

## Endocrinopathies in thalassemia - a review

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### Abstract

Improved treatment has increased survival of patients with thalassemia. However, they still suffer from several endocrine complications mainly as a result of iron overload from multiple transfusions. Endocrinopathies manifest as early as the first decade of life, affecting growth, puberty, psychological development and quality of life. The presence of concomitant anemia, chronic liver disease and cardiomyopathy affect the development and treatment of endocrine disorders, making endocrinopathies in thalassemia a complex disorder. This review focuses on the pathogenesis, diagnosis and treatment of endocrinopathies in transfusion and non transfusion dependent thalassemia. The main points that should be considered in the management of endocrine disorders in a patient with thalassemia are highlighted in this review.

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### Introduction

Thalassemia is primarily a disorder of hemoglobin synthesis, and thus causes chronic anemia. However, anemia is just the tip of the iceberg. In thalassemia, chronic tissue hypoxia and prolong iron deposition in different organs, both due to disease itself and treatment, precipitate a multitude of disorders including endocrinopathies. The prevalence of endocrinopathies in thalassemia is difficult to determine due to variations in hemoglobin level as well as the duration, type and degree of chelation. The Thalassemia International Federation Study Group on Growth and Endocrine Complications reported that hypogonadism was the most common endocrinopathy (40.8%), closely followed by growth retardation (30.8%) with hypothyroidism being the least common (3.2%) in 3817 patients with thalassemia major (TM) [1]. Another study in 426 patients with TM showed that the risk of developing an endocrine complication was 9.7% in 5 years, despite adequate chelation [2].

Thalassemia can be classified depending on the need for transfusion. Non-deletional HbH,  $\beta$  –

thalassemia major and severe HbE/ $\beta$ -thalassemia require regular blood transfusions and are classified as transfusion dependent thalassemia (TDT) [3]. Patients with TDT suffer from iron overload and require aggressive chelation therapy. Endocrine complications are more prevalent and serious in these individuals. On the other end of the spectrum are the non-transfusion dependent thalassemia (NTDT) ( $\alpha$  –thalassemia trait,  $\beta$  – thalassemia minor, mild and moderate HbE/ $\beta$  – thalassemia, HbC/ $\beta$ -thalassemia and deletional HbH disease) [3]. Since they have mild disease and do not require regular transfusions, there is less organ damage due to iron deposition. However, endocrinopathies can still occur in NTDT and regular screening is advised.

Although endocrinopathies are the third most common cause of death in patients with TM [4], only a half of them consult an endocrinologist [5]. Treatment of endocrinopathies in thalassemia is complex due to multisystem involvement and lack of appropriate guidelines. Collaboration between hematologist, endocrinologist, hepatologist,

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cardiologist and gynecologist is therefore central to the management of this disorder. In this review, we describe the pathogenesis, diagnosis and treatment of endocrinopathies in thalassemia, with emphasis on TDT.

