

Early Pituitary Dysfunction in Thalassemia: Insights from the Thyrotroph Thyroxine Resistance Index (TT4RI) and TSH Index (TSHI)

Yan Li

First Affiliated Hospital of GuangXi Medical University

Zhenming Fu

303 Hospital of People's Liberation Army

Shenglun Xiao

303 Hospital of People's Liberation Army

Hong Chen

First Affiliated Hospital of GuangXi Medical University

Xiaolin Yin

303 Hospital of People's Liberation Army

Lei Wang

303 Hospital of People's Liberation Army

Shuang Li

303 Hospital of People's Liberation Army

Shiwu Cheng

303 Hospital of People's Liberation Army

Zuojie Luo

luozuojie@gxmu.edu.cn

First Affiliated Hospital of GuangXi Medical University

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Abstract

Background: Thalassemia patients with iron overload often develop a "mixed" hypothyroidism involving both primary thyroid and pituitary failure, but no widely accepted method exists to assess the pituitary component.

Objectives: To evaluate whether TT4RI and TSHI provide insights into early pituitary dysfunction in thalassemia patients, particularly those with subclinical hypothyroidism (SCH) and those with apparently normal thyroid function.

Methods: In this retrospective case-control study, we enrolled 335 thalassemia patients (209 transfusion-dependent [TDT] and 126 non-transfusion-dependent [NTDT]) and 124 healthy controls. TT4RI and TSHI were calculated from thyroid function tests, including thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3). Elevated TT4RI (>66.52, 95th percentile of controls) and TSHI (>3.71) were compared between SCH and euthyroid patients.

Results: In euthyroid TDT patients, TT4RI and FT3/FT4 ratio were significantly higher than in controls, and this elevation was significant only in those aged ≥ 10 years. Among SCH patients ($n=32$, TSH <10 $\mu\text{IU/mL}$, normal FT4), TT4RI and TSHI were elevated in 81.3% (26/32) and 53.1% (17/32), respectively, versus 3.9% (8/206) and 7.3% (15/206) in euthyroid patients (both $P<0.001$). No correlation was found with ferritin levels.

Conclusions: TT4RI and TSHI are frequently elevated in thalassemia patients with SCH, suggesting that altered pituitary sensitivity to thyroid hormone feedback may be common in this population. Among euthyroid patients aged ≥ 10 years, TT4RI was higher in TDT patients than in controls, suggesting pituitary dysfunction may occur before thyroid function is within the normal range.

1. Introduction

Thalassemia is a hereditary hemolytic anemia caused by defects in globin genes. It is primarily classified into transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) based on clinical severity [1, 2]. Advances in transfusion therapy and iron chelation have significantly improved life expectancy, making chronic organ complications due to iron overload a central challenge in clinical management. Endocrine glands are sensitive to iron deposits, leading to hypogonadism, growth retardation, hypothyroidism, hypoparathyroidism, glucose profile anomalies, adrenal insufficiency, reduced bone mineral density [3]. Endocrine disorders are among the most frequent complications in patients with transfusion-dependent β -thalassemia [4], occurring even in patients with satisfactory ferritin levels or cardiac T2* values [5].

Hypothyroidism is one of the most common endocrine disorders in thalassemia patients [6]. In TDT patients, reported rates range from 6% to 35%, and they remain considerable in NTDT patients [1, 7]. Iron overload is the core pathological mechanism: free iron can directly damage thyroid follicular cells,

reducing thyroid hormone synthesis (primary hypothyroidism). At the same time, iron deposits in the pituitary and hypothalamus, disrupting feedback regulation (central hypothyroidism) [6, 8]. As a result, hypothyroidism in thalassemia is conceptualized as a "mixed disorder" encompassing both components (primary hypothyroidism and central hypothyroidism) [9].

This mixed pathophysiology presents a clinical dilemma. Although primary hypothyroidism would typically drive thyroid stimulating hormone (TSH) elevation, the concomitant pituitary suppression may prevent TSH from rising adequately. Consequently, a patient with both primary and central hypothyroidism may have a lower TSH level than a patient with primary hypothyroidism. Standard guidelines for the general population typically recommend initiating levothyroxine therapy when TSH reaches 10 $\mu\text{IU/mL}$ [10]. In thalassemia, however, guidelines have lowered this threshold to 8 $\mu\text{IU/mL}$ [2].

Univariate reference ranges for TSH and thyroid hormones have limitations in guiding clinical decisions for patients with subtle thyroid dysfunctions [11]. Advances in mathematical modeling of pituitary-thyroid feedback control have led to the development of calculated parameters—such as the secretory capacity of the thyroid gland, the sum activity of peripheral deiodinases, and TSH index—that provide a more nuanced assessment of thyroid homeostasis [11]. These approaches have been applied in various clinical settings, including subclinical thyroid disease and non-thyroidal illness syndrome [1]. The thyrotroph thyroxine resistance index (TT4RI), first introduced by Yagi et al. in 1997 [12], and the TSH index (TSHI), developed by Jostel et al. in 2009 [13], have been used as a marker of pituitary sensitivity. Both indices increase when the pituitary becomes less sensitive to thyroid hormone, meaning a lower FT4 level is required to trigger a given TSH response [12, 13]. These indices have been studied in various clinical settings, including obesity, metabolic syndrome, type 2 diabetes, and critical illness, where they provide information about HPT axis function not apparent from TSH alone [14, 15].

