

ORIGINAL PAPER

Endocrine dysfunction in children with transfusion-dependent thalassemia major: a cross-sectional study

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ABSTRACT

Introduction: Thalassemia major is the most common inherited anemia requiring lifelong transfusion support. While transfusions improve survival, iron overload from repeated transfusions predisposes patients to multi-organ damage, particularly endocrine dysfunction. This study aimed to evaluate the prevalence of endocrinopathies in transfusion-dependent thalassemia major and their correlation with serum ferritin levels.

Material and methods: A cross-sectional study was conducted among 67 children (< 18 years) with confirmed transfusion-dependent β -thalassemia major attending a tertiary care centre. Clinical examination, anthropometry, and biochemical evaluation including thyroid profile, parathyroid hormone, calcium, fasting and postprandial glucose, and serum ferritin were performed. Endocrine dysfunctions were defined using standard diagnostic criteria. Statistical analysis was carried out using Pearson correlation, χ^2 , and ANOVA tests.

Results: The mean age of participants was 7.7 ± 3.7 years. Short stature was observed in 74.6% of children, and 46.3% had at least one endocrine abnormality. Primary hypothyroidism and altered glucose tolerance each were present in 20.9%, while hypoparathyroidism was noted in 16.4%. Mean serum ferritin was 2676.7 ± 1165.5 ng/ml. Serum ferritin showed a significant positive correlation with age, transfusion burden, duration of chelation therapy, glucose parameters, liver enzymes, hepatosplenomegaly, blood urea, and TSH ($p < 0.05$), but not with T3, T4, parathyroid hormone, or growth hormone. Endocrine abnormalities were significantly more frequent in patients with poor compliance to chelation therapy (61.9% vs. 20%, $p = 0.001$).

Conclusions: In this cross-sectional study, endocrine abnormalities were identified in 46.3% of transfusion-dependent thalassemia major patients, with a higher prevalence observed among those reporting irregular chelation adherence. Serum ferritin levels were significantly associated with thyroid function and glucose tolerance. These findings underscore the relevance of routine endocrine evaluation and assessment of chelation adherence in this population. However, the cross-sectional nature of the study limits interpretation to associations, and no causal relationships or long-term prognostic implications can be inferred.

KEY WORDS:

blood transfusion, chelation therapy, endocrinopathies, thalassemia, serum ferritin.

INTRODUCTION

Thalassemia results from defects in normal haemoglobin production, and represents the most common inherited anemia worldwide. Patients with severe form

of thalassemia (thalassemia major or transfusion-dependent thalassemia) require regular blood transfusions to maintain an appropriate haemoglobin level [1].

Inadequately transfused children develop typical features of Cooley's anemia like stunted growth with bossing

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TABLE 1. Correlation of various parameters with the raised serum ferritin level

No.	Parameters	Mean	SD	Correlation with serum ferritin	
				Pearson correlation	p-value
1	Age [years]	7.7	3.7	0.676	< 0.001
2	Hemoglobin [gm/dl]	5.68	0.83	– 0.215	0.081
3	MCV [fl]	64.8	9.7	– 0.125	0.313
4	MCH [pg]	23.9	3.1	– 0.072	0.562
5	WBC count [cell/mm ³]	6571.6	2236.7	– 0.189	0.125
6	Average blood transfusion volume per recipient at each visit [ml]	174.7	104.7	0.594	< 0.001
7	Duration of chelation therapy [year]	3.32	1.19	0.464	< 0.001
8	Serum iron level [g/dl]	384.1	168.1	0.707	< 0.001
9	FBS [mg/dl]	99.8	10.3	0.376	< 0.001
10	PPBS [mg/dl]	141.1	18.9	0.501	< 0.001
11	S. calcium [mmol/l]	1.08	0.17	– 0.257	0.036
12	Liver enlargement [cm]	3.77	1.17	0.551	< 0.001
13	Spleen enlargement [cm]	7.46	2.13	0.530	< 0.001
14	SGOT [IU/l]	56.9	71.2	0.483	< 0.001
15	SGPT [IU/l]	64.1	59.3	0.569	< 0.001
16	S. bilirubin (total) [mg/dl]	1.03	0.6	0.190	0.124
17	Blood urea [mg/dl]	21.6	22.5	0.254	0.038
18	S. creatinine [mg/dl]	0.62	0.20	– 0.092	0.461
19	TSH [mIU/l]	3.57	2.69	0.400	0.001
20	T3 [pmol/l]	4.60	0.72	– 0.160	0.196
21	T4 [pmol/l]	15.56	3.56	– 0.161	0.193
22	PTH [pg/ml]	17.58	8.05	– 0.162	0.191
23	GH [ng/ml]	7.86	3.62	0.177	0.153

