproportionately high due to consanguineous marriages, limited carrier screening, and inadequate healthcare infrastructure. India and Bangladesh report high rates of growth retardation and endocrine dysfunction among thalassemia patients, often exacerbated by delayed transfusion initiation and suboptimal chelation therapy [3]. Pakistan, with an estimated carrier rate of 5–7%, faces similar challenges. A recent study from Peshawar revealed that 52.7% of transfusion-dependent children exhibited short stature, with elevated serum ferritin levels strongly associated with growth retardation [4]. Another study from Jamshoro found that 62.5% of beta-thalassemia major patients had growth retardation, and 73.9% had at least one endocrine complication, with serum ferritin levels significantly correlated with endocrine dysfunction [5].

Iron overload, resulting from repeated transfusions, is the primary driver of endocrine complications in TDT. Excess iron accumulates in endocrine organs, impairing their function and leading to conditions such as hypothyroidism, hypogonadotropic hypogonadism, and IGF-1 deficiency. While T2* MRI is the gold standard for assessing iron deposition in organs, its limited availability in Pakistan necessitates reliance on surrogate markers such as serum ferritin (SF) and transferrin saturation (TS). These markers, though widely used, require validation in local populations to ensure their predictive value for endocrine dysfunction [6].

Although endocrine dysfunction in transfusion-dependent beta-thalassemia (TDT) has been widely documented in pediatric populations, adult patients particularly those with growth retardation remain underrepresented in the literature. Existing studies from South and Southeast Asia have primarily focused on children, with limited data on endocrine outcomes in adults surviving into their third decade of life. Furthermore, while serum ferritin and transferrin saturation are routinely used as surrogate markers of iron overload, their predictive value for endocrine dysfunction in adult TDT patients has not been adequately validated. The role of pancreatic iron deposition, assessed via MRI T2, in influencing endocrine parameters such as thyroid function and IGF-1 levels also remains poorly characterized. In Pakistan, where advanced imaging modalities are not widely accessible, there is a critical need to establish clinically relevant correlations between accessible iron markers and endocrine outcomes to inform screening and management protocols.

Addressing this gap is essential for improving long-term outcomes in adult beta-thalassemia patients, who are increasingly surviving into adulthood due to improved transfusion practices. Growth retardation and endocrine dysfunction significantly impair quality of life, reproductive health, and psychosocial development. In resource-limited settings like Pakistan, where MRI T2 is not routinely available, validating the utility of serum ferritin and transferrin saturation as indicators of endocrine risk is both practical and necessary. Moreover, understanding the relationship between pancreatic iron burden and hormonal profiles may offer new avenues for risk stratification and early intervention. By focusing on adult patients with documented growth retardation, this study contributes novel insights into the endocrine sequelae of iron overload and supports the development of age-specific monitoring strategies. Therefore, the objective of this study was to evaluate the correlation between iron overload assessed through serum ferritin, transferrin saturation, and MRI T2 pancreas and endocrine function, specifically thyroid hormones and IGF-1 levels, in adult transfusion-dependent beta-thalassemia patients with growth retardation.

2. Materials and Methods

2.1. Study Design and Sample Size

This study employed a cross-sectional design to evaluate the correlation between iron overload and endocrine function in adult patients with transfusion-dependent beta-thalassemia (TDT) presenting with growth retardation. The research was conducted at the Department of Oncology, Pakistan Institute of Medical and Sciences (PIMS), Islamabad from January 2024 to January 2025. Sample size of 62 calculated using an expected correlation coefficient (r) of 0.35, level of significance level (α) of 0.05 and statistical power ($1-\beta$) at 80% to ensure adequate sensitivity for detecting a true

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effect using MedCalc's sample size calculator [7] and by guidelines from Bujang and Baharum, who recommended a minimum of 50-85 subjects for moderate correlations in clinical settings [8].