In this study, we examined whether TT4RI and TSHI could provide insights into early pituitary dysfunction in thalassemia patients, focusing on those with subclinical hypothyroidism as well as those with apparently normal thyroid function.

2. Materials and Methods

2.1 Study Design and Participants

This single-center, retrospective case-control study was conducted at the 923rd Hospital of the Joint Logistics Support Force. The study protocol was approved by the Institutional Ethics Committee (Approval Number: 923LL-KY-2025LW-011-03). Informed consent was waived due to the retrospective nature of the study.

We enrolled 335 patients with confirmed thalassemia from the Department of Hematology between January 1, 2020, and May 31, 2025. Patients were categorized as TDT ($n = 209$) or NTDT ($n = 126$) based on transfusion requirements. The control group consisted of 124 healthy individuals who underwent routine health check-ups at the same center during the same period.

Inclusion criteria for thalassemia patients were: 1) confirmed genetic and clinical diagnosis of thalassemia; 2) complete thyroid function tests: TSH, FT4, FT3; 3) negative thyroid antibodies in patients with thyroid dysfunction. Thyroid antibodies include thyroid peroxidase antibody (TPOAb), thyroglobulin antibodies (TgAb) and thyrotropin receptor antibody (TRAb).

Exclusion criteria for all participants were: 1) history of thyroidectomy or radioiodine therapy; 2) known pituitary or hypothalamic diseases; 3) acute critical illness or infection at the time of testing; 4) use of medications interfering with thyroid function (e.g., amiodarone, lithium) within the past three months; 5) pregnancy.

2.2 Data Collection and Definitions

Demographic and clinical data, including age, sex, height, weight, thalassemia type, transfusion regimen, chelation therapy, hemoglobin, ferritin, liver function, splenectomy history, and diabetes mellitus status were extracted from electronic medical records. Genotypes were determined by gap-PCR and reverse dot-blot hybridization.

Thyroid function tests (TSH, FT4, FT3) were measured by chemiluminescent immunoassay (BECKMAN COULTER AU5800). Because reference ranges varied across testing batches (TSH upper limit: 4.75–5.91 $\mu\text{IU/mL}$; FT4 upper limit: 16.02–22.00 pmol/L ; FT3 upper limit: 5.70–7.37 pmol/L), we applied batch-specific reference ranges to define thyroid dysfunction for each patient.

Thyroid Dysfunction Definitions:

Overt Hypothyroidism: TSH > patient-specific upper limit of normal (ULN) with low FT4.

Subclinical Hypothyroidism (SCH): TSH > patient-specific ULN with normal FT4.

Central Hypothyroidism: Low or inappropriately normal TSH with low FT4.

Euthyroid: TSH within patient-specific ULN.

We defined mixed hypothyroidism for descriptive purposes as SCH accompanied by elevated TT4RI (> 66.52), indicating concurrent pituitary resistance to thyroid hormone feedback. This definition is exploratory and should not be interpreted as a validated diagnostic criterion.

TT4RI and TSHI were calculated as follows [12, 13]:

$$\text{TT4RI} = \text{FT4 (pmol/L)} \times \text{TSH (\mu IU/mL)}$$

$$\text{TSHI} = \ln \text{TSH (\mu IU/mL)} + 0.1345 \times \text{FT4 (pmol/L)}$$

The FT3/FT4 ratio was calculated as an indicator of peripheral deiodinase activity [11].

Growth and BMI were assessed using WHO growth standards for children and Chinese guidelines (WS/T 428-2013) for adults.

2.3 Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 25.0. Normality was assessed using the Shapiro-Wilk test. Normally distributed data are presented as mean $\pm$ SD; non-normally distributed data as median (IQR). Comparisons were made using Kruskal-Wallis H test with post-hoc Dunn's test, Chi-square test, or Fisher's exact test as appropriate. Cut-off values for TT4RI (> 66.52) and TSHI (> 3.71) were derived from the 95th percentile of healthy controls. A two-tailed $P < 0.05$ was considered statistically significant. Considering the known influence of age on thyroid function in thalassemia [16], analyses were stratified by age (< 10 vs. ≥ 10 years). To address sample size limitations in subgroup analyses, we combined TDT and NTDT patients into a single thalassemia cohort after confirming consistent results between subgroups.

3. Results

3.1. Baseline Characteristics

The study included 209 TDT patients, 126 NTDT patients, and 124 healthy controls (Table 1). Age differed significantly across groups ($P < 0.05$), reflecting the different natural histories of TDT and NTDT. Ferritin levels were significantly higher in the TDT group than in the NTDT group ($P < 0.001$). TSH and FT4 were significantly different between thalassemia patients (combined TDT+NTDT) and healthy controls (all $P < 0.001$).

