

# Growth and endocrine disorders in thalassemia: The international network on endocrine complications in thalassemia (I-CET) position statement and guidelines

Vincenzo De Sanctis, Ashraf T. Soliman<sup>1</sup>, Heba Elsedfy<sup>2</sup>, Nicos Skordis<sup>3</sup>, Christos Kattamis<sup>4</sup>, Michael Angastiniotis<sup>5</sup>, Mehran Karimi<sup>6</sup>, Mohd Abdel Daem Mohd Yassin<sup>7</sup>, Ahmed El Awwa<sup>1</sup>, Iva Stoeva<sup>8</sup>, Giuseppe Raiola<sup>9</sup>, Maria Concetta Galati<sup>10</sup>, Elsaid M. Bedair<sup>11</sup>, Bernadette Fiscina<sup>12</sup>, Mohamed El Kholy<sup>2</sup>

*Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy, <sup>1</sup>Department of Pediatrics, Division of Endocrinology, <sup>11</sup>Department of Radiology, Hamad General Hospital, Doha, Qatar, <sup>2</sup>Department of Pediatrics, Ain Shams University, Cairo, Egypt, <sup>3</sup>Department of Paediatrics, Division of Pediatric Endocrinology, Makarios Hospital, Nicosia, Cyprus, <sup>4</sup>Department of Paediatrics, University of Athens, Athens, Greece, <sup>5</sup>Thalassaemia International Federation, Nicosia, Cyprus, <sup>6</sup>Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran, <sup>7</sup>Department of Hematology, Alamal Hospital, Hamad Medical Center, Doha, Qatar, <sup>8</sup>University Paediatric Hospital, Sofia, Bulgaria, <sup>9</sup>Department of Paediatrics, Pugliese-Ciaccio Hospital, <sup>10</sup>Department of Haematology, Thalassaemia and Prenatal Diagnosis Regional Center, Pugliese-Ciaccio Hospital, Catanzaro, Italy, <sup>12</sup>Department of Pediatrics, NYU School of Medicine, New York, USA*

## ABSTRACT

The current management of thalassemia includes regular transfusion programs and chelation therapy. It is important that physicians be aware that endocrine abnormalities frequently develop mainly in those patients with significant iron overload due to poor compliance to treatment, particularly after the age of 10 years. Since the quality of life of thalassemia patients is a fundamental aim, it is vital to monitor carefully their growth and pubertal development in order to detect abnormalities and to initiate appropriate and early treatment. Abnormalities should be identified and treatment initiated in consultation with a pediatric or an adult endocrinologist and managed accordingly. Appropriate management shall put in consideration many factors such as age, severity of iron overload, presence of chronic liver disease, thrombophilia status, and the presence of psychological problems. All these issues must be discussed by the physician in charge of the patient's care, the endocrinologist and the patient himself. Because any progress in research in the field of early diagnosis and management of growth disorders and endocrine complications in thalassemia should be passed on to and applied adequately to all those suffering from the disease, on the 8 May 2009 in Ferrara, the International Network on Endocrine Complications in Thalassemia (I-CET) was founded in order to transmit the latest information on these disorders to the treating physicians. The I-CET position statement outlined in this document applies to patients with transfusion-dependent thalassemia major to help physicians to anticipate, diagnose, and manage these complications properly.

**Key words:** Endocrine complications, growth, guidelines, iron overload, thalassemia, treatment

## INTRODUCTION

The hemoglobinopathies (thalassemias and sickle-cell disease)

are the most commonly inherited genetic disorders, with some 240 000 infants born annually with major hemoglobinopathies and at least 190 million carriers worldwide.<sup>[1,2]</sup>

The current management of thalassemia (TM) includes regular transfusion programs and chelation therapy. Current guidelines recommend a pretransfusion threshold not exceeding 9.5% g/dl, which seems to be associated with adequate marrow inhibition and a relatively low iron burden.<sup>[2-5]</sup> The aim is to transfuse 10-20 ml/kg body weight of packed filtered red cells over a period of 2-3 h every 2 to 5 weeks throughout life.<sup>[2-5]</sup>

