



Framework for the comprehensive screening for endocrine disorders in patients with transfusion-dependent thalassemia in low-resource settings

Saadia Abbas¹ · Muhammad Osama Khan¹ · Aahan Arif¹ · Hafsa Majid² · Lena Jafri² · Aisha Shaikh³ · Khadija Humayun⁴ · Aysha Habib Khan^{2,5} · Bushra Moiz²

Received: 5 March 2025 / Accepted: 14 August 2025 / Published online: 24 September 2025

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Abstract

Despite advances in managing transfusion-dependent thalassemia (TDT), endocrine complications continue to be a major concern, especially in low-resource settings where delayed diagnosis and inadequate screening lead to higher morbidity. This study aims to develop a practical, evidence-based framework for screening endocrine and metabolic disorders in TDT patients aged 1–16 years in resource-limited environments. Five major guidelines were reviewed, including those from the Thalassemia International Federation (2025), UK Thalassemia Standards (2023), Italian Society for Thalassemia (2022), International Network on Endocrine Complications in Thalassemia (2013), and Oakland Children's Hospital (2012). A multidisciplinary panel of experts analyzed these guidelines along with local data to create a structured screening approach. Local literature highlights significant endocrine challenges, including stunted growth (50.5%, 95% CI: 29.6–71.4) and hypogonadism or delayed puberty (45.8%, 95% CI: -6.5–98.2). Less common issues include hypothyroidism (19.9%), hypoparathyroidism (12.8%), and impaired glucose metabolism (5.0%). A comparative analysis reveals that all guidelines emphasize the importance of clinical evaluation and laboratory testing. However, there are variations in testing panels and screening protocols. The proposed framework highlights clinical assessment as the first step, followed by targeted laboratory testing when resources are limited. Key recommendations include optimizing transfusion and iron chelation to reduce complications, as well as age-specific screening for early detection of endocrinopathies in patients with TDT. This consensus-based approach seeks to standardize endocrine screening for TDT patients, promoting early intervention and referral. Successful implementation will involve training healthcare providers to improve thalassemia care in low-resource settings.

Introduction

Transfusion-dependent thalassemia (TDT) is an autosomal recessive disorder characterized by the specific type of globin chains involved. The most severe form, homozygous beta thalassemia, results from a deficiency of β -globin chains in adult hemoglobin (HbA), leading to the production of unpaired α -globin chains. Therefore, individuals with TDT typically present with severe anemia before their first year of life, necessitating lifelong blood transfusions and iron chelation therapy to sustain life [1]. Sub-optimally managed patients can develop iron overload due to increased iron absorption, red cell transfusions, and inadequate iron chelation, leading to complications such as cardiac siderosis, hepatosplenomegaly, bone deformities, and growth retardation. Iron

Saadia Abbas, Muhammad Osama Khan and Aahan Arif contributed equally to this work.

✉ Aysha Habib Khan
aysha.habib@aku.edu

- ¹ Medical College, Aga Khan University Hospital, Karachi 74800, Pakistan
- ² Department of Pathology and Laboratory Medicine, Aga Khan University, Karachi 74800, Pakistan
- ³ Department of Medicine, Aga Khan University Hospital, Karachi 74800, Pakistan
- ⁴ Department of Pediatrics and Child Health, Aga Khan University, Karachi 74800, Pakistan
- ⁵ Department of Pathology & Laboratory Medicine Medical College, The Aga Khan University, Stadium Road, P.O. Box 3500, Karachi 74800, Pakistan

overload, particularly unbound iron, generates free radicals that damage organs, including endocrine glands. Recently, endocrinopathies have emerged as the most significant complication of TDT, occurring at rates two to three times higher than those of cardiac and hepatic disorders. The pancreatic beta cells, parathyroid gland, and anterior pituitary are especially vulnerable, resulting in irreversible damage that leads to diabetes mellitus, hypoparathyroidism, hypogonadism, short stature, and acquired hypothyroidism [2]. Improving the quality of life for patients with TDT is a key management goal. The most recent and extensive study conducted in Italy revealed that in high-income countries, the risk of developing a new endocrinopathy within five years is approximately 10%, even among patients with satisfactory ferritin levels, liver iron concentration (LIC), and cardiac T2* values [3]. It is believed that this risk is higher and occurs earlier in low-income countries. Therefore, close monitoring of growth and pubertal development is essential for the early detection of abnormalities and timely intervention [4].

In Pakistan, it is estimated that 5,000 children are born each year with TDT, and the carrier frequency ranges from 5 to 7%, which amounts to 10 million carriers in the country [5]. However, due to insufficient carrier detection programs, the actual figure may be even higher. Factors contributing to the high carrier rate include a lack of awareness, illiteracy, consanguineous marriages, and limited access to healthcare, particularly in rural areas [6]. Globally, prevention efforts focus on increasing public awareness through premarital and antenatal screening at 10–12 weeks of pregnancy to detect affected fetuses [7]. Though the prenatal diagnosis of thalassemia has been available in Pakistan since 1994 [8], it failed to reduce the prevalence of the disease. The management of TDT is well-established and has improved over the years. However, most clinical guidelines (GLs) are based on standards from high-income countries (HICs), where issues with healthcare access and financial constraints are less significant than in low- and middle-income countries (LMICs) and low-income countries (LICs). GLs for initiating, dosing, and scheduling chelation therapy in TDT patients are often not adhered to in LMIC and LIC, including Pakistan, which lacks local GLs.

This study reviews the literature and available GLs for the early detection of complications. The aim is to provide a practical, evidence-based framework for screening metabolic and endocrine complications in TDT patients aged 1 to 16 years. These recommendations could serve as a model for other LMICs facing similar healthcare challenges, offering a framework to improve patient care in resource-limited settings.

Methodology

Formulating a team

The Bone and Mineral Diseases Research Group at Aga Khan University is dedicated to improving the management of metabolic bone and mineral disorders, which are significant health concerns in LMICs, including Pakistan. Among these, thalassemia has emerged as a high-priority area requiring focused efforts to enhance the quality of life for affected patients. Through a cross-sectional study assessing bone health in patients with TDT, the need for coordinated, comprehensive action was identified, rather than isolated, fragmented efforts. Specifically, there is a pressing need for GLs tailored to low-resource settings that appeal to a diverse group of healthcare professionals.

To address this, we formed a multidisciplinary team consisting of hematologists, chemical pathologists, endocrinologists, bone health specialists, and research associates with experience in managing patients with TDT. This collaborative effort aims to develop practical, evidence-based GLs for improving care in resource-constrained environments as follows:

I. Collection of Evidence on Endocrine Complications in Pakistan

Literature Search.