Table 1
Baseline Characteristics of the Study Population

Characteristic	TDT (n = 209)	NTDT (n = 126)	Control (n = 124)	P-value
Overall				
Age (years)	11 (8,14.5)	22 (14,34)	23 (18,30.7)	***
<10 years, n (%)	78 (37.3%)	14 (11.1%)	14 (11.3%)	
Age (years)	7 (5.75, 8)	7.5 (4, 9)	7.5 (5.75, 9)	0.569
≥ 10 years, n (%)	131 (62.7%)	112 (88.9%)	110 (88.7%)	
Age (years)	13 (12,17) ^{a, c}	24 (16,34.5) ^b	24 (21,32.25)	
Male, n (%)	107 (51.9%)	32 (25.4%)	76 (61.3%)	
SF(ng/mL)	3015 (1584.5, 4261)	666.4 (233.2, 1403.5)	Not tested	***
Hb	80 ± 14	85 ± 21	-	
Liver Dysfunction	142 (67.9%)	108(85.7%)	0	
Splenectomy	41 (19.6%)	36 (28.6%)	0	
Diabetes Mellitus	7 (3.3%)	2 (1.6%)	0	
TSH (μIU/mL)	2.75 (1.91, 4.11) ^a	2.39 (1.78, 3.59) ^a	1.83 (1.36, 2.56)	
FT4 (pmol/L)	13.72 (11.22, 15.72) ^a	13.83 (10.87,15.99) ^a	15.65 (12.87, 17.17)	
FT3 (pmol/L)	5.42 (4.97,6.14) ^c	5.12 (4.46, 5.92) ^{a, b}	5.57 (5.11,6.03)	
Footnotes: Data are median (IQR) or n (%). P-values by Kruskal-Wallis or Chi-square test. ***P < 0.001. Superscripts indicate significant post-hoc differences (P < 0.05): a vs. Control; b vs. TDT. c vs. NTDT. SF: Serum Ferritin. Hb: Hemoglobin. For patients with TDT, Hb means pre-transfusion hemoglobin, and for patients with NTDT, Hb means steady-state hemoglobin. TSH:thyroid stimulating hormone. FT4: free thyroxine. FT3: free triiodothyronine.				

Clinical characteristics are summarized in Table 1. In the TDT group, pre-transfusion hemoglobin was 80 ± 14 g/L; liver dysfunction was present in 142 patients (67.9%); splenectomy in 41 (19.6%); diabetes in 7 (3.3%); regular iron chelation adherence in 116 (55.5%). In the NTDT group, steady-state hemoglobin was 85 ± 21 g/L; liver dysfunction in 108 (85.0%); splenectomy in 36 (28.3%); diabetes in 2 (1.6%). Growth retardation or short stature was observed in 39 TDT patients (18.7%) and 22 NTDT patients (17.3%); wasting/underweight in 46 TDT patients (22.0%) and 53 NTDT patients (14.6%). Genotype distributions are presented in Table 1B.

Table 1
B. Genotype distribution in TDT and NTDT patients

Genotype	TDT (n = 209)	NTDT (n = 126)
β-globin		
β0/β0	114 (54.5%)	2 (1.6%)
With α-globin	10 (4.8%)	0
β0/β+	72 (34.4%)	11 (8.7%)
With α-globin	8 (3.8%)	2 (1.6%)
β0/HbE	11 (5.3%)	9 (7.1%)
With α-globin	1 (0.5%)	0
β0/βN	2 (1.0%)	7 (5.6%)
With α-globin	0	3 (2.4%)
β+/β+	3 (1.4%)	3 (2.4%)
β+/HbE	-	1 (0.8%)
α-globin		
--SEA/αCSa	7 (3.3%)	76 (60.3%)
--SEA/-α3.7	-	11 (8.7%)
--SEA/αα	-	3 (2.4%)
αCSa/αα	-	2 (1.6%)
--SEA/-α4.2	-	2 (1.6%)

3.2. Progressive Thyroid Axis Impairment Revealed by Age Stratification

Analysis of euthyroid patients, stratified by age, showed no significant differences in thyroid parameters among TDT, NTDT, and control groups in the < 10 years subgroup (all $P > 0.05$). In the ≥ 10 years euthyroid subgroup (Table 2, Fig. 1), clear abnormalities emerged. Compared to controls, both TDT and NTDT groups had significantly lower FT4 ($P < 0.001$) and higher TSH ($P < 0.001$). TT4RI was significantly elevated only in the TDT group compared to the control group ($P < 0.001$). The FT3/FT4 ratio was also significantly elevated only in the TDT group ($P < 0.001$). No significant difference in median TSHI was found among groups ($P > 0.05$).