2.2. Study Population and Eligibility Criteria

Participants were recruited using purposive sampling technique from outpatient department (OPD) and included individuals age 18 years or older with a confirmed diagnosis of homozygous beta-thalassemia or beta-HbE thalassemia, verified through high-performance liquid chromatography (HPLC) or microcapillary electrophoresis. Growth retardation was defined based on anthropometric criteria consistent with WHO standards for height-for-age z-scores below −2 SD [9]. Exclusion criteria included patients who tested positive for hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (anti-HCV) antibodies, as well as individuals who declined to provide informed consent.

2.3. Ethical Considerations

Study protocol was reviewed and approved by the Ethical Committee of the Riphah International University (Reference ID: IRB/23/35197-21/23). All participants provided written informed consent prior to enrollment, and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

2.4. Sample Collection and Laboratory Analysis

Venous blood samples were collected from each participant prior to their scheduled transfusion. Two tubes were drawn per subject: one containing 7 mL and the other 3 mL of blood. All laboratory analyses were performed at the Clinical Pathology Laboratory of Pakistan Institute of Medical Sciences (PIMS), Islamabad. Iron overload was assessed using serum ferritin (SF) and transferrin saturation (TS). Serum iron (SI) and total iron-binding capacity (TIBC) were measured using the direct colorimetric method on the Roche COBAS® Integra 400 Plus / COBAS® 6000 platform. SF and TS levels were determined using chemiluminescence immunoassay (CMIA) on the Beckman Coulter Access 2 / DxI 800. Endocrine function was evaluated through measurements of thyroid-stimulating hormone-sensitive (TSHs), free thyroxine (FT4), and insulin-like growth factor-1 (IGF-1). TSHs and FT4 were analyzed using Roche Elecsys® e411 / e601 / e602 (ECLIA), while IGF-1 levels were quantified using the solid-phase Electrochemiluminescence immunoassay (ECLIA) method on Lifotronic eCL8000 analyzer.

2.5. Statistical Analysis

Data were analyzed using SPSS version 26.0 and R version 4.3.1. Continuous variables were summarized as mean ± SD or median (IQR), and categorical variables as frequencies (%). Group comparisons were performed using independent t-tests, Mann–Whitney U tests, chi-square, or Fisher's exact tests. For multigroup comparisons, ANOVA or Kruskal–Wallis tests were applied with Bonferroni-adjusted post hoc analysis. Correlations between biochemical markers (iron indices, IGF-1, TSH, FT4) were assessed using Pearson or Spearman coefficients, with partial correlations controlling for age and sex. Multivariable logistic regression identified predictors of clinically significant LGIB, with model fit evaluated using the Hosmer–Lemeshow test and AUC-ROC. Interaction terms (e.g., IGF-1 × age group) and age-stratified models were explored. Missing data were imputed using chained equations (MICE), and outliers were winsorized. Sensitivity analyses excluded patients with thyroid or growth disorders. A p-value < 0.05 was considered statistically significant.

3. Results

Out of 62 study participated, 34 males (54.8%) and 28 females (45.2%). The majority of participants were diagnosed with homozygous beta-thalassemia (96.8%), while only 3.2% had HbE

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beta-thalassemia. Median age of subjects was 22 years, ranging from 18 to 26 years. Pre-transfusion hemoglobin levels averaged 8.5 g/dL (SD = 1.2), indicating moderate anemia prior to transfusion. Anthropometric measurements revealed a median body weight of 42.0 kg (range: 28–55 kg), a median body mass index (BMI) of 18.2 kg/m² (range: 14.8–22.5), and a mean height of 148.2 cm (SD = 7.9). The mean mid-parental height was 161.8 cm (SD = 8.5), suggesting a significant deviation from expected growth potential. Iron overload markers showed a markedly elevated median serum ferritin level of 5,850 ng/mL (range: 600–20,800) and a transferrin saturation median of 92% (range: 15–106%), consistent with severe iron burden. Endocrine parameters revealed a median TSHs level of 3.42 mU/L (range: 0.65–8.1), a median FT4 level of 1.09 ng/dL (range: 0.75–1.92), and a median IGF-1 concentration of 58.0 ng/mL (range: 20–198), indicating potential thyroid and growth hormone axis dysfunction. Moreover, MRI T2* pancreas values were available for a subset of patients, with a median of 12.9 ms (range: 4.2–54.8), reflecting varying degrees of pancreatic iron deposition as showed in Table 1.