### Pathogenesis

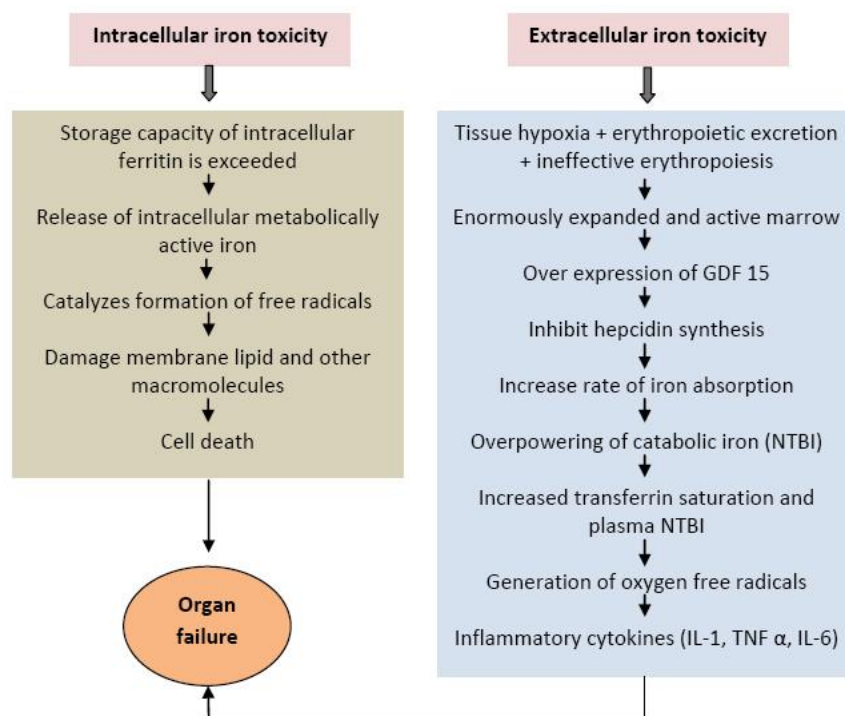
In thalassemia, similar to other organs such as liver and heart, iron overload damages endocrine glands. Excess iron accumulation results from repeated blood transfusions and increased iron absorption due to ineffective erythropoiesis. This leads to increased intracellular and extracellular iron deposition, which trigger a cascade of events culminating in cell damage primarily through generation of reactive oxygen species (Figure-1) [3,6-8]. As a consequence, several endocrine glands are affected resulting in different types of endocrinopathies. Figure-2 briefly depicts the different endocrinopathies in thalassemia, their important contributing factors and parameters for assessment.

### Endocrinopathies in TDT

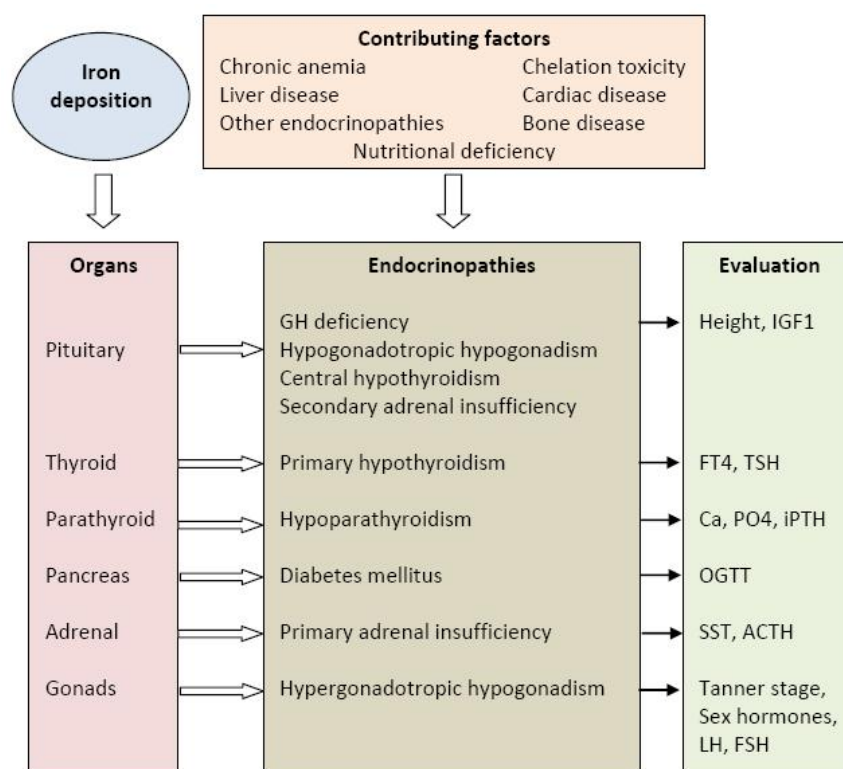
There are a multitude of endocrine disorders in TDT, with pituitary disorders being the most common. Severe pathology coupled with frequent transfusions and aggressive chelation make endocrine glands more susceptible to damage in TDT. Each disorder is described below along with a table (Table-1) outlining the key points of each endocrinopathy in TDT.