Table 2
Comparison of Thyroid Function Parameters among Euthyroid Participants in the Age ≥ 10 Years Subgroup

Characteristic	TDT (n = 112)	NTDT (n = 94)	Control (n = 110)
Age (years)	13 (12,17) ^{a, c}	25 (16,35.3) ^b	24 (21,32.3)
S F (ng/mL)	3065 (1458, 4921) ^c	595 (215, 1169) ^b	Not tested
Hb (g/L)	86 $\pm$ 2	81 $\pm$ 1	-
TSH (μ IU/mL)	2.49 (1.82, 3.59) ^a	2.17 (1.59, 3.01) ^a	1.73 (1.33, 2.42)
FT4 (pmol/L)	13.40 (10.82, 15.20) ^a	14.13 (10.89,15.87) ^a	15.91 (12.98, 17.17)
FT3 (pmol/L)	5.41 (4.91,6.09) ^c	5.04 (4.46, 5.64) ^{a, b}	5.53 (5.1,5.91)
TSHI	2.75 (2.28,3.07)	2.67 (2.17, 3.12)	2.65 (2.20,3.09)
TT4RI	34.25 (22.67, 45.64) ^a	28.96 (19.83, 44.31)	25.85 (19.78, 36.65)
FT3/FT4 Ratio	0.40 (0.34,0.49) ^{a, c}	0.35 (0.30, 0.47) ^b	0.35 (0.31, 0.43)
Footnotes: Data are median (IQR). Includes only euthyroid participants. P-value by Kruskal-Wallis H test. Superscripts indicate significant post-hoc differences (P < 0.05): a vs. Control; b vs. TDT; c vs. NTDT. SF: Serum Ferritin. Hb: hemoglobin. For patients with TDT, Hb means pre-transfusion hemoglobin, and for patients with NTDT, Hb means steady-state hemoglobin. TT4RI and TSHI cut-off values from 95th percentile of healthy controls.			

Footnotes: (a) Free Thyroxine (FT4), (b) thyrotroph thyroxine resistance index (TT4RI), and (c) FT3/FT4 ratio among healthy controls, non-transfusion-dependent thalassemia (NTDT) patients, and transfusion-dependent thalassemia (TDT) patients who were biochemically euthyroid. Data are presented as median with interquartile range. *P < 0.05. The findings illustrate the mixed disorder pattern in TDT: lower FT4, elevated TT4RI (indicating reduced pituitary sensitivity), and an increased FT3/FT4 ratio (suggesting compensatory peripheral deiodination).

3.3. Characteristics of TT4RI and TSHI in SCH Patients

Among the 335 thalassemia patients, 32 met the criteria for SCH (TSH above patient-specific ULN with normal FT4 and TSH < 10 μ IU/mL)—17 TDT and 15 NTDT patients. Their clinical and laboratory characteristics are summarized in Table 3. Using the 95th percentile values from healthy controls as cut-offs (66.52 for TT4RI, 3.71 for TSHI), we compared the proportion of patients with elevated indices between SCH and euthyroid patients. Because the diagnostic performance of TT4RI and TSHI was consistent between TDT and NTDT subgroups (TT4RI: 82.4% vs. 80.0%, P for interaction = 0.86; TSHI: 52.9% vs. 53.3%, P for interaction = 0.98), we combined the two subgroups for primary analysis to enhance statistical power (Table 4, Fig. 2). In the combined cohort, TT4RI was elevated in 81.3% (26/32) of SCH patients, significantly higher than in euthyroid patients (3.9%, 8/206, P < 0.001). TSHI was elevated in 53.1% (17/32) of SCH patients, significantly higher than in euthyroid patients (7.3%, 15/206,

P < 0.001). In contrast, FT4 alone (using the 5th percentile of healthy controls, 10.6 pmol/L as cut-off) did not effectively distinguish SCH from euthyroid patients (all P > 0.05).

Table 3
Clinical and laboratory characteristics of patients with SCH

Characteristic	TDT (n = 17)	NTDT (n = 15)
Age (years)	14 (10–43)	23 (10–47)
Male/Female	11/6	6/9
SF (ng/mL)	4892 ± 623	1792 ± 349
Pre-transfusion Hb (g/L)	73 ± 5	-
steady-state Hb (g/L)	-	73 ± 4
Liver dysfunction (%)	82.4% (14/17)	80.0% (12/15)
Splenectomy (%)	17.6% (3/17)	40.0% (6/15)
Diabetes (%)	5.9% (1/17)	13.3% (2/15)
Growth retardation	88.2% (15/17)	40.0% (6/15)
Low BMI	88.2% (15/17)	93.3% (14/15)
Thyroid antibodies	All negative	All negative
Footnotes: SF: Serum Ferritin. Thyroid antibodies include: thyroidperoxidase antibodies, antithyroglobulin antibody and thyrotropin receptor antibody. Growth retardation: height-for-age Z-score < -2 (children) or short stature in adults. Low BMI: BMI-for-age Z-score < -2 (children) or BMI < 18.5 kg/m ² (adults).		