To assess the endocrine status related to TDT in Pakistan, the research team (AA, SA, and MOK) conducted a comprehensive literature review in June 2025. The search was performed across PubMed, PakMediNet (a local database), and Google Scholar using search strings divided into three main components: thalassemia and its synonyms, endocrine complications and their synonyms, and Pakistan along with related terms. The data range spanned from 2005 to 2025. These components were combined to formulate the following search string.

("Beta Thalassemia Major" OR "Beta-Thalassemia Major" OR "beta-Thalassemia" [MeSH] OR "Thalassemia") AND ("Endocrine complications" OR "Short Stature" OR "Thyroid" OR "Parathyroid" OR "Endocrine" OR "Diabetes" OR "Stunting" OR "Gonad" OR "Puberty" OR "Growth") AND ("Pakistan").

Selection Criteria.

Articles were selected based on the PICO (Population, Intervention, Comparison, Outcome) framework, using the following criteria: Population: Patients in Pakistan with TDT; Intervention: Not applicable; Comparison: Patients without TDT; Outcomes:

Endocrine complications of TDT, including issues related to growth, puberty, gonadal function, thyroid and parathyroid function, mineral metabolism, and pancreatic function. Proper management of transfusion and chelation therapies is the primary goal that healthcare providers and patients in low-income countries should pursue to better manage endocrinological complications. Therefore, studies were also included if they outlined limitations in optimal therapy, such as transfusion regime, pre-transfusion Hb, age at the start of chelation therapy, serum ferritin, liver iron concentration (LIC), and cardiac T2*.

Study selection.

All articles identified using the search strategy were imported into Microsoft Excel, where duplicates were removed. The titles and abstracts were screened according to eligibility criteria, followed by in-depth evaluation of the full-text articles. Only those articles that met the inclusion criteria were considered for the final review.

Data Extraction and Management:

Research associates extracted relevant data into Microsoft Excel, including the author's name, year of publication, location of study, participant ages, and the prevalence of endocrine disorders. The prevalence was computed by pooling the reported frequencies in various studies, and the population denominator was the total number of patients with TDT who were studied for a specific endocrinopathy. This data served as the basis for understanding the spectrum and frequency of endocrine complications in TDT patients in Pakistan.

II. Identification of GLs for Endocrine Complications

A comprehensive review of internationally published GLs (GLs) was performed to assess the global standards of care for patients with TDT and related endocrine complications. This enabled us to compile evidence-based, feasible recommendations tailored to resource-limited settings. Four major GLs were reviewed and synthesized: GLs for the management of

transfusion-dependent β -thalassemia in Thalassemia International Federation, 5th edition (2025) (TIF) [9], Standards for the clinical care of children and adults with thalassemia in the UK 4th edition (2023) (UKTSS) [10], the International Network on Endocrine Complications in Thalassemia (2013) (ICET) [11] and Standard of care GLs in the Children's Hospital and Research Centre, Oakland (2012) (USS) [12]. A recently published good clinical practice paper by the Italian Society for Thalassemia and Hemoglobinopathies (SITE) was also considered for data synthesis [13]. The key recommendations from these GLs were consolidated into a summary to inform the development of our region-specific guidance for early detection and management of endocrine complications in low-resource settings.

III. Consensus Recommendations from Experts.

Based on a detailed analysis of the literature on TDT in Pakistan and a review of available international GLs, the team collaborated to establish consensus-driven, age-specific recommendations for screening and managing endocrine complications in patients with TDT. These recommendations aim to be practical and applicable in low-resource environments, ensuring that critical care is accessible to the affected populations.

Results

- I. Limitations in the management of conventional therapy: Table 1 presents literature data on pre-transfusion Hb values, age at the initiation of the regular transfusion regimen, age at the start of chelation therapy, ferritin levels, LIC, and cardiac T2*, highlighting the limitations of conventional treatments with transfusions and chelation therapy in low-income countries. These reports showed that patients with TDT began transfusions before the age of 1 year. However, they were anemic, with low pre-transfusion hemoglobin and a delayed onset of chelation therapy. Consequently,

Table 1 Risk factors for endocrinopathies in patients with transfusion-dependent thalassemia in Pakistan

Parameters observed Mean $\pm$ SD	Units	Patients studied			Desirable targets for comparison	Reference
		n	Age in years [†]	Results		
Age at first transfusion	years	350	10.8 $\pm$ 7.2	1.95 $\pm$ 1.3	< 2	[14]
Age at chelation	years	100	5-20	6.54 $\pm$ 3.24	< 2	[15]
Pre-transfusion hemoglobin	g/dL	367	10.6 $\pm$ 3.3	7.66 $\pm$ 1.34	9-10.5	[16]
Serum ferritin	ng/ml	79	10.8 $\pm$ 4.5	4236.5 $\pm$ 2378.3	<1000	[17]
Liver iron concentration (LIC) ^{††}	mg Fe/g dry weight	-	-	-	<3-5	-
Cardiac T2* Median (range)	ms	83	19 (5-45)	10.5 (2 to 45)	>20	[18]

[†] As reported in the study as either mean $\pm$ SD or median (range)/range

^{††}No report

patients experienced ferritinemia and cardiac siderosis. Overall, studies indicated reduced access to optimal transfusion and chelation regimens, posing a risk for developing endocrine complications.

II. Findings from Review of Literature on Endocrine Complications from Pakistan

Demographics

Table 2 outlines the prevalence of endocrine complications in patients with thalassemia in a total of 26 articles published in Pakistan from 2005 to 2025. Endocrinopathies were reported in 1061 of 4274 patients with TDT (24.8%)[14, 16, 19–42]. The age range varied from less than 1 year to 30 years; however, in most studies, the mean age was approximately 10 years. The age and sex for those patients who had endocrinopathies were not clearly defined.

Major Endocrine complications

These studies reported the prevalence of five major endocrinopathies, including stunted/abnormal growth [14, 16, 19–27], delayed puberty/hypogonadism[19, 24, 28, 29], hypothyroidism[20, 21, 24, 30–36], hypoparathyroidism/disturbance in bone metabolism[19, 24, 30, 37–39], and impaired glucose metabolism/diabetes mellitus[19, 20, 24, 30, 36, 40–42]. The pooled prevalence of 26 studies showed short stature in 50.5% (95% CI: 29.6–71.4) and hypogonadism/delayed puberty in 45.8% (95% CI: –6.5–98.2) patients with TDT. These were the two most significant challenges. Comparatively less frequent endocrinopathies included hypothyroidism, hypoparathyroidism, and diabetes mellitus, as observed in 19.9% (95% CI: 11.9–27.8), 12.8% (95% CI: –0.12–25.9), and 5.0% (95% CI: –2.2–12.2) of the patients, respectively (Figure 1). Bony deformities in 21.4% of the patients [21, 25], along with a decrease in bone age[23] and bone density[22], were also reported. Studies did not discriminate between hypogonadism vs. delayed puberty. A gender bias was observed as delayed puberty was reported with male predominance [28] (83.6% vs. 54.7%) in one report, while female predominance [29] (66% vs. 25.7%) was observed in the other study, though the mean age was approximately 18 years in both studies. This disparity was probably secondary to the different clinical criteria used in defining delayed puberty and hypogonadism. Only one study reported sex hormone assays, revealing low serum testosterone in 56.4% of males and low serum estradiol in 19.5% of females [28]. Five studies[31–35] differentiated subclinical vs. overt hypothyroidism in 460 patients and reported subclinical disease in 127 of

460 (27.6%) and overt disease in only 3 (0.8%) of the patients. Similarly, only one study[37] reported subclinical hypoparathyroidism and observed predominantly subclinical disease in 367 patients (34% vs 3% clinical disease). Impaired glucose metabolism was observed in 85 of 531 patients (16.1%) across three studies [40–42], while diabetes mellitus was reported in three of 531 patients (0.6%).