FBS – fasting blood sugar, GH – growth hormone, MCH – mean corpuscular haemoglobin, MCV – mean corpuscular volume, PPBS – post prandial blood sugar, PTH – parathyroid hormone, SGOT – serum glutamic oxaloacetic transaminase, SGPT – serum glutamic pyruvic transaminase, WBC – white blood cells

of skull, overgrowth of maxillary region and face gradually assuming mongoloid appearance [2].

Regular blood transfusion has improved the life expectancy of thalassaemic child, but the accumulation of iron contained in the transfused red cells is responsible for damage to the tissues [3]. Iron toxicity begins when iron load exceeds binding and tissue storage capacity. Liver is the primary site of iron storage, once liver iron storage capacity is exceeded, iron is deposited in other tissues of the body like heart, spleen and endocrine glands [4]. The accumulated iron leads to organ dysfunctions including cardiomyopathies, endocrinopathies, gonadal insufficiency and osteoporosis [5].

Even with careful management of patients, disorders of endocrine glands such as growth retardation, hypogonadism, insulin dependent diabetes, hypothyroidism, hypoparathyroidism occur. The iron over load is tested biochemically by estimating serum ferritin levels [6].

Despite regular blood transfusion and chelation therapy, endocrine abnormalities remain one of the ma-

jor complications in patients with β -thalassemia major. Given limited paediatric Indian data, this study aimed to assess endocrine abnormalities in transfusion-dependent thalassemia major and their association with serum ferritin levels.

MATERIAL AND METHODS

This observational cross-sectional study was conducted at the Thalassemia Day Care Centre of the Department of Paediatrics in a tertiary health centre. Sample size was based on the number of eligible patients attending the centre during the study period. A total of 67 children aged less than 18 years with confirmed transfusion-dependent β -thalassemia major attending the day care centre were enrolled.

Children with congenital endocrine disorders, HIV infection, other identifiable causes of endocrine dysfunction, pre-existing glucose intolerance or endocrinopathies prior to transfusion or diagnosis of thalassemia, and those

whose guardians did not provide consent were excluded from the study.

Approval was obtained from the Institutional Ethics Committee prior to study initiation. Children who were confirmed cases of β -thalassemia major and less than 18 years of age were enrolled. The nature and purpose of the study was first explained to the child and her parents. Informed and written consent was obtained from all guardians/parents of the children prior to allocation of the children to the study.

Chelation adherence was defined operationally as $\geq 80\%$ of prescribed deferasirox doses taken consistently over the preceding 6 months (regular compliance) vs. $< 80\%$ adherence or interruptions > 2 weeks (irregular compliance). Dosing was weight-based (20–40 mg/kg/day) and adjusted according to serum ferritin levels and tolerance. Compliance was assessed through caregiver/patient reporting and medical record review. Transfusion volume presented in Table 1 refers to the average annual transfusion volume per patient, calculated from medical records. Due to limitations in record-keeping, transfusion data were documented as volume (ml) rather than number of units.

A detailed history was taken and complete clinical examination was performed, including anthropometric measurements, pallor, jaundice, hepatomegaly, cirrhotic manifestations, splenomegaly. For assessment of nutritional status, weight, height, and body mass index was recorded. Blood transfusion history was documented at our centre in terms of the total volume administered per transfusion episode, as recorded in medical charts. For each patient, the mean transfusion volume was calculated in millilitres per episode. Using the cohort's mean body weight, transfusion burden was further expressed as millilitres per kilogram per transfusion, and extrapolated to an estimated annual transfusion burden in ml/kg/year. Due to limitations in record-keeping, transfusion data was available only as transfusion volume (ml) rather than the number of blood units.