### Hypogonadism

Hypogonadism is the most common endocrinopathy in TM. [9] It can manifest as delayed puberty during adolescence or infertility, secondary amenorrhea and erectile dysfunction in later life. Long term complications include not only sexual dysfunction and infertility but also osteoporosis and decreased quality of life [9]. Iron overload in the pituitary gland and gonads causes low gonadotropin response to gonadotrophic releasing hormone (GnRH) as well as low gonadotropin and sex hormone secretion. There is also reduced



**Figure-1:** Pathogenesis of iron toxicity in thalassemia. GDF 15 - growth differentiation factor 15, NTBI - non-transferring bound iron, IL - interleukin, TNF - tissue necrosis factor [3,6-8].



**Figure-2:** Endocrinopathies in thalassemia – etiology and the parameters for assessment.

GH - Growth hormone, IGF1- insulin like growth factor 1, FT4 - free thyroxine, TSH - thyroid stimulating hormone, Ca - calcium, PO4 - phosphate, iPTH - intact parathyroid hormone, OGTT - oral glucose tolerance test, SST - short synacthen test, ACTH - adrenocorticotrophic hormone, LH - leutinising hormone, FSH - follicle stimulating hormone.

pulsatility of gonadotropins. Serum ferritin more than 2,500 ng/ mL level during puberty is a risk factor for hypogonadism [10]. In addition, pituitary hemochromatosis is progressive despite intensive chelation, leading to unavoidable hypogonadism. Patients with severe genetic defects have greater inherent iron loading that preferentially affects gonadotroph cells in the pituitary. Defective secretion of growth hormone also has detrimental effects on puberty. Liver disease, chronic hypoxia and associated endocrine complications such as diabetes and hypothyroidism are contributing factors [9].

The main presentation encountered is delayed puberty. Absence or incomplete development of secondary sexual characteristics at 13 years for girls and 14 years for boys and/or failure to complete

secondary sexual maturation within 5 years after onset of puberty indicates pubertal delay. Clinical evaluation involves assessment of Tanner stage (breast development in girls and testicular volume (TV) in boys). Tanner stage 2 indicates onset of puberty and is characterized by appearance of breast bud in girls and TV of 4 ml in boys. Therefore absence of breast bud or TV less than 4 ml indicates absence of pubertal development [11]. Hypothalamic-gonad axis is assessed by measuring estrogen/testosterone, leutinizing and follicle stimulating hormone (LH, FSH), and GnRH stimulation test. Low sex hormone with raised gonadotropins signals primary gonad failure, whereas low gonadotropins are consistent with pituitary failure. Pituitary failure is confirmed with suboptimal response of LH to GnRH stimulation

[11]. This indicates severe iron deposition in the pituitary [9]. Pituitary magnetic resonance imaging (MRI) can be done to detect pituitary iron deposition. Images later in the disease course show small pituitary gland [9]. It is important to do liver function test as treatment with estrogens alters liver function. Patients with coexistent liver disease due to secondary haemochromatosis or viral hepatitis should wait until liver function improves before starting estrogen. Hypothyroidism needs to be addressed in the treatment of pubertal delay [3]. Additional tests include blood count, ferritin, bone age and pelvic ultrasound. Treatment depends on age, degree of damage to the hypothalamus and gonads, chronic liver disease and child's psychological condition [9].

Treatment is with estrogen or testosterone supplementation [11]. As with other patients, low doses with gradual escalation to mimic normal puberty should be given, starting at a bone age of 12 years [3,5,11]. In our centre, we start with 0.125 mg per day of conjugated estrogen and gradually increase to 0.625 mg over 2 years in girls. Cyclic progesterone treatment is started after 2 years of estrogen or when breakthrough bleeding occurs. Similarly in boys, 125 mg testosterone is given, increasing gradually to 250 mg every 3 weeks. Treatment is continued lifelong in males and until menopause in females. Growth, Tanner staging and ultrasonography are used to monitor progression of puberty [11]. Timely replacement of sex steroids is also important to avoid development of osteoporosis in these individuals [9].