III. Review of Good Clinical Practice/GLs on Thalassemia

A consolidated summary of these recommendations from the four main GLs [9–12] and the guidance paper [3] is outlined in Table 3.

a) Growth disorders

There is a general recommendation to use growth charts as a screening tool for early detection of declining growth velocities and percentiles, followed by a recommended intervention and action plan. The age at initial screening varies among these GLs, from the first visit at a thalassemia center [9, 10, 13, 43] from 5 years of age or 3 years post-transfusion [12]. There is a clear consensus that growth monitoring should be performed biannually or annually, using a growth chart. Laboratory testing is recommended for stunted growth, including routine biochemical tests, as well as assessment of thyroid function, growth hormone, and calcium and phosphorus levels. Evaluation of bone age [10, 43] and an MRI of the pituitary gland [11, 13] is additionally suggested for growth failure.

b) Hypothyroidism

Laboratory testing for TSH and FT4 should be performed annually for all patients starting at age 9. However, some also consider testing as early as age 5[12], or later at 10 for screening[10]. For primary disease, anti-TPO and thyroid ultrasound are suggested as the next level testing [9]. In cases of secondary disease, hormone assays and MRI of the pituitary gland are advised to rule out pituitary failure as a reason for hypothyroidism [9, 13].

c) Hypoparathyroidism

Serum calcium (corrected for albumin) and phosphorus should be checked in all patients at age 10[9–11, 13], or as early as 5 years[12], following USS GLs. Opinions differ on PTH testing, with some viewing it as a secondary test for hypocalcemia [9, 13] and others as a primary screening test for hypoparathyroidism[10–12]. Additionally, some consider vitamin D[10, 12], magnesium[10], and alkaline phosphatase[10] as screening tests.

d) Impaired glucose metabolism

Table 2 Risk factors for endocrinopathies in patients with transfusion-dependent thalassemia in Pakistan

A								
Physical growth abnormalities								
Year [reference]	City	N	Age (years) range Mean ($\pm$ SD)	Short stature or abnormal growth N (%)	Bone deformity N (%)	Serum IGF-1 Bone density	Growth hormone/ bone age	
2007[19]	D I Khan	123	0.33-21 -	65 (52.8)	-	-	-	
2013[26]	Rawalpindi	100	6-14 9.94 $\pm$ 2.93	57(57)	-	-	-	
2017[24]	Karachi	72	10-20 -	54(75.0)	-	-	-	
2017[21]	Peshawar	150	0.5-20	34(22.7)	63(42.0)	-	-	
2018[20]	Peshawar	100	Not Reported	81(81.0)	-	-	-	
2018[25]	Karachi	200	10-32 -	-	12(6.0)	-	-	
2018[16]	Karachi	367	5-17 10.6 $\pm$ 3.3	240 (65.4)	-	-	-	
2018[27]	Faisalabad	90	6-10 7.85 $\pm$ 1.50	37(41.1)	-	-	-	
2019[22]	Lahore	65	5-11	-	-	Reduced	-	
2019[14]	Lahore, Multan, Karachi, Peshawar	350	0.5-28 10.8 $\pm$ 7.2	32 (9.14)	-	-	-	
2019[23]	Peshawar	156	9-15 11.9 $\pm$ 2.2	-	-	-	Reduced	
B								
Hypogonadism								
Year [reference]	City	N	Age (years) range Mean ($\pm$ SD)	Sex n	Low Testosterone/ estradiol N (%)	Low FSH N (%)	Low LH N (%)	Delayed puberty N (%)
2007[19]	D I Khan	123	0.33-21 -	-	-	-	-	2(1.7)
2017[24]	Karachi	72	10-20 -	-	-	-	-	51(70.8)
2017[28]	Hayatabad	97	15-32 18.0 $\pm$ 3.0	55 Male 41 Female	31(56.4) 8 (19.5)	21(38.2) 6(14.6)	23 (41.8) 9 (21.9)	46 (83.6) 23(54.7)
2021[29]	Rawalpindi & Islamabad	120	13-30 18.9 $\pm$ 4.2	70 Male 50 Female	- -	- -	- -	18 (25.7) 30 (60)
C								
Hypothyroidism (HypoT)								
Year [reference]	City	N	Age (years) range		Subclinical N (%)	Overt N (%)	Total N (%)	
2010[35]	Lahore	70	5-14 9.2 $\pm$ 2.6		17 (24.2)	1(1.4)	18 (25.7)	
2014[30]	Islamabad	96	- 13.8 $\pm$ 3.8		-	-	13(13.5)	
2016[34]	Rahim Yar Khan	144	5-16 7.97 $\pm$ 2.73		42 (29.2)	3 (2.08)	45(31.2)	
2016[31]	Rawalpindi	56	4-18 7.16 $\pm$ 4.06		21(37.5)	0	21(37.5)	
2017[21]	Peshawar	150	0.5-20 -		-	-	2(1.3)	

Table 2 (continued)