Table 4
Performance of TT4RI and TSHI in Differentiating SCH Patients from Euthyroid Patients

Groups	n	TT4RI > 66.52 n (%)	P-value^	TSHI > 3.71 n (%)	P-value^
TDT-SCH	17	14 (82.4%)	< 0.001	9 (52.9%)	< 0.001
TDT-Euthyroid	112	6 (5.4%)		14 (12.5%)	
NTDT-SCH	15	12 (80.0%)	< 0.001	8 (53.3%)	< 0.001
NTDT-Euthyroid	94	2 (2.1%)		1 (1.1%)	
Thalassemia-SCH (combine)	32	26 (81.3%)	< 0.001	17 (53.1%)	< 0.001
Thalassemia-Euthyroid (combine)	206	8 (3.9%)		15 (7.3%)	
Footnotes: SCH*: Subclinical Hypothyroidism (TSH < 10 µIU/mL with normal FT4). ^P-value for difference between SCH and Euthyroid groups within the same population (Chi-square/Fisher's exact test). Cut-offs: TT4RI > 66.52, TSHI > 3.71 (95th percentile of controls). Subgroup analysis showed consistent results between TDT and NTDT patients (P for interaction = 0.86 for TT4RI and 0.98 for TSHI).					

Footnotes: The bar graph shows the proportion of patients with TT4RI > 66.52 or TSHI > 3.71 (95th percentile of healthy controls) in the combined thalassemia cohort, stratified by thyroid status (SCH vs. euthyroid). Elevated TT4RI and TSHI were more frequently observed in SCH patients than in euthyroid patients (TT4RI: 81.3% vs. 3.9%; TSHI: 53.1% vs. 7.3%). Data suggest that altered pituitary sensitivity to thyroid hormone feedback may be common in thalassemia patients with SCH. ***P < 0.001 vs. euthyroid group within the same population (Chi-square test).

4. Discussion

For TT4RI, Lu Y et al. (Front Endocrinol, 2023) reported that in healthy Chinese adults, TT4RI values typically range from 28.61 (IQR: 20.93–38.78) in men and 30.66 (IQR: 22.23–41.98) in women [19]. Our healthy control group showed a median TT4RI of 25.85 (IQR: 19.78–36.65), which is consistent with these literature values. For TSHI: Jostel et al. (Clin Endocrinol, 2009) originally defined the reference range with a mean of 2.7 and standard deviation of 0.676 in healthy individuals [12]. Our healthy controls demonstrated a median TSHI of 2.65 (IQR: 2.20–3.09), which falls well within this reported range. Our 95th percentile cut-off of 3.71 is close to the upper limit of normal established in previous reports.

In this descriptive study, we examined the distribution of TT4RI and TSHI in thalassemia patients with SCH. Subgroup analysis showed consistent results in TDT and NTDT patients (TT4RI: 82.4% vs. 5.4% and 80.0% vs. 2.1%), allowing us to combine the two groups for primary analysis. In the combined analysis, 81.3% of thalassemia patients with SCH had elevated TT4RI, while this was observed in only 3.9% of

euthyroid thalassemia patients. TSHI showed a similar but less pronounced pattern: 53.1% of SCH patients had elevated TSHI versus 7.3% of euthyroid patients. Elevated TT4RI and TSHI were significantly more common in SCH patients than in euthyroid patients, suggesting that altered pituitary sensitivity to thyroid hormone feedback may be a frequent feature in thalassemia patients with SCH. This observation is consistent with the established pathophysiology of iron overload. Iron can settle in both the thyroid and the pituitary [6, 8], hitting hormone production and feedback control. TT4RI and TSHI – which combine FT4 and TSH into one number – might be picking up the combined effect of both problems.

4.1. Age-Dependent Thyroid Axis Impairment and Evidence of Early Pituitary Dysfunction

A notable finding of this study is the age-dependent pattern of thyroid axis impairment. In patients under 10 years of age, we observed no significant differences in any thyroid parameter among TDT, NTDT, and control groups. However, in patients aged ≥ 10 years, clear abnormalities emerged. Compared to controls, both TDT and NTDT patients had significantly lower FT4 levels, indicating that primary thyroid injury—likely due to iron deposition in the thyroid gland—is a shared feature across thalassemia subtypes.

However, the pattern of pituitary involvement differed between the two groups. The TT4RI in euthyroid TDT patients ($n = 112$) was significantly higher than that in controls (34.25 vs. 25.85, $P < 0.001$), suggesting that pituitary sensitivity to thyroid hormone feedback may be blunted even before overt thyroid dysfunction becomes apparent. This observation implies that pituitary damage may occur early in the course of iron overload, potentially preceding primary thyroid failure. It also suggests that TT4RI might serve as a sensitive marker for detecting subclinical pituitary dysfunction in thalassemia patients who are still biochemically euthyroid. These patients may warrant closer monitoring for the subsequent development of overt hypothyroidism.

Notably, in the ≥ 10 years euthyroid subgroup, while both TDT and NTDT patients exhibited lower FT4 levels compared to controls, the elevations in TT4RI and FT3/FT4 ratio were observed exclusively in the TDT group. This differential pattern suggests that the degree of pituitary involvement may differ between TDT and NTDT. The greater iron burden in TDT patients—reflected by significantly higher ferritin levels (3065 vs. 595 ng/mL in NTDT)—may contribute to more pronounced pituitary dysfunction in this group. These findings highlight the heterogeneity of thyroid axis impairment across thalassemia subtypes and suggest that TT4RI may be particularly useful in identifying early pituitary dysfunction in the more heavily iron-loaded TDT population.