Table 1. Baseline Characteristics of Research Subjects (n = 62).

Variables	**n (%) / Median (min–max) / Mean (SD)**
Gender, n (%)	
Male	34 (54.8)
Female	28 (45.2)
Diagnosis, n (%)	
Homozygous Beta Thalassemia	60 (96.8)
HbE Beta Thalassemia	2 (3.2)
MRI T2 Pancreas (ms), median (min–max)*	12.9 (4.2–54.8)
Age (years), median (min–max)	22 (18–26)
Pre-transfusion hemoglobin (g/dL), mean (SD)	8.5 (1.2)
Mid-Parental Height (cm), mean (SD)	161.8 (8.5)
Weight (kg), median (min–max)	42.0 (28–55)
BMI (kg/m²), median (min–max)	18.2 (14.8–22.5)
Height (cm), mean (SD)	148.2 (7.9)
TSHs (mU/L), median (min–max)	3.42 (0.65–8.1)
IGF-1 (ng/mL), median (min–max)	58.0 (20–198)
Serum ferritin (ng/mL), median (min–max)	5,850 (600–20,800)
Transferrin saturation (%), median (min–max)	92 (15–106)
FT4 (ng/dL), median (min–max)	1.09 (0.75–1.92)

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Thyroid function assessment revealed that the majority of subjects (66.1%) were euthyroid, indicating normal thyroid hormone levels. However, subclinical hypothyroidism was observed in 19 patients (30.6%), characterized by elevated thyroid-stimulating hormone (TSHs) with normal free thyroxine (FT4) levels. Overt hypothyroidism was identified in 2 patients (3.2%), reflecting more advanced thyroid dysfunction. In terms of growth hormone axis evaluation, insulin-like growth factor-1 (IGF-1) levels were found to be low in a substantial proportion of the cohort. Specifically, 49 patients (79.0%) exhibited IGF-1 concentrations below the age-adjusted reference range, consistent with impaired growth hormone activity. Only 13 patients (21.0%) demonstrated normal IGF-1 levels as described in Table 2.

Table 2. Proportion of Endocrine Function in Adult Beta TDT Patients with Growth Retardation (n = 62).

Variables	**n (%)**
Thyroid function	
Euthyroid (normal)	41 (66.1)
Hypothyroidism	2 (3.2)
Subclinical hypothyroidism	19 (30.6)
IGF-1	
Normal	13 (21.0)
Low	49 (79.0)

The results in Table 3 indicated no statistically significant correlation between TS and TSHs (r = 0.012, p = 0.922), suggesting that iron saturation does not influence TSH levels in this cohort. Similarly, the correlation between TS and FT4 was negligible (r = 0.025, p = 0.845), indicating no meaningful association between iron saturation and thyroid hormone output. A weak negative correlation was observed between TS and IGF-1 (r = −0.158), but this relationship did not reach statistical significance (p = 0.224).

Table 3. Correlation Between Transferrin Saturation with TSH, FT4, and IGF-1 (n = 62).

Variables	**r**	***p*-value**
Transferrin saturation – TSHs	0.012	0.922
Transferrin saturation – IGF-1	−0.158	0.224
Transferrin saturation – FT4	0.025	0.845

No significant correlation was observed between serum ferritin and TSHs (r = 0.082, p = 0.516), indicating that iron burden does not appear to influence TSH levels as illustrated in Table 4. However, a statistically significant weak negative correlation was found between serum ferritin and FT4 (r = −0.348, p = 0.005), suggesting that higher iron load may be associated with reduced thyroid hormone levels. Similarly, serum ferritin demonstrated a significant negative correlation with IGF-1 levels (r = −0.302, p = 0.015), indicating that increased iron burden may impair growth hormone axis function.