2017[32]	Peshawar	115		13-32	25(21.7)	0	25(21.7)	
				18.5				
2017[33]	Faisalabad	75		5-15	22(29.3)	0	22(29.3)	
2017[24]	Karachi	72		10-20	-	-	10(13.8)	
2018[20]	Peshawar	100		Not Reported	-	-	10(10.0)	
2021[36]	Multan	160		5-12	-	-	24(15.0)	
D								
Hypoparathyroidism (HPT) & associated issues								
Year [reference]	City	N	Age (years) range Mean (±SD)	Low Micronutrients				HPT
				Zn N (%)	Ca N (%)	PO4 N (%)	Vit-D N (%)	N (%)
2007[19]	D I Khan	123	0.33-21	-	-	-	-	2(1.7)
			-					
2014[30]	Islamabad	96	13.8±3.8	-	-	-	-	23(24)
			5-15					
2015[39]	Karachi	63	10.8±3.5	-	-	-	-	14(22.2)
			5-24					
2016[38]	Karachi	36	12.6 ± 5.9	-	24(66.6)	7(19.4)	26(72.2)	5(13.8)
			10-20					
2017[24]	Karachi	72	-	-	-	-	-	2 (2.7)
			5-17					
2019[37]	Karachi	367	-	-	155(42.2)	17(4.6)	287(78.2)	203 (55.3) *
E								
Abnormal Glucose metabolism								
Year [reference]	City	N		Age (years) range Mean (±SD)		IGT		DM
2007[19]	D I Khan	123		0.33-21		-		1(0.8)
				-				
2014[30]	Islamabad	96		13.8±3.8		-		1(1.1)
				10-20				
2017[24]	Karachi	72		-		-		4(5.6)
				5-15		63 (24.2)		-
				-				
2018[20]	Peshawar	100		Not Reported		-		5(5.0)
2018[40]	Lodhran	120		3-17		15(12.5)		-
				8.0±4.2				
2020[41]	Rahim Yar Khan	151		11-22		7(4.6)		3(2.0)
				13.32 ± 2.08				
2021[36]	Multan	160		5-12		-		41 (25.6)
				8.58±1.98				

*192 patients (34%) were subclinical, and 11 (3.0%) were primary HPT

HypoT (hypothyroidism); HPT (Hypoparathyroidism); DM (Diabetes Mellitus); IFG (Impaired fasting glucose); GHD (Growth hormone deficiency); VDD (vitamin D deficiency); IGT (Impaired Glucose Tolerance); Zn (Zinc); Ca (calcium); PO4 (Phosphate); Vit-D (Vitamin D)

Initial testing with fasting glucose and/or an oral glucose tolerance test should begin at age 10, then be performed every two years until the age of 16[10–13] or 18[9], and annually thereafter. Cutoffs for impaired metabolism and diabetes are clearly outlined in all guidance documents. Additional tests that may aid in diagnosing diabetes include

fructosamine[9], Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)[9, 13], and insulin secretion tests[11]. Hemoglobin A1c should not be used for diagnosis [9] because HbF (and not HbA) is the main hemoglobin in patients with TDT.
e) Delayed puberty

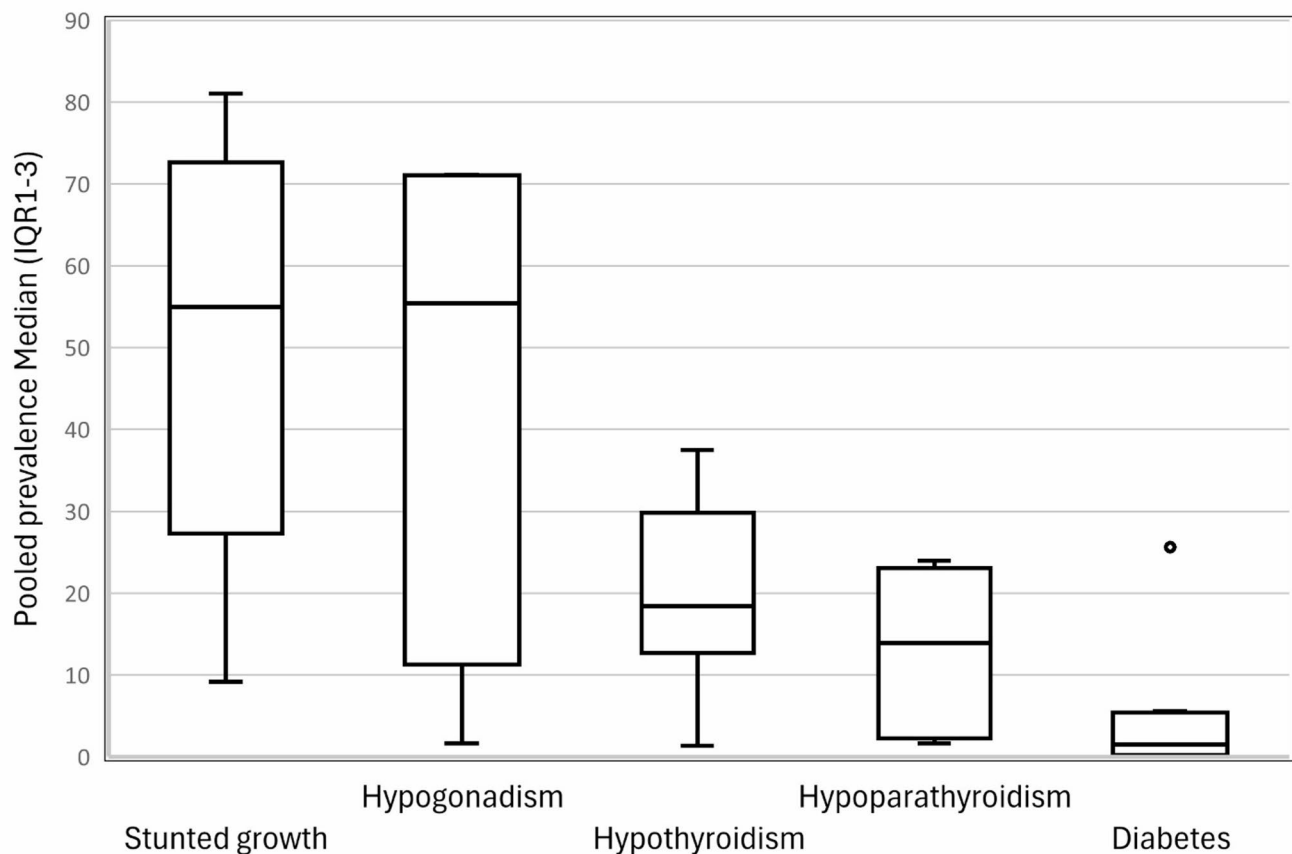


Fig. 1 Pooled prevalence of five main endocrine complications in patients with transfusion-dependent thalassemia in Pakistan as derived from published data

Growth rate and Tanner staging (assessment of breast and testicular development in females and males, respectively) are the initial evaluations for delayed puberty. These should be performed every six months, starting at age 13 in females and 14 in males [9]. Screening age may also be as early as 10 years [10] or 12 years [11–13]. In cases of delayed puberty, FSH, LH, and estradiol/testosterone should be measured to confirm the diagnosis. Additionally, some suggest thyroid and GH assays [9, 13] for delayed puberty. Assessment of bone age and pelvic ultrasound (in females) should also be performed. For suspected pituitary disease, GnRH [9, 11–13] and a pituitary MRI are also recommended [9, 13].

f) Female hypogonadism

A menstrual diary should be kept and reviewed every six months. If a patient develops oligomenorrhea or amenorrhea, evaluation for hypogonadism should be initiated. This includes laboratory tests for FSH, LH, and 17-beta estradiol, along with a pelvic ultrasound to differentiate between primary and secondary causes. Additional tests for thyroid function,

prolactin, androgens, and a pregnancy test may be helpful [9]. Secondary disease should be confirmed through pituitary hormone assays [13] and MRI [9].

g) Male hypogonadism

The evaluation requires laboratory testing for FSH, LH, and testosterone [9–11, 13], although there is a suggestion to test only for testosterone [12] as well. A pituitary hormonal assay and MRI are necessary to rule out hypogonadism caused by pituitary failure [9, 13].