From each participant, 8 ml of venous blood was collected aseptically: 2 ml in EDTA for complete blood count and 6 ml in plain vacutainers for serum ferritin, thyroid hormones, calcium, parathyroid hormone, and kidney/liver function tests:

- hypothyroidism was defined as per the standard cut-offs of T3, T4 and TSH in different age groups. Normal FT4 and FT3 and greater than normal TSH were considered evidence for subclinical hypothyroidism;
- hypoparathyroidism was diagnosed if parathyroid hormone (PTH) was less than 15 pg/ml (normal range 15–65 pg/ml);
- all patients included in the study underwent both fasting blood glucose and oral glucose load tests. For the oral glucose tolerance test, children were administered 1.75 g glucose per kilogram body weight (maximum 75 g), as per paediatric standards. Blood glucose was measured at baseline (fasting) and 2 hours post-

load. Glucose tolerance was classified into three categories based on the fasting blood glucose level: I) fasting blood glucose < 100 mg/dl was considered normal; II) fasting blood glucose of 100–125 mg/dl was defined as impaired fasting glucose; and III) fasting blood glucose ≥ 126 mg/dl warranted the diagnosis of diabetes. Impaired glucose tolerance was defined as a blood glucose level of 140–199 mg/dl, and diabetes was defined as a glucose level ≥ 200 mg/dl, 2 h after oral glucose load. Individuals with impaired fasting glucose and/or impaired glucose tolerance were designated as altered glucose tolerance test [7];

- short stature was diagnosed when the patient's height was more than two standard deviations below the median height for age and gender. Growth hormone estimation was based on random levels; stimulation tests were not performed.

STATISTICAL ANALYSIS

The data was entered in MS Excel spreadsheet. Analysis was done by the Statistical Package for the Social Sciences, version 25.0 software (IBM, Inc., Chicago, IL, USA). Quantitative data was expressed by mean and standard deviation. Qualitative data was expressed by the percentages and the significance level of differences between the proportions was observed by χ^2 test or Fisher's exact test. Cross tabulation was done to assess the relationship between dependent and independent variables. The results were expressed as percentages and a p -value < 0.05 was considered for declaring the difference statistically significant.

RESULTS

The study was conducted among 67 children who were less than 18 years of age and were diagnosed as β -thalassemia major.

CLINICO-HAEMATOLOGICAL PROFILE OF CHILDREN WITH B-THALASSEMIA

In this study, the mean age was 7.7 ± 3.7 years with minimum age of 2 years and maximum age of 17 years. In our study 74.6% of the children had short stature, while the remaining 25.4% of patients had normal stature. Nearly two-thirds of patients (62.7%) demonstrated irregular compliance with chelation therapy, while remaining 37.3% had regular compliance to oral chelating agent deferasirox (Figure 1).

In our cohort, mean value of serum ferritin was 2676.7 ± 1165.5 ng/ml, with a minimum level of 1010 ng/ml and a maximum level of 4987 ng/ml. 46.3% of patients had one or more endocrine disorders. In the present study, primary hypothyroidism and altered glucose tolerance test was found in 20.9% of the patients each whereas 16.4% of patients had primary hypoparathyroidism.