Erectile dysfunction is a commonly encountered problem in these patients. In addition to hypogonadism, diabetes mellitus, adrenal insufficiency, thyroid disorders, liver disease and medications (thalidomide) contribute this disorder, making treatment difficult. Treatment consists of discontinuing offending drugs and correction of contributing conditions. Phosphodiesterase inhibitors such as tadalafil can be prescribed if erectile dysfunction persists. Care must be taken when prescribing these drugs in patients with coexistent heart disease, especially those on nitrate therapy [11]. It should be noted that thalidomide used in treatment of thalassemia can cause hypergonadotropic hypogonadism with

development of small ovarian follicles and low anti-mullerian hormone in females. This does not appear to be related to cumulative doses of the drug. It is usually seen 6 months after starting therapy and is mostly reversible. 92% of women resumed menstruation after an average of 3 months after cessation of the drug. However, in some, there was a delay of 18 months [12]. Similarly, it can also affect males.

### Growth retardation

Growth retardation is the second most common complication of thalassemia major, occurring in 30.8% cases [1]. It manifests mainly in late childhood and early adolescence, becoming more apparent during puberty. A multitude of factors influence growth retardation. Apart from the obvious cause of transfusion iron overload, delayed growth results from chronic anemia, chelation toxicity, nutritional deficiencies, growth hormone deficiency, hypogonadism, hypothyroidism, diabetes, psychosocial stress, chronic liver and cardiac disease, increased energy expenditure, altered calcium homeostasis and bone disease. Children with thalassemia may have both structural and functional defect in the growth hormone – insulin like growth factor 1 (IGF 1) axis. Pituitary siderosis as evidenced by MRI studies showing iron deposition in the pituitary gland and midbrain on MRI is the most common structural abnormality. Empty sella and small pituitary gland are also seen on imaging, indicating pituitary atrophy. Infiltration also involves the stalk. These changes are associated with decreased production of growth hormone from the hypothalamus and pituitary. Several studies have also shown low IGF1 in patients with thalassemia, despite normal GH levels, imparting a resistance to growth hormone action. Serum ferritin level greater than 3,000 ng/mL during the first decade of life is a predictor of short stature in adult life [10].

Definition and anthropometry to evaluate short stature are similar to those in non-thalassemic patients. Height below fifth centile or growth velocity of less than 5 cm per year defines short stature [11]. It is important to look for clinical signs of other endocrinopathies, liver and cardiac disease. Special attention should be given to

peripheral blood count, ferritin, thyroid and liver function tests, calcium profile, oral glucose tolerance test, bone age and echocardiography to assess coexisting comorbidities and endocrinopathies that affect growth [5]. Growth hormone stimulation test and IGF1 level are done to evaluate growth. In our centre, we use 125-500 mg levodopa (depending on weight). Growth hormone less than 10 ng/ml 60 minutes after pharmacologic stimuli is considered abnormal. IGF1 values are interpreted according to age and sex of the patient [11].

Treatment should address multiple factors. Blood transfusion to maintain hemoglobin above 9g/dl, chelation to attain serum ferritin below 1000 ng/ml, correction of nutritional deficiencies, induction of puberty and management of hypothyroidism, diabetes, bone, liver and cardiac disease should be done [5]. In case of growth hormone deficiency, recombinant growth hormone can be given [11]. However, a higher dose is required and growth rate is slower due to growth hormone insensitivity [5].

### Diabetes mellitus

The prevalence of diabetes mellitus in thalassemia major increases with age, occurring mostly early in the second decade. Prevalence ranges from 0-17% (average 9.9%). A meta-analysis showed that the prevalence of diabetes mellitus, impaired fasting glucose, and impaired glucose tolerances was 6.54%, 17.21%, and 12.46%, respectively [13]. It is another specified type of diabetes, although it shares the insulin deficiency of type 1 and resistance of type 2 diabetes [14]. It is common in inadequately iron chelated patients, but is also seen in well transfused and regularly chelated patients. Diabetes mellitus results from both liver and pancreatic  $\beta$ -cell siderosis, leading to defects in insulin secretion and resistance. Iron overload in the pancreas leads to destruction of islet cells and defective insulin synthesis, while hepatic iron deposition causes increased glucose output. Other factors such as viral hepatitis, chronic anemia, zinc deficiency, excessive fatty acid oxidation and increased collagen deposition also contribute to insulin resistance [13]. Criteria for diagnosis are the same as in other patients. Comprehensive

evaluation is also similar. However, it should be remembered that hemoglobin A1c (HbA1c) is not a reliable indicator of glycemia due to reduced red cell lifespan, ineffective haemopoiesis and frequent blood transfusions. Instead diagnosis should depend on an oral glucose tolerance test (OGTT) and monitoring should rely on self monitoring of blood glucose (SMBG) [5]. Considering multiple comorbidities, insulin is the best treatment option [5]. Adequate chelation should also be instituted.