IV. Consensus Recommendations from Experts for Low-Resource Settings

Our multidisciplinary experts have developed age-specific screening protocols and evidence-based endocrine assessments for TDT patients in resource-limited settings, such as Pakistan. These guidelines, summarized in Table 4, aim to provide practical and resource-efficient strategies for the early detection of endocrine issues in thalassemia patients. Studies conducted in Pakistan have identified risk factors for endocrinopathies, as shown in Table 1. Therefore, we recommend

Table 3 Comparative analysis of for screening endocrinopathies in patients with transfusion-dependent thalassemia at various ages[9–13]

Age for screening	Clinical assessment					Laboratory/Radiology assessment and referral*				
	TIF 2025	UKTSS 2023	SITE 2022	ICET 2013	USS 2012	TIF 2025	UKTS 2023	SITE 2022	ICET 2013	USS 2012
First assessment (TIF/UKT S/SITE/ICE T)	First level: Growth (Standing/ Sitting height, weight, BMI, growth rate, Tanner staging and genetic target) monitoring through the growth velocity chart 	Same as TIF-screening	Same as TIF-screening	Same as TIF-screening Frequency:  6-12 monthly	Same as TIF-screening Frequency:  6-12 monthly	Blood work				
5 years or 3 years of transfusion (USS)						Second level: Disease and general assessment. If the above tests are normal, then IGF-1 and GH stimulation test (x 2)	IGF-1, and IGF BP-3 Growth hormone stimulation test	Essential: Routine tests†† Addition al: IGF1 dosage/dynamic test For GH deficiency: Morning cortisol /ACTH, FT4, TSH	For stunting: Routine biochemistry Ca, PO4, albumin, FT4, TSH, IGF-1, and Cortisol Growth hormone stimulation test	For stunting: Dietary assessment, Ca, PO4, albumin, FT4, TSH, IGF-1, and IGF BP-3
						√	-	√	√	√ and culture
To identify growth and height disorders 	Frequency:  6 monthly					Radiology				
						-	Bone age	GH def: MRI 	Bone age MRI 	-
									Refer	Refer

Table 3 (continued)

5 years (USS) 9 years (TIFF/SITE/ICE T) 10 years (UKTS)  To identify hypothyroidism 	-	-	-	-	-	Blood work <i>First level:</i> TSH, FT4 Frequency:  12 monthly <i>Second level:</i> For primary disease: Anti-TPO For secondary disease: Morning cortisol /ACTH, prolactin, IGF-1, testosterone (M) and estradiol (F)	Same as TIF-screening	Same as TIF-screening Other tests: Anti-TPO, TGA, Morning cortisol /ACTH, For secondary Disease: Morning cortisol /ACTH, FSH, LH, prolactin, IGF-1, testosterone (M) and estradiol (F)	Same as TIF-screening	Same as TIF-screening
						<i>Second level:</i> Primary disease: Ultrasound thyroid Secondary disease: MRI 		Same as TIF		
									Refer	Refer

Table 3 (continued)

10 years (TIF/UKTS/SI TE/ICET) 5 years (USS)						Blood work				
						<i>First level:</i> Fasting glucose/ OGTT every 2 years till 18 years, then annually.	OGTT Frequen cy:	Same as TIF- screening Impaired fasting: same as TIF	OGTT Preferabl e: Insulin secretion	OGTT Frequen cy: Same as UKTS
										
To identify a glucose metabolism disorder 						HOMA-IR for insulin resistance. Serum fructosamine . <i>Second level:</i> Impaired fasting: OGTT C-peptide	 At age 10, and then every two years till 16, and then annually		Frequen cy: Same as UKTS	
To identify hypo- Parathyroidis m 						<i>First level:</i> Ca (corrected), P Frequency:  12 monthly <i>Second level:</i> Hypocalcemi a: PTH, Mg, Cr, 25-OH Vit D, 24-hr urine Ca	Same as TIF- screenin g Addition al: Vit-D, Mg, ALP Hypocalc emia: PTH	Same as TIF- screening Hypocalce mia: Same as TIF	Ca PO4 PTH	Ca Vitamin D PTH Frequen cy: Same as TIF
									Refer	Refer

Table 3 (continued)

	Delayed Puberty					Blood/other work				
	<i>First level:</i> Growth rate and Tanner Staging Frequency:  6 monthly	Tanner staging Menstrual history Frequency:  12 monthly	Same as TIF	Tanner Staging Frequency:  6 monthly	Tanner Staging Frequency:  6 monthly	<i>Second level:</i> FSH, LH, Testosterone (M)/Estradiol (F), TSH, FT4, IGF-1 Low Gn: GnRH stimulation test	Estradiol	FSH, LH, estradiol (F)/testosterone (M) Addition: TSH, FT4, prolactin, IGF-1	FSH, LH, estradiol (F)/testosterone (M) Low Gn: GnRH stimulation test	FSH, LH, Estradiol Low Gn: GnRH stimulation test
10 years (UKTS) 12 years (SITE/USS / ICET) 13 Years F 14 Year M (TIF)  To identify delayed puberty and hypogonadism 						<i>First level:</i> Bone age assessment Ultrasound pelvis (F) <i>Second level:</i> Low Gn: MRI brain 		Same as TIF	Bone age assessment. Ultrasound pelvis (F)	Bone age
	Hypogonadism					<i>Confirmatory:</i> FSH, LH, 17-beta oestradiol, <i>Additional:</i> TSH, FT4, prolactin, androgens, PT	FSH, LH, Estradiol	same as TIF + Cortisol, morning ACTH, IGF-1		Same as TIF
 6 monthly  Clinical evaluation										
						US pelvis Secondary disease: MRI pituitary with contrast		Bone age. Ultrasound pelvis.		
						<i>First level:</i> FSH, LH testosterone <i>Second level:</i> For pituitary disease: Morning cortisol/ACTH, TSH, FT4, prolactin (M), IGF-1	FSH, LH, Testosterone	18 years of age: Same as TIF Next tests: Prolactin, morning Cortisol, ACTH, FT4, TSH, IGF-1		Testosterone Frequency:  12 monthly
						US testis Secondary disease: MRI 		Bone age Secondary disease: MRI 		Bone age
								Other test PAP	Refer	Refer

Table 3 (continued)

