

3. Endocrine Complications

Principles

- To ensure normal growth, sexual development and fertility.
- To prevent treatment-related endocrine complications.
- To detect and treat endocrine disturbances promptly and effectively.

Recommendation

- Each specialist centre should collaborate with a pediatric or an adult endocrinologist with knowledge of endocrine complications in thalassemia.³²⁵
- Children should be routinely monitored for growth and development until they have attained adult height and full sexual development. Any abnormalities to suggest an endocrinopathy should be investigated and managed accordingly.
- Adolescents and adults should be routinely monitored for endocrinopathies including diabetes mellitus, hypothyroidism, hypoparathyroidism, hypogonadotropic hypogonadism, and growth hormone deficiency.^{8,9,11,18} Abnormalities should be identified early and treatment initiated in consultation with an endocrinologist.
- There may be a role in the future for MRI pituitary assessment.³²⁶

Background

Endocrine complications including short stature (34%), delayed puberty, hypogonadotropic hypogonadism (35 – 55%), hypothyroidism (10%), hypoparathyroidism (4%), and diabetes mellitus (5.6 – 20%) are common in thalassemia major, and are primarily due to iron overload of the anterior pituitary and endocrine glands.^{317,318} Over half of patients have evidence of an endocrinopathy with more than a third having multiple, though prevalence varies by geographic region and chelation history.^{319,320} The prevalence of endocrine disorders is lower in Non-Transfusion Dependent Thalassemia, though oxidate stress still contributes.^{321,322} Bone marrow transplantation cannot fully restore endocrine function, and depending on conditioning regimen and transplant complications may worsen them.³²⁴

Interventions

Short Stature

All children should be assessed for short stature with standing and sitting height measurements every 6 months.^{343,344} Ethnic appropriate growth charts should be used, where available.

Endocrine evaluation should be initiated if there is a fall-off on growth curves, decreased height velocity, or delayed bone age.³⁴⁵

The diagnosis of growth hormone deficiency, other hormonal or nutritional deficiencies or deferoxamine toxicity should be considered.

Growth hormone stimulation testing should be done and, if indicated, growth hormone therapy started.^{327,328,344}

Delayed Puberty and Hypogonadism

Delayed puberty and hypogonadism is the most common endocrine complication, and thus, all children should be assessed yearly from the age of 10 years. If there is pubertal delay characterized by no pubertal changes in girls by age 13 years and in boys by age 14 years, or arrested puberty, a pediatric endocrinologist should be consulted.

Hypogonadism in boys is suggested by the absence of testicular enlargement (less than 4 ml), and in girls by the absence of breast development by the age of 16 years.

All patients with delayed puberty or hypogonadism should receive appropriate investigations including bone age and hormonal assessments, hormonal replacement therapy (topical or parenteral³²⁹), and subsequent follow-up by an endocrinologist.^{329,350-354}

Adults should be routinely assessed for secondary hypogonadism, impotence, or infertility. Patients with cardiac iron deposition are at greater risk of HH (188). Pituitary MRI, may in the future have a role for risk stratification of hypogonadism.³³¹

Correction of hypogonadism is not as beneficial to bone disease in thalassemia as in other causes of premature gonadal failure.³³²

There may be a role for supplementation with L-carnitine on supporting pubertal development.³³³

Hypothyroidism

TSH levels should be measured annually beginning at 12 years of age since hypothyroidism often develops after adolescence. Hypothyroidism should be treated with thyroid hormone replacement.

Serum ferritin is a marker of risk for hypothyroidism.³³⁴ Central hypothyroidism is an uncommon cause of hypothyroidism n TM.³³⁵

Hypoparathyroidism

Hypoparathyroidism usually develops after the age of 16 years. All patients over the age of 12 years should have calcium and phosphate levels checked at least every 6 months. If these are abnormal, parathyroid hormone level should be measured. Nocturnal calcium and PTH levels may assist in making the diagnosis.³³⁶ Hypoparathyroidism should be managed as per endocrine standards.³³⁶

Impaired Glucose Tolerance and Diabetes

Risk factors for developing diabetes in this population include age, iron overload, poor chelation compliance, chronic liver disease, cirrhosis, viral hepatitis, and genetic factors.³³⁷⁻³³⁹

There is a correlation between diabetes and age, serum ALT, HCV status, and ferritin, and cardiac iron deposition. There has not been shown to be a direct relationship between diabetes risk and pancreatic iron.^{330,337,338}

A fasting plasma glucose test should be done regularly starting at puberty.³³⁷

An oral glucose tolerance test can detect early impairment of glucose metabolism .

Impaired glucose tolerance and diabetes should be managed as per Canadian Diabetes Association Guidelines⁹⁶ and in conjunction with a diabetes clinic with emphasis on glycemic control, diet, exercise, and management of complications.

Fructosamine is often preferred to HbA1c for monitoring of glycemic control in Thalassemia, though there is moderate correlation between the two measurements.³³⁹

Improvement of iron load with adequate combination chelation therapy may decrease insulin resistance and decrease glucose intolerance.^{346,348,349}

Patients with diabetes are at higher risk of cardiac complications and should be monitored more closely in consultation with a cardiologist.²⁵⁴

Adrenal Insufficiency

Adrenal insufficiency has not been frequently reported in thalassemia patients.^{340,341} If symptoms are reported, it can be screened for using morning cortisol and the cortisol responses following ACTH stimulation.³⁴²