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Table 4. Correlation Between Serum Ferritin with TSH, FT4, and IGF-1 (n = 62).

Variables	**r**	***p*-value**
Serum ferritin – FT4	−0.348	0.005*
Serum ferritin – TSHs	0.082	0.516
Serum ferritin – IGF-1	−0.302	0.015*

Median serum ferritin levels were slightly higher in males [6,050 ng/mL (IQR: 4,800–8,200)] compared to females [5,650 ng/mL (IQR: 4,200–7,900)], though the difference was not statistically significant (p = 0.462). Transferrin saturation values were comparable between groups, with males showing a median of 94% (IQR: 82–105) and females 91% (IQR: 80–103) (p = 0.513). Thyroid function parameters, including TSHs and FT4, showed minimal variation between sexes. Median TSHs levels were 3.38 mU/L in males and 3.47 mU/L in females (p = 0.782), while FT4 levels were 1.08 ng/dL and 1.10 ng/dL, respectively (p = 0.744). Similarly, IGF-1 concentrations were not significantly different, with males having a median of 56.5 ng/mL and females 59.0 ng/mL (p = 0.638) as showed in Table 5.

Table 5. Comparison of Endocrine Parameters Between Male and Female Patients (n = 62).

Variables	**Male (n=34) Median (IQR) / Mean (SD)**	**Female (n=28) Median (IQR) / Mean (SD)**	***p*-value**
Serum ferritin (ng/mL)	6,050 (4,800–8,200)	5,650 (4,200–7,900)	0.462
Transferrin saturation (%)	94 (82–105)	91 (80–103)	0.513
TSHs (mU/L)	3.38 (2.40–4.92)	3.47 (2.35–5.02)	0.782
FT4 (ng/dL)	1.08 (0.90–1.25)	1.10 (0.88–1.26)	0.744
IGF-1 (ng/mL)	56.5 (40–78)	59.0 (42–82)	0.638

A significantly higher proportion of patients with elevated ferritin levels (>5,000 ng/mL) exhibited low IGF-1 levels [89.2% vs. 64.0%, p = 0.018], suggesting a strong association between iron overload and impaired growth factor production as mentioned in Table 6. In contrast, the prevalence of overt hypothyroidism was low overall, with only two cases observed in the high ferritin group (5.4%) and none in the lower ferritin group (p = 0.505), indicating no statistically significant association. Subclinical hypothyroidism was more common among patients with ferritin >5,000 ng/mL [35.1% vs. 24.0%], but this difference did not reach statistical significance (p = 0.367).

Table 6. Association Between Serum Ferritin Levels and Endocrine Dysfunction.

Endocrine Dysfunction	**Ferritin ≤5,000 ng/mL (n=25) n (%)**	**Ferritin >5,000 ng/mL (n=37) n (%)**	**P-value**
Low IGF-1	16 (64.0)	33 (89.2)	0.018*

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Hypothyroidism (overt)	0 (0.0)	2 (5.4)	0.505
Subclinical hypothyroidism	6 (24.0)	13 (35.1)	0.367

No significant correlation was observed between MRI T2 pancreas values and serum TSHs (r = −0.082, p = 0.518), indicating that pancreatic iron load does not appear to influence thyroid-stimulating hormone levels. However, a modest but statistically significant positive correlation was found between MRI T2* values and FT4 levels (r = 0.268, p = 0.037), suggesting that lower pancreatic iron burden may be associated with better preservation of thyroid function.

Similarly, MRI T2* pancreas values showed a significant positive correlation with IGF-1 concentrations (r = 0.312, p = 0.015), indicating that reduced pancreatic iron overload may be linked to improved growth factor status as mentioned in Table 7.

Table 7. Correlation Between MRI T2 Pancreas Values and Endocrine Parameters*.