*As the disorder is indicated by clinical assessment.†General assessment includesphlogosis indicators, hepatic and renal function, electrolytes, blood gases, total proteins with electrophoresis, physical and chemical examination of urine, screening for celiac disease, free thyroxine (FT4), thyroid-stimulating hormone (TSH), calcium (Ca), phosphorus (P), alkaline phosphatase, parathyroid hormone (PTH), and vitamin D. †† Same as † with addition of Pre-transfusion hemoglobin and C-reactive protein ¶Refer to an endocrinologist. ACTH (adrenocorticotrophic hormone), ALP (alkaline phosphate), anti-TPO (antithyroperoxidase), Cr (creatinine), F (female), FSH (follicle stimulating hormone), Gn (gonadotropin), HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), IGF BP3 (Insulin-like Growth Factor Binding Protein 3), IGF-1 (insulin-like growth factor-1), LH (luteinising hormone), M (male), MRI (magnetic resonance image), OGTT (oral glucose tolerance test), PO4 (phosphate), PT (pregnancy test), TGA (Tissue Transglutaminase). **Guidelines used:** Thalassemia International Federation, 5th edition (2025) (TIF), Standards for the clinical care of children and adults with thalassemia in the UK 4th edition (2023) (UKTSS), Italian Society for Thalassemia and Hemoglobinopathies (2022) (SITE), the International Network on Endocrine Complications in Thalassemia (2013) (ICET), Standard of care GLs in the Children's Hospital and Research Centre, Oakland (2012) (USS)

initiating growth monitoring as early as possible during infancy, once a diagnosis is confirmed. Given our limited resources, we suggest monitoring physical and reproductive health clinically, with laboratory tests performed only when needed based on significant clinical signs. However, initial laboratory screening remains essential for detecting hypothyroidism, hypoparathyroidism, and impaired glucose metabolism, as these conditions are often subclinical to start with. In such cases, we recommend minimal necessary testing, with additional tests considered if resources permit. Additionally, we advise healthcare providers in thalassemia centers to implement simple measures, such as evaluating and managing iron overload, adjusting diets, and treating calcium and vitamin D deficiencies. Patients identified at risk of endocrine complications should be referred to an endocrinologist for further management.

Discussion

Studies in Pakistan and similar low-resource settings have clearly shown that patients with TDT are chronically anemic despite blood transfusions. The desired targets include pre-transfusion hemoglobin levels between 9 and 10.5 g/dL, initiation of early iron chelation therapy at the age of 2 years, with the goals of maintaining serum ferritin below 1000 ng/mL and achieving a cardiac T2* of over 20 milliseconds. Iron overload in patients with TDT is a recurrent complication and has been reported from various LMICs.

TDT represents a complex clinical landscape, especially in resource-limited settings like Pakistan, where bone marrow transplantation, the only curative option, remains inaccessible for most due to high costs [44]. As a result, most patients rely on lifelong blood transfusions and iron chelation therapy. While these treatments have extended survival into adulthood, they carry a significant risk: progressive iron buildup in vital organs, including the heart, liver, and endocrine glands, which can lead to irreversible damage and reduced quality of life. The resulting endocrine

complications are diverse and debilitating, requiring urgent clinical attention [45]. Although endocrine testing is often cost-prohibitive in many settings, recent initiatives, such as the Thalassemia International Federation (TIF) [9] and SITE's [13] two-tiered testing approach, aim to improve accessibility without compromising diagnostic accuracy. Both strategies [9, 13] focus on building an organizational model based on initial diagnosis using simple, inexpensive tests that can be implemented at all centers caring for patients with TDT. The second-level diagnosis and treatment should be reserved for patients with abnormal results from the first level, involving a consultant endocrinologist and/or collaboration with other specialized centers, along with a clear management plan. The hub-and-spoke model for managing endocrine complications in patients with TDT offers the potential to ensure early diagnosis worldwide while centralizing complex cases requiring specialized staff and specific diagnostic tests, thereby reducing costs and increasing access to care.

Short stature is among the earliest and most noticeable effects of iron overload, characterized by a disproportionate upper-to-lower segment ratio, a concerning sign in pediatric TDT. Studies from Pakistan reveal alarming data, with up to 65% of affected children (aged 7–11 years) displaying stunted growth, often alongside severe iron overload (median serum ferritin exceeding 5000 ng/mL) [16]. This growth delay results from a complex interaction of chronic anemia, tissue hypoxia, chronic liver disease, iron overload, overchelation, and disrupted hormonal regulation (hypothyroidism, delayed puberty/hypogonadism) [46]. Notably, the growth hormone–IGF-1 axis is frequently affected, and nutritional deficiencies can worsen the condition [27]. The high rate of suboptimal therapy reported in nearly two-thirds of patients further exacerbates these issues [16], emphasizing the urgent need for affordable and consistent treatment options. A survey from 29 thalassemia centers in developing countries indicated that short stature was present in over 30% of 3,817 patients [47]. A similar high prevalence of growth abnormalities was reported from Iran (52%) [48], Iraq (34%) [49], and India (68%) [50]. The recently published GLs by TIF [9] and others [10–13] recommend

Table 4 Recommendations for Metabolic Bone Diseases & Endocrine Evaluation for Patients with Transfusion-dependent Thalassemia in Low-Resource Setups (essential workup is shown in bold)

Age: 1-8 years					
Growth	Growth charts	Every 6 months OR If the patient is stunted	Growth retardation	A child is considered short if: a. Height is < the 3 rd percentile for age and sex. b. Height is within normal, but growth velocity (GV) over 6-12 months is for: ≤1 year <25cm/yr 2-4 year <10cm/yr 5-8 year <5cm/yr Patient is excessively short for his/her mid-parental height after 2 years of age	Evaluate for associated factors: Pre-transfusion hemoglobin Proper iron chelation Nutrition Assessment Calorie intake Hepatosplenomegaly Hypothyroidism (TSH) SGPT IGF-1 assay X-ray Bone Age Psychological stress <i>Refer to an endocrinologist if there is faltering growth or abnormal results of any of the mentioned parameters.</i>
Age 9-16 years					
Screening	Evaluation/ tool	Frequency	Monitoring	Interpretation	Actions/referral
Starting age					
Growth 9-10 years	Growth Charts	Every 6 months	Pubertal growth spurt	A child is considered short if: a. Height is < the 3 rd percentile for age and sex. b. Height is within normal, but growth velocity (GV) over 6-12 months is <5cm/year Patient is excessively short for his/her mid-parental height after 2 years of age.	Essential laboratory tests: Serum Ca, P, AlkPO4, PTH, Vitamin D, Fasting Glucose, (followed by an OGTT as per need), SGPT, and FSH, Serum TSH, X-ray: Bone Age <i>Refer to an endocrinologist if GH deficiency is suspected or if there are abnormal results of any of the mentioned parameters.</i>
Hypothyroidism 9 years	May be asymptomatic. Clinical disease may show fatigue, retarded growth, weight loss/ increase in cold/ heat intolerance etc.)	Every year	TSH, FT4	Primary HypoT Sub-clinical Mild Overt FT4 N ↓ ↓ TSH ↑ ↑ ↑↑	Observation/optimization of iron chelation therapy. Repeat TSH after 3 months <i>Refer to an endocrinologist for further management/ TSH remains elevated after 3 months.</i>