Another notable finding was the elevated FT3/FT4 ratio, which was observed exclusively in the TDT group. This ratio is a surrogate marker of peripheral deiodinase activity, particularly type 2 deiodinase, which converts T4 to the more biologically active T3 [11]. In our TDT patients, the elevated FT3/FT4 ratio may represent a compensatory mechanism to maintain tissue function. This may partly explain why patients with significant biochemical abnormalities sometimes remain asymptomatic.

4.2. The High Prevalence of Central Hypothyroidism in Thalassemia

Our findings align with previous reports highlighting the high prevalence of central hypothyroidism in thalassemia patients. A cross-sectional study by Seow et al. [17] found that 63.6% of transfusion-dependent thalassemia patients had central hypothyroidism, suggesting that pituitary involvement is the dominant mechanism of thyroid dysfunction in this population. Similarly, a comprehensive review by Carsote et al. (2022) concluded that hypothyroidism in patients with major β -thalassemia is mostly related to pituitary gland involvement, rather than primary thyroid failure [3].

However, while these earlier studies relied largely on conventional biochemical criteria (low or inappropriately normal TSH with low FT4) to diagnose central hypothyroidism, our approach using TT4RI and TSHI provides a more nuanced assessment of pituitary sensitivity. The fact that over 80% of SCH patients had elevated TT4RI suggests that the pituitary component may be even more prevalent than previously recognized. Moreover, our observation that TT4RI was already elevated in euthyroid TDT patients suggests that pituitary dysfunction may begin earlier than the clinical diagnosis of central hypothyroidism would indicate. This earlier detection, however, does not by itself justify intervention — it simply identifies a subgroup that may warrant closer observation.

4.3. Clinical Implications, Limitations, and Future Directions

The clinical implications of these findings are twofold. First, our data suggest that TSH alone may be an unreliable marker of thyroid status in thalassemia patients due to the high prevalence of pituitary dysfunction. This is consistent with the thalassemia-specific guidelines that have already lowered the treatment threshold to 8 μ IU/mL [2]. Second, TT4RI may serve as a useful screening tool to identify thalassemia patients who are at risk of developing clinically significant hypothyroidism, even when their TSH remains within the normal range. Our findings with TT4RI and TSHI extend this approach to the thalassemia population, suggesting that mathematically derived indices may complement conventional TSH-based assessment in complex patient groups.

Nevertheless, several important caveats must be emphasized. First, this is a retrospective, single-center study with a limited sample size (32 SCH patients). Second, we lack an independent reference standard for pituitary function — such as pituitary MRI (to assess iron deposition) or TRH stimulation testing. Therefore, we cannot determine whether elevated TT4RI or TSHI truly reflects structural pituitary damage or a functional adaptation. Third, the absence of longitudinal data means we cannot assess whether patients with elevated TT4RI or TSHI would benefit from levothyroxine therapy or whether these indices predict treatment response. These limitations mean that our findings should be considered exploratory and descriptive rather than definitive.

4.4. Iron Chelation and Thyroid Function

The lack of correlation between serum ferritin and thyroid parameters, consistent with some reports [18], may reflect limitations of ferritin as a marker of tissue iron burden [19]. Non-transferrin-bound iron and labile plasma iron may be more relevant mediators of endocrine tissue damage [20], and their relationship with TT4RI/TSHI warrants investigation in future studies. Previous studies suggest that intensification of iron chelation may improve thyroid function in iron-overloaded patients [5, 21]. Iron chelation can not only prevent worsening but also potentially reverse thyroid dysfunction [21]. Whether intensified chelation affects TT4RI or TSHI remains an open question requiring prospective investigation. In our cohort, among the 116 TDT patients adherent to regular chelation, ferritin levels tended to be lower than in non-adherent patients, though the cross-sectional nature of our data precludes causal inference.

4.5. Study Limitations

This study has several important limitations:

Retrospective, single-center design: Limits generalizability and cannot establish causality.

Small sample size: The SCH subgroup comprised only 32 patients, limiting statistical power and subgroup analyses.

Lack of independent reference standard: No pituitary MRI, TRH stimulation, or other gold-standard assessment of pituitary function was available.

No longitudinal data: We cannot assess treatment outcomes or whether TT4RI/TSHI changes over time.

No iodine assessment: Iodine status was not measured, although all patients resided in a non-iodine-deficient area.

5. Conclusion

TT4RI and TSHI are frequently elevated in thalassemia patients with SCH, suggesting that altered pituitary sensitivity to thyroid hormone feedback may be common in this population. In addition, among euthyroid patients aged ≥ 10 years, TT4RI in the TDT group was significantly higher than that in both the NTDT group and the control group. This finding suggests that pituitary damage may already occur in TDT patients while thyroid function is still within the normal range. Based on these observations, we suggest that thalassemia patients with elevated TT4RI, even when thyroid function tests remain normal, may warrant closer monitoring for the subsequent development of overt hypothyroidism.