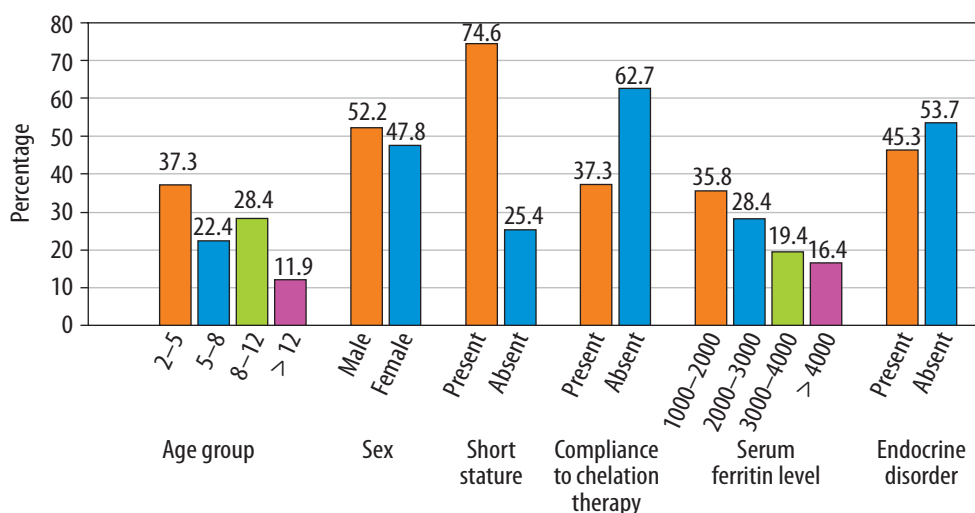


FIGURE 1. Clinical and haematological profile of children with β-thalassemia

CORRELATION OF VARIOUS PARAMETERS WITH A RAISED SERUM FERRITIN LEVEL

By applying Pearson correlation, serum ferritin levels have a statistically significant association with age, blood transfusion amount, duration of chelation therapy, serum iron levels, fasting blood sugar and post prandial blood sugar, hepatomegaly, splenomegaly, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), blood urea and serum TSH level ($p < 0.05$). The serum ferritin level has statistically non-significant association with T3, T4 hormone, parathyroid and growth hormone ($p > 0.05$) (Table 1). Transfusion volume presented in Table 1 refers to the average volume per transfusion episode. Based on a mean body weight of 11.6 ± 4.8 kg, the average transfusion burden was approximately 15.1 ml/kg per transfusion. With monthly transfusions, this corresponds to an estimated annual transfusion burden of ~180 ml/kg/year.

RELATION OF SERUM FERRITIN LEVELS WITH GROWTH HORMONE, PARATHYROID HORMONE AND TSH HORMONES

By applying one-way ANOVA test, the relationship of thyroid stimulating hormone with the serum ferritin level

was statistically significant ($p < 0.05$) while the association of growth hormone and PH with the serum ferritin level was statistically non-significant ($p > 0.05$) (Table 2). Growth hormone estimation was based on random levels only, without stimulation testing. Accordingly, the observed lack of significant correlation between serum ferritin and growth hormone (GH) should be interpreted as exploratory, given the limitations of random sampling in capturing true GH deficiency.

DISTRIBUTION OF ALL PATIENTS BASED ON ENDOCRINE DISORDER AND ORAL IRON CHELATING AGENT (DEFERASIROX) COMPLIANCE

Among patients with regular compliance ($n = 25$), endocrine abnormality was present in only 20% of patients, while among patients with irregular compliance ($n = 42$), endocrine abnormality was present in 61.9% of patients. By applying χ^2 test, the relationship of presence of endocrine abnormality and poor compliance was found to be statistically significant ($p < 0.01$) (Table 3). Among the 20.9% ($n = 14$) of patients with altered glucose tolerance, 13.4% ($n = 9$) had impaired fasting glucose, 7.5% ($n = 5$) had impaired glucose tolerance while none met criteria for diabetes mellitus.

TABLE 2. Relation of serum ferritin levels with growth hormone, parathyroid hormone and TSH hormones

Serum ferritin level [ng/ml]	TSH, mean (SD)	Growth hormone, mean (SD)	Parathyroid hormone, mean (SD)
1001–2000	2.33 (1.42)	8.02(3.83)	20.12 (6.63)
2001–3000	3.98 (2.95)	6.27 (3.10)	16.35 (4.17)
3001–4000	3.33 (2.22)	8.85 (3.50)	15.54 (4.89)
> 4000	5.83 (3.44)	9.09 (3.58)	16.61 (15.54)
Total	3.57 (2.69)	7.86 (3.62)	17.58 (8.05)
F statistics	5.385	2.089	1.293
p-value	0.002	0.111	0.285

GH – growth hormone, PTH – parathyroid hormone

TABLE 3. Distribution of patients based on endocrine disorders and deferasirox compliance

Endocrine abnormality	Deferasirox compliance		Total (%)
	Regular (%)	Irregular (%)	
Present	5 (20.0)	26 (61.9)	31 (46.3)
Absent	20 (80.0)	16 (38.1)	36 (53.7)
Total	25 (100.0)	42 (100.0)	67 (100.0)

 $\chi^2 = 11.069$

df = 1

 $p\text{-value} = 0.001$

In addition to univariable analyses, an exploratory logistic regression model was constructed to assess the independent association between chelation adherence and endocrine abnormalities after adjustment for age and serum ferritin. Odds ratios (OR) with 95% confidence intervals (CI) were reported, and statistical significance was set at $p < 0.05$. Irregular chelation adherence remained significantly associated with endocrine abnormalities (adjusted OR 5.2, 95% CI: 1.4–19.1, $p = 0.014$). Age and serum ferritin showed non-significant trends toward association. These findings suggest that the observed relationship between chelation adherence and endocrine dysfunction is not solely explained by age or ferritin burden.