Table 4 (continued)

Parathyroid & bone mineral abnormalities 10 years	May be asymptomatic. Symptoms of hypocalcemia, such as tetany, cardiac failure, bone pains, paresthesia, fractures, and bony abnormalities, may be present in clinical disease.	Every year	Essential: Ca, P Desirable/Next level for hypocalcemia: iPTH, Vitamin D	Primary HPT Subclinical Overt	Ca ↓ or N ↓	P ↑ ↑	PTH ↓ ↓	Vit-D ↓ ↓	Anemia and iron overload control A diet rich in calcium and low in phosphorus is advised. Lifestyle modification with emphasis on physical activity Daily recommendation: Calcium (800–1500 mg), Vitamin D replacement (3000-10,000 IU for 1-3 months and Calcitriol (0.25-2.0µg/dl in severe renal or liver disease)[9] <i>Refer to an endocrinologist if there are abnormal results of any of the mentioned parameters.</i>
Impaired glucose metabolism 10 years	Impaired fasting and impaired glucose tolerance may be asymptomatic. Symptoms of polyuria, polydipsia, and weight loss.	Every year	Essential: FBG Desirable: OGTT	Impaired fasting Impaired Glucose tolerance Diabetes	FBG mg/dL 100-126 - >126 On two events	RBG mg/dL - - >200 If symptomatic	OGTT mg/dL - 140-200 >200 After 2 hours	Follow a proper diet Assessment of iron burden Optimization of iron chelation <i>Refer to an endocrinologist if FBG> 126mg/dl (on two occasions) OR RBG >200mg/dl (with symptoms)</i>	
Puberty issues and gonadal dysfunction 13 years for girls and 14 years for boys.	Tanner staging And a menstrual diary	6 monthly	Delayed puberty Arrested puberty	Testis volume <4ml in males by 14 years Absent breast development (Tanner 2) in females by 13 years Lack of pubertal progression over a year or longer	Essential: FSH Desirable/next level: LH, FSH & Estradiol (girls)LH, FSH & Testosterone (boys)TSH <i>Refer to an endocrinologist if puberty is delayed or arrested.OR Abnormal results of any of the mentioned parameters</i> <i>Refer to an endocrinologist if Suspecting delayed/arrested pubertyOR Abnormal results of any of the mentioned parameters</i>				

monitoring growth and growth velocity using growth charts twice a year or annually, starting at the earliest possible age. If stunting is observed, more thorough laboratory testing for growth hormone, thyroid hormone, and metabolic bone disease is necessary, along with imaging to determine if the pituitary failure is the primary cause. The recommendations provided in this framework emphasize the monitoring of growth, evaluation of hepatosplenomegaly, maintenance of target pre-transfusion hemoglobin levels, nutritional intake, and optimization of iron chelation as inexpensive and straightforward measures that can be taken in any thalassemia center. Minimal laboratory tests, such as SGPT, TSH, and IGF-1, are suggested if stunting in early childhood is observed to promptly identify and treat underlying factors associated with retarded growth. The actual GH deficiency is relatively uncommon in patients with TDT and can only be confirmed by a complete diagnostic workup. More commonly, hypogonadism is the cause of slow growth velocity, and if a patient is failing to enter puberty, then management of this condition may significantly improve growth [51]. Thalassemia growth, especially in the 9–16-year age group, is affected by several factors. Therefore, we suggest more extensive but essential testing in adolescents aged 9–10 years to identify hormonal abnormalities associated with thyroid, parathyroid, glucose metabolism, and gonadal dysfunction, as well as liver disease, which may contribute to stunted height in this age group.

Hypothyroidism is a common complication of suboptimal iron chelation in patients with TDT because of the destruction of thyroid tissue due to iron deposition [51]. It is usually observed in the second decade as subclinical disease (high TSH, normal T4) and progresses to overt disease (high TSH and low T4) if left untreated. Because the symptoms are vague and nonspecific, the published GLs suggest laboratory testing for both TSH and T4 in all patients starting from the age of 9 years [9–13]. Studies in Pakistan have indicated a prevalence of almost 20% for subclinical hypothyroidism in patients with TDT, while the incidence of overt disease is <1% [20, 21, 24, 30–36]. This prevalence is higher compared to other LMICs like India (4.8%) [52] and Iraq (7.3%) [49]. The recommendations provided in this framework are based on the published data. It is also noticeable that appropriate iron chelation may reverse the initial stages of the disease; therefore, early detection and treatment are essential [51]. However, we do not suggest testing for autoimmune thyroiditis or central hypothyroidism as these are rare in patients with TDT [51, 52].

Hypoparathyroidism is also a significant complication in patients with TDT because of its complex relationship with bone metabolism. Parathormone primarily maintains calcium and phosphate balance by increasing intestinal absorption and renal resorption of calcium, while also

inhibiting phosphate resorption in the kidneys. Therefore, chronic parathormone deficiency due to iron toxicity leads to hypocalcemia and hyperphosphatemia in patients with TDT. Hypoparathyroidism can initially be subclinical and may gradually progress to an overt disease associated with cardiac arrhythmias, tetany, paresthesia, calcification in various organs, and brain fog. The prevalence of hypoparathyroidism ranges from 1 to 7% in different studies worldwide [45, 47, 53]. In contrast, a high pooled prevalence of 13% was reported in Pakistan [19, 24, 30, 38, 39], with a proportion of subclinical to clinical disease of 11:1 in one study [37]. All GLs recommend screening for calcium and phosphorus starting at age 10 years, as hypoparathyroidism is usually seen in the second decade in patients with TDT [9–13]. However, some suggest adding PTH and vitamin D tests to the primary screening tool [11, 12], while others recommend these as follow-up tests for patients who exhibit hypocalcemia [9, 13]. In this framework, calcium and phosphorus are suggested as primary tests, and care providers are encouraged to treat calcium and phosphorus deficiencies. As PTH and vitamin D tests are expensive, they are recommended for patients with abnormalities identified in primary screening, such as TIF [9] and SITE [13] recommendations.