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**Corresponding Author:** Dr. Vincenzo De Sanctis, Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy. E-mail: vdesanctis@libero.it

The natural course of the disease is dramatically altered by transfusion side effects, which need to be monitored and treated. Iron overload resulting in end-organ damage and blood-borne infectious agents still represent the principal causes of morbidity and mortality.<sup>[1-9]</sup>

## TRANSFUSION-RELATED IRON OVERLOAD AND IRON TOXICITY

The precise underlying mechanism of iron overload-induced organ dysfunction presently remains unclear. However, when iron levels in the body become too high, this leads to saturation of transferrin, and non-transferrin-bound iron (NTBI) species circulate in the plasma. Unbound iron within cells or in plasma is labile and can redox cycle between Fe<sup>2+</sup> and Fe<sup>3+</sup>, thereby generating reactive oxygen species (ROS), leading to lipid peroxidation. Lipid peroxidation under conditions of iron overload leads to the generation of both unsaturated (malondialdehyde and hydroxynonenal) and saturated (hexanal) aldehydes. Both have been implicated in cellular dysfunction, cytotoxicity, and cell death.<sup>[10,11]</sup> Certain tissues are particularly susceptible to excess iron incorporation when NTBI is present.

Apart from iron overload, other factors responsible for organ damage have been previously pointed out, including chronic hypoxia due to anemia that may potentiate the toxicity of iron deposition in endocrine glands.<sup>[12]</sup> Also, viral infections as well as individual susceptibility have been implicated in causing endocrine dysfunction.<sup>[13]</sup>

## IRON CHELATION THERAPY

Current practice is to begin iron chelation therapy when the serum ferritin levels reach 1000 ng/ml or when child reaches 3 years of age or has received about 10-20 transfusions.<sup>[2,3,13]</sup>

Iron chelators in current clinical use include monotherapy with subcutaneous or intravenous desferrioxamine (DFO), oral deferiprone or oral deferasirox, and combination therapy with SC DFO and deferiprone.<sup>[7]</sup>

DFO is most commonly self-administered as a subcutaneous infusion over 8-10 h, 3-7 nights weekly. Oral deferiprone and deferasirox are mainly used for patients in whom chelation with DFO has been inadequate or intolerable.<sup>[3,13-15]</sup> Recently, oral monotherapy with deferasirox has been used, as it is equally effective to DFO and deferiprone.<sup>[16]</sup>

Effective chelation reduces or prevents iron accumulation and iron-mediated organ damage, resulting in a consistent decrease of morbidity and mortality.<sup>[3-5,13-15]</sup>

## PREMISE OF INTERNATIONAL NETWORK ON ENDOCRINE COMPLICATIONS IN THALASSEMIA ACTIVITIES

Optimal quality care for hemoglobin disorders is the basic prerequisite to achieve long survival and a good quality of life. To achieve this aim in dealing with a multi-organ pathology as encountered in TM, a coordinated multidisciplinary team of specialists is required. Such a team must include an endocrinologist, preferably experienced in the management of hormonal deficiencies caused early in life by transfusion-induced iron overload in TM patients.<sup>[17]</sup>

Endocrine complications are very common in multi-transfused TM patients (De Sanctis V, unpublished data, Berlin 2010) [Table 1]. Despite this, a recent survey conducted by the Thalassemia International Federation (TIF) on 316 regularly transfused patients older than 10 years across Europe for the Enerca Project (European Rare Anaemias) showed that only 177 (56%) are ever seen by an endocrinologist. Of these, 134 (42%) are seen at least annually, while the rest seem to be followed occasionally (every 2 years or less).<sup>[18]</sup> A similar survey was conducted by TIF in the Middle East (data unpublished, 2009) on 90 health professionals who look after TM patients from various countries in the region; 86.4% of them reported a lack of multi-disciplinary support. Of 96 multi-transfused patients from the same region, 62.4% stated that they have never visited an endocrinologist, 3.6% have been seen occasionally (every 2 years or less), and 34% have been seen yearly.<sup>[17]</sup>

**Table 1: Incidence/prevalence of endocrinopathies in iron overloaded  $\beta$ -thalassemia major patients in different geographical areas**