In summary, TT4RI may offer valuable insights into early pituitary dysfunction in thalassemia, whether in TDT patients with apparently normal thyroid function or in thalassemia patients with SCH. However, the clinical utility of these indices remains to be established; prospective studies with independent reference standards are needed. For now, they should be considered exploratory tools that complement standard thyroid function assessment.

Declarations

Ethics Statement

The studies involving humans were approved by the Institutional Ethics Committee of

the 923rd Hospital of the Joint Logistics Support Force of the People's Liberation Army. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because of the retrospective nature of the study.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Consent to Participate: Informed consent was waived due to the retrospective nature of the study.

Data Availability: The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Author Contribution

Yan Li: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Project Administration. Zhenming Fu: Investigation, Resources, Data Curation. Shenglun Xiao: Data Curation, Resources, Investigation. Hong Chen: Software, Validation, Writing – Review & Editing. Xiaolin Yin: Data Curation, Resources. Lei Wang: Project Administration, Visualization, Resources. Shuang Li: Investigation, Resources, Data Curation. Shiwu Cheng: Supervision, Funding Acquisition, Writing – Review & Editing. Zuojie Luo: Supervision, Funding Acquisition, Writing – Review & Editing, Conceptualization. All authors contributed to the article and approved the submitted version.

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Data Availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

Fig 1

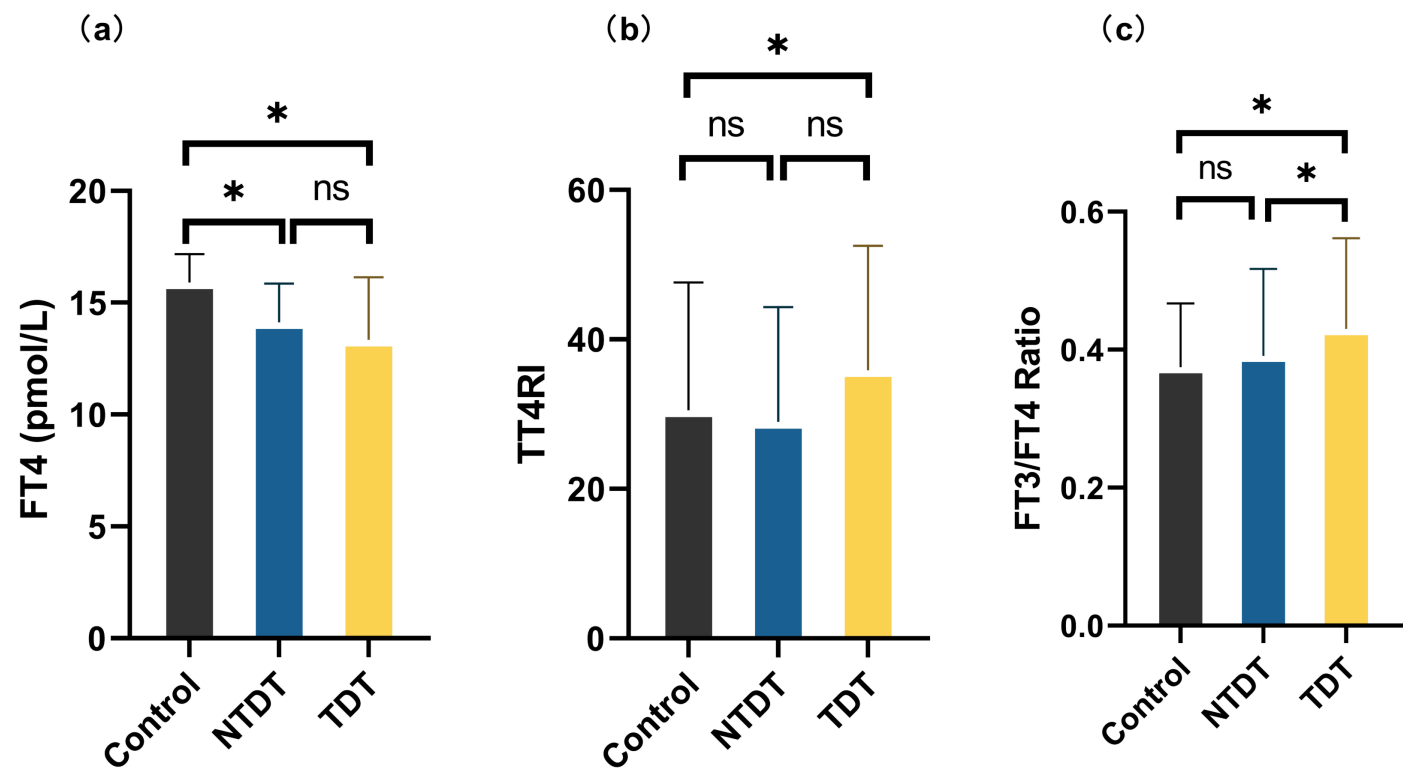


Figure 1

Thyroid Axis Characteristics in Euthyroid Thalassemia Patients (Age ≥10 Years).