### Hypoparathyroidism

Hypoparathyroidism is commonly encountered in patients with TM, with a prevalence of 9.9%. It manifests in the 2nd decade of life, so screening should begin from age 10 years. Mild asymptomatic hypocalcemia with normal parathyroid level is more common than symptomatic cases, therefore screening is paramount [15]. Like other endocrine complications, it results from excess iron deposition in the parathyroid glands. Patients present with tingling, numbness, latent tetany, seizures, prolong QT and refractory congestive heart failure. Since these patients may have cardiomyopathy, they are more prone to cardiac complications in the event of hypocalcemia. Blood reports show a low calcium, high phosphate and low parathyroid hormone. Plasma fibroblast growth factor 23 (FGF 23) is lower in TM patients with hypoparathyroidism [15]. Electrocardiography (ECG) should be done to exclude any arrhythmia. Treatment is as usual with calcium and active vitamin D supplementation. Calcium should be maintained between 8.5 to 9 mg/dl [11].

### Thyroid dysfunction

Hypothyroidism is a prevalent endocrine complication in TM, which occurs more frequently in the second decade of life [16]. The spectrum of thyroid dysfunction in patients with TM ranges from subclinical hypothyroidism (the most prevalent abnormality) to primary as well as secondary hypothyroidism [14]. Thyroid dysfunction arises mostly due to gland infiltration, direct iron cytotoxicity, chronic tissue hypoxia, free radical injury and organ siderosis. The symptoms of hypothyroidism though nonspecific can affect

multiple organ systems, therefore an annual laboratory evaluation of thyroid function through serum thyroid - stimulating hormone (TSH) and serum free thyroxine (FT4) is recommended in all patients with TM taking regular transfusions [17]. The clinical presentation of patients with subclinical hypothyroidism may be subtle, without any symptoms and detected only during routine screening of thyroid function. Short stature, delayed puberty, fatigue, cold intolerance, weight gain and constipation are common clinical features linked to overt hypothyroidism. Cardiac failure and pericardial effusion have also been noted in overt hypothyroidism. This may affect TM patients who have existing cardiomyopathy due to iron overload. It has been also reported that thalassemia patients with primary hypothyroidism have more frequent endocrinopathies such as diabetes mellitus (79%), hypoparathyroidism (65%) and delayed puberty (37%) [17]. Early diagnosis and treatment of these complications are important to ensure a good quality of life and to reduce morbidity and mortality. Thyroxine therapy is recommended in patients with central hypothyroidism or TSH > 10 mU/L [17]. However, over replacement also linked to arrhythmia and accelerated bone loss. Thyroid cancer along with other malignancies like hepatocellular carcinoma and haematological malignancies are emerging issues for the thalassemia patients with increased life expectancy following regular transfusions, adequate chelation and treating complications. Though studies did not find any correlation between the thyroid dysfunction and factors like duration, amount of blood transfusion, serum ferritin level and iron chelation therapy [14], periodic assessment of iron overload, thyroid function and follow up to improve adherence to chelation are strongly recommended.

#### **Adrenal insufficiency**

Adrenal insufficiency is not a common feature of TM. Iron overload occurs mainly in the pituitary, but also may affect adrenals. Manifestations of adrenal insufficiency (asthenia, weight loss) are

difficult to recognize as they are masked by symptoms of thalassemia. Adrenal crisis is rare [3]. Diagnosis is based on the short Synacthen test (serum cortisol < 550 nmol/L after 250 µg of Synacthen) [11]. Patients should be screened for adrenal function every 1-2 years. Treatment is with hydrocortisone 15–20 mg daily [11]. Special attention should be given during stressful conditions as it may precipitate a crisis. This is of particular importance as patients with TM commonly encounter stressful conditions like blood transfusions, invasive procedures and surgery [5].