DISCUSSION

A total of 67 children with transfusion-dependent thalassemia major were studied, and no significant sex difference in short stature was observed, consistent with findings by Najafipour [8], who reported short stature in 72% of males and 73% of females. The pathogenesis of growth failure is multifactorial, and is mainly due to chronic anemia and hypoxia, chronic liver disease, zinc and folic acid deficiency, iron overload, endocrinopathies and GH-IGF-1 axis dysregulation [9]. Similarly, Merchant *et al.* [10] observed growth retardation in both sexes without a significant sex difference, attributing growth failure mainly to iron overload and endocrine dysfunction. Kyriakou *et al.* [9] also noted that growth impairment affects both sexes equally, with severity influenced more by iron burden, chelation adequacy, and pubertal delay than by sex. As highlighted by Verma *et al.* [11], serum ferritin correlates with growth impairment, suggesting iron burden as a key driver. Also, exploring the relationship between growth percentiles and serum ferritin, or between IGF-1 and ferritin, would provide valuable insights into the impact of iron overload on growth in thalassemia.

In the current study, serum ferritin levels showed a statistically significant positive association with liver enzymes SGOT and SGPT, indicating hepatic involvement secondary to iron overload. Similar findings were reported by Suman *et al.* [12], who demonstrated that hepatic dysfunction, reflected by elevated transaminase levels, begins to manifest when serum ferritin exceeds 1000 ng/ml and becomes highly significant beyond levels of 2000 ng/ml.

This rise in liver enzymes is attributed to progressive iron deposition within hepatocytes, leading to oxidative stress, cellular injury, and hepatocellular necrosis. Bejaoui *et al.* [3] also highlighted that the liver is the primary site of iron storage in transfusion-dependent thalassemia, and once hepatic iron-binding capacity is exceeded, iron-mediated toxicity results in liver dysfunction. Furthermore, Noetzli *et al.* [4] emphasized that chronic iron overload leads to ongoing hepatic damage, which may progress to fibrosis and cirrhosis if not adequately chelated. These findings collectively support the observation that elevated serum ferritin serves as an early biochemical marker of iron-induced liver injury in multi-transfused thalassemia patients.

In our cohort, subclinical hypothyroidism was observed in 20.9% of patients, a prevalence comparable to that reported by Merchant *et al.* [10] in multi-transfused Indian thalassemia patients. The significant association between elevated serum ferritin levels and subclinical hypothyroidism in our study suggests a direct role of iron overload in thyroid dysfunction. Excess iron accumulates in endocrine tissues, including the thyroid gland, leading to increased generation of reactive oxygen species, lipid peroxidation, and mitochondrial damage, which impair thyroid hormone synthesis and secretion. Additionally, iron-induced damage to the hypothalamic-pituitary-thyroid axis may contribute to elevated TSH levels despite normal peripheral thyroid hormone concentrations. The concurrent significant association between raised serum ferritin levels and altered glucose tolerance further supports the concept of iron-mediated endocrine toxicity, as iron deposition in pancreatic β -cells causes oxidative stress, insulin secretory dysfunction, and peripheral insulin resistance. These findings are consistent with the observations of Belhoul *et al.* [13], who demonstrated a significant correlation between serum ferritin levels and hypothyroidism in patients with β -thalassemia major. Together, these studies emphasize that iron overload acts as a common pathogenic driver of multiple endocrine abnormalities, reinforcing the need for early endocrine surveillance and aggressive chelation therapy in patients with persistently elevated ferritin levels.

In the present study, the prevalence of hypoparathyroidism was 16.4%, comparable to the 14% reported by Hamidieh *et al.* [14] among patients with β -thalassemia major. This similarity across different populations indicates that hypoparathyroidism is a relatively frequent endocrine abnormality in multi-transfused thalassemia patients. The underlying mechanism has been proposed to involve iron deposition within the parathyroid glands, potentially resulting in cellular dysfunction and reduced PTH secretion.