Bone disease in thalassemia is unique, caused by marrow expansion, iron toxicity, nutritional deficiencies [54], chelation therapy, physical inactivity, endocrine dysfunction (including growth hormone, thyroid, parathyroid, pancreatic, and gonadal axes), and renal/hepatic impairment [55]. This multifaceted condition leads to significant health problems due to osteopenia, osteoporosis, fractures, and sarcopenia, affecting both children and adults [56]. The prevalence of osteoporosis was reported as 17% in patients with TDT in Taiwan [54], while the rate of low bone mineral density (BMD) exceeded 60% in a cohort of 210 patients with a mean age of 30 years in Thailand [57]. Data from Pakistan revealed an alarmingly high incidence of bone pain (80%) and fractures (13%) in 367 young patients aged 5 to 17 years [55]. Others have documented notable clinical findings, such as bone deformity [21, 25], decreased bone age [23], and reduced bone density [22], in patients with TDT in Pakistan. TIF suggested performing dual-energy X-ray absorptiometry (DXA) at age 10 year, every 6–12 months to monitor BMD [9]. TIF also emphasized the importance of anemia control, optimal iron chelation, lifestyle modification, and hormonal assessment and treatment (along with hormone replacement in patients with hypogonadism) to prevent and treat bone disease in patients with TDT. Additionally, regular blood transfusions reduce bone marrow expansion, thereby preventing significant cortical thinning and disruption of trabecular bone structure. Within this framework, we recommend maintaining normal calcium and vitamin D levels through lifestyle modifications

and nutritional supplements, as well as optimizing the treatment of TDT. Patients who are having bone pain despite these measures should be referred to endocrinologists for further management.

Abnormalities of glucose metabolism are usually observed in older patients with TDT. It is a progression from increased insulin resistance (with hyperinsulinemia) in the initial phases to decreased insulin secretion as the patients age [51]. Insulin deficiency is primarily attributed to iron deposition in the pancreas and induces cellular apoptosis, reduces pancreatic volume, replaces healthy tissue with fat cells, and impairs pancreatic function [56, 57]. Overenthusiastic iron chelation may also destroy pancreatic cells, leading to diabetes [51]. Impaired glucose metabolism is observed in a substantial number of patients with TDT, with reported frequencies of 9% in Iran [58], 11% in Turkey [59], and 16% in Brazil [60]. The International Diabetes Federation reported a prevalence of 0.008% (8.0 per 100,000 children aged 0–19 years) for type 1 diabetes in Pakistan [61]. Comparatively higher frequency was reported for impaired glucose tolerance (IGT) and diabetes mellitus (DM) in children/adolescents having TDT. For example, MB Ghafoor et al. (2020) reported a prevalence of 4.6% for IGT compared to 1.9% for DM in 151 patients aged 11 to 22 years [26]. Similarly, Q. Tahseen et al. (2017) reported an even higher frequency of IGT at 24.23% in 260 patients between 5 and 15 years of age [27]. This observed variance could be attributed to the study site and case mix, as the 2017 study was conducted in a referral center of a large metropolis. Additionally, a family history of glucose-related disorders has been significantly correlated with the incidence of IGT and DM in thalassemia patients, which may further explain these differences. Moreover, hepatic iron overload is strongly associated with the increased risk of developing diabetes and the antecedent insulin resistance [51]. Abnormalities in glucose metabolism are usually subclinical; therefore, the published GLs [9–13] suggest laboratory testing through fasting blood glucose and or OGTT with further testing to determine insulin resistance [9, 13]. In this framework, we suggest only fasting glucose, which is a simple, inexpensive, and routine test in many clinical laboratories. OGTT can be done at the next level if deemed necessary. We also encourage healthcare providers at the Thalassemia center to assess iron burden and optimize iron chelation to prevent further pancreatic damage.

Iron overload profoundly impacts gonadal tissues, leading to hypogonadism, one of the most prevalent endocrinopathies in TDT patients, with significant quality-of-life implications [15, 17]. Our review identified two Pakistani studies [28, 29] that evaluated pubertal disorders in TDT

patients (aged 13–32 years) using Tanner staging and biochemical markers (LH, FSH, testosterone, estradiol). Both reported high rates of sexual dysfunction (~40% overall), with gender-specific disparities: 37.5% in males [29] and 56.4% in females [28]. These findings highlight a critical research gap in Pakistan, where hypogonadism remains understudied compared to broader endocrine complications in TDT. Contributing factors may include insufficient awareness of iron overload's long-term effects, suboptimal chelation practices, and sociocultural taboos surrounding reproductive health, potentially leading to underreporting. Addressing these barriers through targeted research and culturally sensitive care is vital to improving outcomes in this vulnerable population. TIF [9] and SITE [13] suggest growth monitoring and Tanner staging for screening delayed puberty on a 6-monthly basis starting at age 13 in females and 14 in males. In case of suspected delayed puberty, further hormonal testing (FSH, LH, testosterone, estradiol) is advisable. For hypogonadism, it is suggested to maintain a 6-monthly menstrual diary by females, and patients with oligomenorrhea or amenorrhea should undergo hormonal evaluation. FSH, LH, and testosterone are the primary screening tests for male hypogonadism. In this framework, we suggest a similar course of clinical monitoring, but suggest testing for FSH only as an initial test. Further tests (estrogen/testosterone) can be performed as needed, along with referral to an endocrinologist.

Implications and future directions

The proposed framework has significant implications for enhancing endocrine care in resource-limited settings. Standardizing screening protocols allows for earlier detection of complications such as growth impairment and hypogonadism, enabling timely intervention to prevent irreversible outcomes. For patients and families, this approach reduces diagnostic delays and makes care more accessible by emphasizing clinical assessments before costly lab tests, especially where specialist access is limited. However, challenges like infrastructure constraints and low awareness must be addressed. Training non-specialist providers to conduct initial screenings and community education initiatives can help overcome these barriers. Successful implementation will involve integrating the framework into national thalassemia programs, supported by policy changes and partnerships with NGOs to secure resources. Long-term monitoring of patient outcomes will be vital to refining the approach. Ultimately, this strategy shifts the focus from reactive to preventive care, decreasing the endocrine burden on TDT patients while remaining practical for low-resource health systems.

Conclusions

The study has revealed a high prevalence of endocrinopathies in patients with TDT in Pakistan. Patients in low-resource countries face such complications due to limited access to standard therapies, such as optimal transfusion and chelation regimens. This underscores the importance of proper management of transfusion and chelation therapies, which is the primary goal that healthcare providers and patients in low-income countries must prioritize to prevent endocrinopathies and other complications.

Author contributions Saadia Abbas: Data curation, Methodology, Writing- Original draft preparation. Muhammad Osama Khan: Data curation, Methodology, Writing- Original draft preparation. Aahan Arif: Data curation, Methodology, Writing- Original draft preparation. Hafsa Majid: Methodology, Writing- Reviewing & editing, Lena Jafri: Methodology, Writing, Reviewing & editing. Aisha Shaikh: Reviewing & editing. Khadija Humayun: Writing, Reviewing & editing. Aysha Habib Khan: Methodology, Writing, Reviewing & editing, Supervision. Bushra Moiz, Writing, Reviewing and Expert input.

Funding This work does not receive any funding.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Human ethics and consent to participate Not applicable.

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