Endocrine complications (% in both sexes)	Cyprus (n=436)	Greece (n=262)	Italy (n=1,861)	North America (n=262)	Iran (n=220)	Turkey (n=252)
Hypogonadism	35.2	42	49	42	35	50
Diabetes mellitus/IGT	9.4	5/27	4.9	5	8.7	9.3/6.6
Short stature/GHD	35	32	-/12.4	32/3	39.3	-/10
Primary hypothyroidism	5.9	4	6.2	4	7.7	29
Hypoparathyroidism	1.2	4	3.6	4	7.6	4

GHD: Growth hormone deficiency, IGT: Impaired glucose tolerance (from *Thalassemia News* 2001, page 12)

The major difficulties reported by hematologists or pediatric endocrinologists experienced in TM or TM syndromes<sup>[17]</sup> in following growth disorders and endocrine complications concern:

- Facilities (27%)
- “Familiarity” with medical treatment of endocrine complications (40%)
- Presence of pediatric endocrinologist for consultation on growth disorders and endocrine complications (27%)
- Interpretation of endocrine tests (30%)
- Others (17%)
- Cost (65%)

## OBJECTIVES OF THE INTERNATIONAL NETWORK ON ENDOCRINE COMPLICATIONS IN THALASSEMIA EDUCATIONAL TRAINING PROGRAM

The International Network on Endocrine Complications in Thalassemia (I-CET) was founded on the 8 May 2009, in Ferrara, Italy, to transfer any progress in research in the field of growth and endocrine complications in TM into real-life applications for patients with these disorders.<sup>[17]</sup>

To accomplish this goal, the endocrine I-CET program aims to train pediatricians/physicians and hematologists to:

1. Acquire adequate and updated knowledge about growth and endocrine manifestations in patients with TM, TM syndromes, and sickle cell disease;
2. Improve their ability to select and interpret data originating from laboratory and radiological investigations to solve these problems;
3. Reach and follow an international acceptable standard on management of these growth and endocrine complications in TM;
4. Become competent to maintain optimal comprehensive care of children and adolescents suffering from endocrine disorders due to TM and
5. Encourage research in the field of these disorders in TM syndromes.

## COURSE OUTLINE

1. The course defines and discusses the endocrine disorders in TM and TM syndromes and their relation to the transfusion regimen, iron overload, chelation therapy, and severity of the disease.
2. Doctors will learn in detail their clinical manifestations and laboratory and imaging tests that are most useful for diagnosis.
3. In-depth case studies will allow participants to put together and interpret all the clinical, hematological,

biochemical, molecular and imaging data to arrive at a probable diagnostic conclusion.

4. Management plans will be discussed for each endocrine abnormality.

## Contents of the I-CET course

- Defining TM and explaining the molecular basis and pathophysiology of TM syndromes
- Identifying the clinical manifestations of growth, pubertal and endocrine disorders in TM syndromes:
- How to measure, interpret, and analyze growth data
- How to assess, interpret, and analyze pubertal development and fertility problems
- Symptoms and signs of glycemic abnormalities
- Symptoms and signs of calcium abnormalities
- Imaging abnormalities
- Defining growth and pubertal abnormalities in TM including their prevalence per age period (childhood, puberty, adolescence, and adulthood)
- Defining glycemic abnormalities and prevalence in TM
- Defining calcium abnormalities and prevalence in TM
- Defining thyroid and parathyroid abnormalities and prevalence in TM
- Identifying proper use and interpreting different laboratory findings in TM including:
  - RBC and hematologic findings, bilirubin, and hepatic functions
  - Serum iron and transferrin levels, transferrin saturation and ferritin concentrations and their relation, especially high ferritin, to endocrine disorders
  - Hepatitis screening and liver function tests and their relation to endocrine abnormalities (growth and glycemic abnormalities)
- When and how to investigate and interpret results related to:
  1. Growth hormone–Insulin like growth factor axis (GH-IGF-I) axis,
  2. Pituitary gonadal axis,
  3. Glucose homeostasis,
  4. Pituitary–thyroid functions,
  5. Calcium homeostasis,
  6. Skeletal changes and bone mineral density, and
  7. Reviewing and interpreting imaging findings in TM or TM syndromes with different endocrine disorders

## GUIDELINES

Monitoring of growth, pubertal development, reproductive ability, and endocrine functions in general are essential to achieve a good quality of life in TM.<sup>[17]</sup>

The position statement, outlined in this document, applies

to transfusion-dependent patients with TM. The following recommendations agreed upon and reviewed by the I-CET members are based on the current evidence-based literature and existing guidelines, in order to bring uniform, consistently good care to patients affected by TM.