However, in our study, no statistically significant association was observed between serum ferritin and PTH levels ($p > 0.05$). This suggests that, despite the proposed biological link, ferritin may not reliably reflect parathyroid dysfunction in all cases. Similar observations have

been reported by Carsote *et al.* [15], who emphasized that endocrine complications in thalassemia are multifactorial and may not be consistently predicted by serum ferritin levels alone.

Similar observations have been reported in other studies. For instance, Belhoul *et al.* [13] found that while iron overload was significantly associated with hypothyroidism and glucose intolerance, the relationship with hypoparathyroidism was less consistent, suggesting that factors beyond ferritin burden – such as genetic susceptibility, duration of transfusion therapy, and adequacy of chelation – may play a role. Likewise, Bilgin *et al.* [16] highlighted that endocrine complications in thalassemia are multifactorial, and although chelation therapy reduces overall risk, hypoparathyroidism may still occur independently of serum ferritin levels.

As noted by Noetzli *et al.* [4], ferritin reflects systemic iron burden but does not accurately capture tissue-specific deposition, particularly in endocrine glands. Advanced imaging modalities such as MRI T2* have demonstrated that iron distribution varies across organs, and parathyroid involvement may not parallel serum ferritin levels.

Taken together, these findings suggest that while hypoparathyroidism is a recognized complication of transfusion-dependent thalassemia, its occurrence may not be directly predicted by serum ferritin levels alone. This underscores the importance of routine endocrine screening in thalassemia patients, regardless of ferritin status, and highlights the need for more sensitive markers of parathyroid iron overload to better understand the pathogenesis of this complication.

In our study, the relationship between the presence of endocrine abnormalities and poor compliance to chelation therapy was found to be statistically significant ($p < 0.01$). This finding underscores the association between consistent iron chelation and reduced prevalence of endocrine complications in children with transfusion-dependent thalassemia major.

Comparable findings were reported by Bilgin *et al.* [16], who demonstrated that irregular or inadequate use of deferasirox was associated with a higher prevalence of endocrine dysfunctions, including hypothyroidism and glucose intolerance. Their study emphasized that chelation not only reduces systemic iron burden but also lowers the risk of iron deposition in endocrine organs, thereby preventing long-term complications. Similarly, Dhamija *et al.* [17], in their three-year experience with Indian children on deferasirox, observed that patients with good compliance had significantly fewer endocrine complications compared to those with poor adherence. They concluded that consistent chelation therapy is essential to prevent iron overload-related damage to the thyroid, pancreas, and parathyroid glands. In our cohort, altered glucose tolerance was observed in 20.9% of patients. The breakdown of glucose abnormalities in our cohort revealed that impaired fasting glucose was more

common than impaired glucose tolerance and none had overt diabetes which was consistent with prior reports that glucose dysregulation in thalassemia often begins with subclinical abnormalities before progressing to frank diabetes. Iron deposition in pancreatic β -cells is known to cause oxidative stress, impaired insulin secretion, and peripheral insulin resistance. In their recent longitudinal study, de Sanctis *et al.* [18] have demonstrated progression from impaired fasting glucose to overt diabetes in thalassemia patients, underscoring the importance of early detection and monitoring.

In our cohort, poor compliance with chelation therapy was significantly associated with a higher prevalence of endocrine abnormalities. While this cross-sectional association cannot establish causality, prior longitudinal studies (e.g., Bilgin *et al.* [16], Dhamija *et al.* [17], and Belhoul *et al.* [13]) have demonstrated that consistent chelation therapy reduces systemic iron burden and lowers the risk of endocrine complications. Thus, our findings align with existing evidence, but the preventive role of chelation therapy should be attributed to these earlier studies rather than inferred from the present design.

While our study design and sample size limit the feasibility of a fully adjusted multivariable analysis, an exploratory logistic regression adjusting for age and serum ferritin confirmed that poor chelation adherence was independently associated with endocrine abnormalities. This strengthens the robustness of our findings, though larger multicentre studies are required to validate these associations and account for additional confounders.