#### **Osteoporosis**

Osteoporosis, a bone mineral density (BMD) T-score < -2.5 or Z score < 2 in children assessed by dual energy x-ray absorptiometry (DEXA) [11], is a common yet unrecognized problem of TM [3]. It occurs in 40-50% cases of TM. There are several contributing factors such as genetic, hypogonadism, iron overload, bone marrow expansion, vitamin deficiencies and lack of physical activity. Annual checking of BMD should start in adolescence [3]. Treatment includes diet rich in calcium, physical activity, calcium (500-1000 mg daily) and vitamin D (400IU daily) supplementation and bisphosphonates [11]. In case of TM, special attention should be given to timely replacement of sex hormones, early treatment of diabetes mellitus, adequate iron chelation and sufficient blood transfusions [3].

#### **Endocrinopathies in NTDT**

Although the prevalence of endocrinopathies is less in NTDT compared to patients requiring regular transfusions, they are still encountered, especially with advancing age. This necessitates regular screening starting early in the second decade. Screening should start at 10 years of age. Table-2 gives a screening and follow up regimen for patients with NTDT [6]. Evaluation and treatment of endocrinological disorders are the same as that of transfusion dependent patients.

**Table-1:** Summary of key points in the management of endocrinopathies in TDT

Endocrine Disorder	Key points
Hypogonadism	Most common endocrinopathy. Evaluation and treatment are the same as non-thalassemia patient. Attention should be given to hypothyroidism, anemia and level of ferritin. Attention should be given to liver function in the treatment with sex steroids. Drugs such as thalidomide can cause hypogonadism.
Growth retardation	Usually manifests in the later part of the first decade of life. Cause is multifactorial with defects in both growth hormone secretion and action. Clinical and hormonal evaluation is the same as non-thalassemia patient. Assessment of anemia, ferritin, other endocrinopathies and comorbidities is paramount. Treatment should address other complications of thalassemia. Growth rate is slower with growth hormone treatment.
Diabetes mellitus	Should be screened after 10 years of age. Criteria for diagnosis, evaluation and treatment are the same as non-thalassemia patients. There is limited role of HbA1c Insulin is the preferred treatment option.
Hypoparathyroidism	Usually manifests in the second decade of life. Diagnosis and treatment is as usual. Special attention should be paid to cardiac complications.
Thyroid dysfunction	Hypothyroidism is uncommon. It affects puberty, growth and quality of life. Hypo and hyperthyroidism affect cardiovascular health.
Adrenal insufficiency	Adrenal insufficiency is not common. It is difficult to detect symptoms of adrenal insufficiency as they mimic those of anemia. Care should be taken during periods of stress.
Osteoporosis	Osteoporosis is common, multifactorial and neglected In addition to conventional treatment, attention should be given to treatment of hypogonadism, diabetes and disease itself.

**Table-2:** Follow up regimen for NTDT [6]

Endocrinopathy	Screening Test	Frequency
Growth retardation	Height , Bone age	6 months
Hypogonadism	Tanner staging	Annually
Diabetes	FBS / OGTT	Annually
Hypothyroidism	FT4, TSH	Annually
Hypoparathyroidism	Ca, PO4, iPTH, Vitamin D	Annually
Osteoporosis	DEXA	Annually

Note: FBS - fasting blood sugar, OGTT - oral glucose tolerance test, FT4 - free thyroxine, TSH - thyroid stimulating hormone, Ca - calcium, PO4 - phosphate, iPTH - intact parathyroid hormone, DEXA - dual energy X-ray absorptiometry.

## Conclusion

In conclusion, endocrinopathies remain a common and unavoidable complication of thalassemia. Early detection of endocrine disorders and prompt referral to endocrinologists for appropriate treatment should be a priority of physicians treating these patients. The fact that thalassemia is actually a multi-organ disorder should be kept in mind during its management. A collaborative approach of concerned specialties is encouraged to improve the quality of life of patients with thalassemia.

## Conflict of interest

The authors hereby, declare that no conflict of interest exists

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