Footnotes: (a) Free Thyroxine (FT4), (b) thyrotroph thyroxine resistance index (TT4RI), and (c) FT3/FT4 ratio among healthy controls, non-transfusion-dependent thalassemia (NTDT) patients, and transfusion-dependent thalassemia (TDT) patients who were biochemically euthyroid. Data are presented as median with interquartile range. *P < 0.05. The findings illustrate the mixed disorder pattern in TDT: lower FT4, elevated TT4RI (indicating reduced pituitary sensitivity), and an increased FT3/FT4 ratio (suggesting compensatory peripheral deiodination).

Fig.2

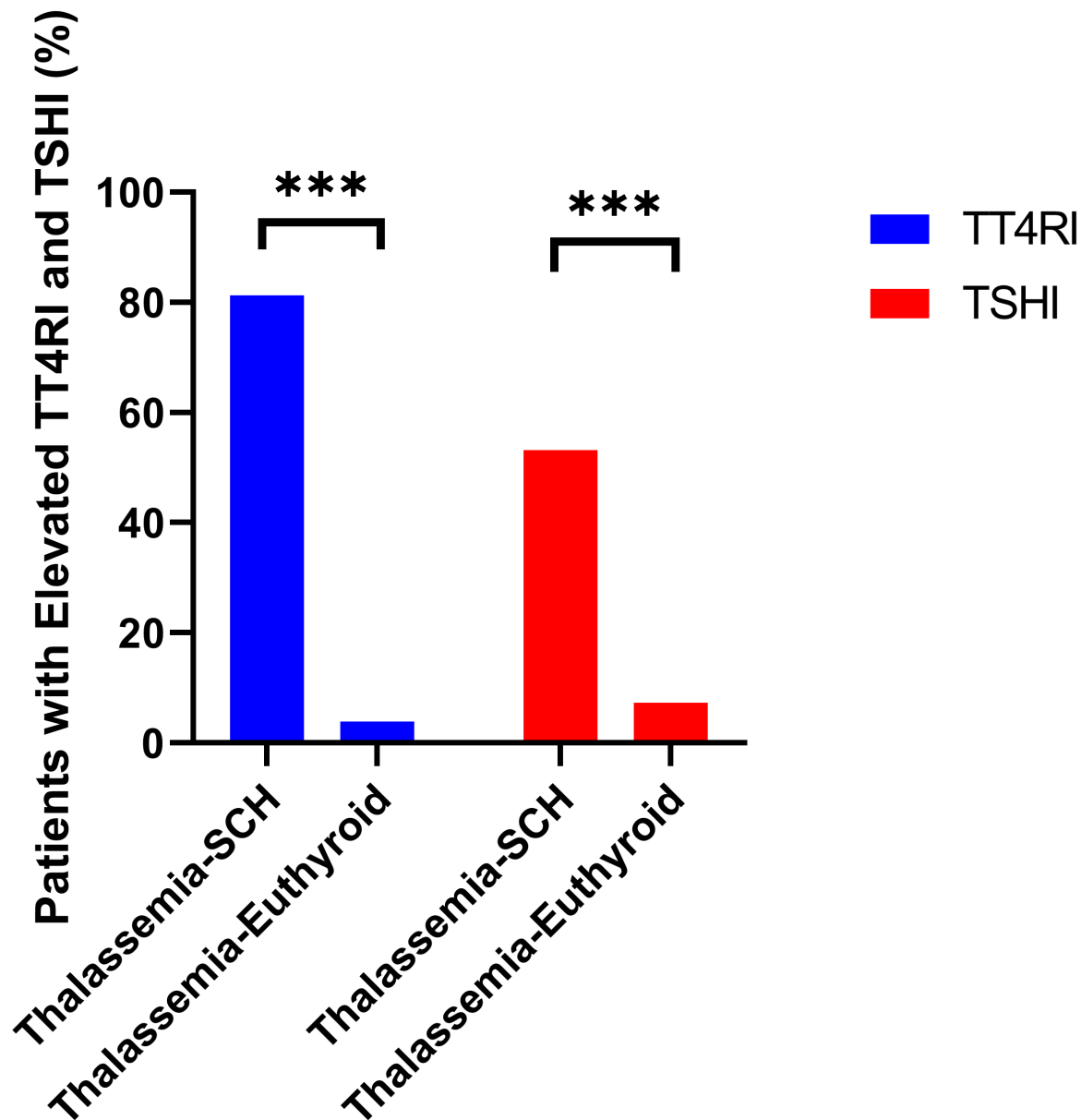


Figure 2

Proportions of thalassemia patients with elevated TT4RI and TSHI in SCH and euthyroid groups.

Footnotes: The bar graph shows the proportion of patients with TT4RI >66.52 or TSHI >3.71 (95th percentile of healthy controls) in the combined thalassemia cohort, stratified by thyroid status (SCH vs. euthyroid). Elevated TT4RI and TSHI were more frequently observed in SCH patients than in euthyroid

patients (TT4RI: 81.3% vs. 3.9%; TSHI: 53.1% vs. 7.3%). Data suggest that altered pituitary sensitivity to thyroid hormone feedback may be common in thalassemia patients with SCH. ***P < 0.001 vs. euthyroid group within the same population (Chi-square test).