Chelation therapy plays a decisive role in reducing the risk of endocrine complications in thalassemia. Our findings, consistent with prior studies, demonstrate that poor compliance to chelation is strongly associated with higher rates of hypothyroidism, glucose intolerance, and hypoparathyroidism. Regular adherence to chelation therapy is therefore essential to prevent iron-induced endocrine toxicity and improve long-term outcomes. This underscores the need for continuous patient and parent education, close monitoring of compliance, and early intervention strategies to ensure optimal outcomes in transfusion-dependent thalassemia major.

In our study, transfusion history was recorded as annual transfusion volume (ml) rather than number of blood units, due to the format of available records. Although transfusion volume provides an estimate of iron burden, reporting the number of transfusion units would have allowed more standardized comparisons across studies. Future research should incorporate both transfusion volume and unit count to better quantify transfusion burden and its correlation with iron overload.

Growth hormone was assessed using random levels only, without stimulation testing. Given the pulsatile nature of GH secretion, random measurements are not diagnostic and may underestimate or overestimate true deficiency. IGF-1 levels were not measured in our cohort

due to financial constraints, and growth percentiles were not analysed against ferritin in the present study. As such, these results are exploratory and may underestimate or overestimate true GH deficiency. Future studies incorporating stimulation testing and IGF-1 profiling are required to more accurately evaluate GH-IGF1 axis dysfunction in thalassemia and may help clarify the mechanistic links between iron burden, GH-IGF-1 axis dysfunction, and impaired growth in transfusion-dependent thalassemia. Also, recent evidence suggests a potential link between IGF-1 deficiency and glucose dysregulation in β -thalassemia major, indicating that disturbances in the GH-IGF-1 axis may contribute to metabolic complications beyond iron overload alone [19].

Socioeconomic and nutritional factors were not assessed in our study, and these may act as important confounders. Poor growth and irregular chelation adherence can both be influenced by family income, food insecurity, and overall nutritional conditions. Future studies should incorporate socioeconomic profiling and detailed nutritional assessment to better disentangle the relative contributions of iron overload vs. environmental and social determinants to endocrine dysfunction in thalassemia.

LIMITATIONS

This study is limited by its cross-sectional design and small, single-centre sample, which restrict causal inference and generalizability. Although serum ferritin is a convenient and widely available marker of iron overload, it is influenced by inflammatory processes and hepatic dysfunction, and may not accurately reflect tissue-specific iron deposition. More sensitive modalities such as MRI T2* are required to better characterize iron burden in endocrine organs. This limitation should be considered when interpreting the association between ferritin and endocrine dysfunction in our study. Our study did not include pubertal assessment (e.g., Tanner staging), which is a recognized limitation. Given that delayed puberty and hypogonadism are common endocrine complications in transfusion-dependent thalassemia, future longitudinal studies with older cohorts should incorporate systematic pubertal evaluation to better characterize the spectrum of endocrine dysfunction. Lastly, chelation adherence, our key exposure variable, was assessed using a combination of caregiver/patient self-report and medical record review. As self-report is subject to social desirability and recall bias, misclassification of adherence status cannot be excluded. Given the central role of chelation adherence in our findings, this limitation should be considered when interpreting the observed associations.

CONCLUSIONS

There is a critical need to improve caregiver awareness regarding the complications of iron overload and

the necessity of strict adherence to chelation therapy. In the present cross-sectional study, endocrine abnormalities were identified in 46.3% of patients with transfusion-dependent thalassemia major, with a significantly higher prevalence among those demonstrating poor adherence to chelation therapy. Serum ferritin levels were significantly associated with multiple endocrine parameters, particularly thyroid dysfunction and impaired glucose tolerance. These findings underscore the importance of regular endocrine surveillance alongside careful monitoring of chelation compliance in this high-risk population.

Nevertheless, the cross-sectional nature of the study limits causal inference and precludes assessment of long-term outcomes. Additionally, the statistical analysis was restricted to univariable correlations and group comparisons. Future large-scale, multicentre studies incorporating multivariable regression analyses are warranted to better account for potential confounders and to validate these associations.

DISCLOSURES

1. Institutional review board statement: This study was approved by the Ethics Committee of the Institutional Ethics Committee of S.N. Medical College, Agra (approval decision Ref. No. SNMC/IEC/2020/140, dated: 12.05.2020).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.
5. Informed consent to publish the cases was obtained from the parents of the thalassaemic children.

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