Variables	**r**	***p*-value**
MRI T2* Pancreas – TSHs	−0.082	0.518
MRI T2* Pancreas – FT4	0.268	0.037*
MRI T2* Pancreas – IGF-1	0.312	0.015*

4. Discussion

This study evaluated the endocrine profile of transfusion-dependent beta-thalassemia patients with growth retardation, focusing on gender-based differences, ferritin-associated dysfunction, and pancreatic iron deposition via MRI T2* imaging. No significant gender differences were observed in endocrine parameters. However, elevated serum ferritin levels (>5,000 ng/mL) were significantly associated with low IGF-1 levels, suggesting a link between iron overload and impaired growth factor production. MRI T2* pancreas values showed significant positive correlations with both FT4 and IGF-1, indicating that pancreatic iron burden may influence thyroid and growth axis function.

Our findings align with recent literature emphasizing the role of iron overload in endocrine dysfunction among beta-thalassemia patients. Multiple studies have demonstrated that elevated ferritin levels are predictive of growth hormone axis impairment and thyroid abnormalities. For instance, Atmakusuma et al. reported a significant correlation between iron overload and reduced IGF-1 levels in adult thalassemia patients with growth retardation [10]. Similarly, Sevimli et al. in 2022 found pancreatic iron deposition to be significantly associated with endocrine complications, including hypothyroidism and short stature [11]. Our results corroborate these findings, particularly the association between low MRI T2* pancreas values and reduced IGF-1, reinforcing the pancreas as a sensitive site for iron-induced endocrine disruption.

The observed lack of significant gender differences in endocrine parameters is consistent with Shah et al., who found no sex-based variation in ferritin-related complications [12]. However, the strong association between ferritin >5,000 ng/mL and low IGF-1 levels in our cohort underscores the need for stratified endocrine surveillance based on iron burden rather than demographic factors. Thyroid dysfunction, although prevalent in thalassemia, showed weaker associations with ferritin in our study, echoing findings by Hussein et al., who noted variable thyroid hormone responses to iron overload [13]. The modest correlation between pancreatic MRI T2* and FT4 (r = 0.268, p = 0.037)

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suggests subclinical thyroid involvement, possibly mediated by pancreatic endocrine stress or systemic iron toxicity.

Emerging evidence supports MRI T2* pancreas as a non-invasive biomarker for endocrine risk stratification. Meloni et al. demonstrated that pancreatic T2* values predict glucose metabolism disturbances and correlate with cardiac iron burden [14]. Our findings extend this utility to thyroid and growth axis parameters, advocating for routine pancreatic MRI in endocrine monitoring protocols. Moreover, integration of MRI-based iron quantification with biochemical markers may enhance early detection and intervention strategies, especially in resource-limited settings where endocrine complications often go underdiagnosed [15].

Despite its strengths, this study has limitations. The cross-sectional design precludes causal inference, and the relatively small sample size may limit generalizability. Longitudinal studies are needed to assess the progression of endocrine dysfunction and the impact of chelation therapy on MRI T2* values and hormonal recovery. Future research should explore multi-organ MRI correlations, incorporate dynamic endocrine testing, and evaluate therapeutic thresholds for ferritin and MRI T2* in predicting endocrine outcomes. Expanding such studies across diverse populations will help refine risk stratification and optimize endocrine care in beta-thalassemia.

5. Conclusions

This study revealed no significant gender-related variation in endocrine parameters; however, elevated serum ferritin levels were significantly associated with low IGF-1 concentrations, indicating impaired growth axis function. Moreover, pancreatic MRI T2 values showed significant correlations with FT4 and IGF-1, suggesting that pancreatic iron burden may serve as a sensitive marker for endocrine compromise. These results underscore the importance of integrating biochemical and imaging modalities for early detection and monitoring of endocrine dysfunction in this high-risk population. Routine assessment of pancreatic iron load, alongside serum ferritin, may enhance risk stratification and guide timely endocrine interventions. Future studies should validate these associations longitudinally and explore therapeutic thresholds for clinical decision-making.

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Informed Consent Statement: Participants signed informed consent forms after receiving detailed information about the study. Consent was obtained or waived by all participants in this study.

Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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