## OUTLINE FOR ENDOCRINE SCREENING

### Growth assessment

Growth retardation is commonly reported in children and adolescents with TM. Although some patients show normal growth and development, many have growth abnormalities during late childhood in addition to failure or attenuation of their pubertal growth spurt.<sup>[13,18,19]</sup> The pathogenesis of growth failure is multifactorial.<sup>[13,18,19]</sup> Key contributing factors to stunted growth in patients with TM include chronic anemia,<sup>[12]</sup> transfusion-related iron overload,<sup>[18-21]</sup> and chelation toxicity.<sup>[22,23]</sup> Other contributing factors include hypothyroidism, hypogonadism, GH deficiency/insufficiency, zinc deficiency, chronic liver disease, under nutrition, and psychosocial stress.<sup>[13]</sup> Malnutrition is a significant cause of growth retardation in thalassemic children living in poor countries. In these children, inadequate nutrient intake (zinc, folic acid, vitamin D, carotenoids, and retinol binding proteins) contribute significantly to their growth impairment.<sup>[24]</sup>

### Patients are assessed for growth every 6 months to one year by

1. Recording of parental heights at the first visit (calculate mid-parental height).
2. Accurate measurement of standing and sitting heights, weight, and head at each visit; measurement of the head circumference especially during the first 2 years of life
3. Plotting growth data on ethnically adjusted charts or international (WHO) adjusted charts
4. Calculating annual growth velocity (GV), body mass index (BMI) and upper/lower segment ratio.
5. Interpreting growth data for early detection of growth delay.  
Note: The average height velocity varies at different developmental phases:
  - Infancy: 23-28 cm/year
  - Childhood: 5-6.5 cm/year
  - Puberty: 8.3 cm/year (girls), 9.5 cm/year (boys)
6. Comparing growth data of the patient (height SDS or centiles) with the population data as well as with the mid-parental height (SDS or centiles).
7. Evaluating pubertal status according to Tanner stages (breast development (girls) and testicular volume (boys))

### Child is considered short if

- Height is less than the 3<sup>rd</sup> percentile or 2 SD below the mean height for age and sex;
- Height is within normal but GV is consistently <25<sup>th</sup> percentile over 6-12 months; or
- The patient is excessively short for his/her mid-parental height, though his absolute height may be within the normal percentiles.

### Annual endocrine screening

This should be started from the age of 9 years, or earlier if clinically indicated (e.g., short stature or decreased GV/year).

The following tests and assessments are recommended annually:

1. Serum TSH and free T4.
2. Serum calcium, ionized calcium, inorganic phosphate, magnesium, and alkaline phosphatase.
3. Fasting glucose/insulin semi-annually, for the assessment of Homeostasis Model Assessment (HOMA index), which is based on the product of the fasting plasma insulin and glucose concentrations (insulin × glucose/22.5), and oral glucose tolerance testing (OGTT) in case of impaired fasting glucose (IFG).
4. Serum IGF-I and IGF BP-3 in growth screening are useful indicators of growth hormone secretion and nutrition, putting in mind that chronic liver diseases and malnutrition may interfere with their secretion.
5. Serum or hair zinc (in selected cases).
6. Bone age (X-ray of wrist and hand).
7. Radiographs of tibia and spine should be evaluated in patients with TM who have body disproportion to exclude the presence of platyspondylosis or metaphyseal cartilaginous dysplasia changes.
8. LH, FSH, and sex steroids, in the pubertal age group.

### Notes

1. An abnormal upper to lower segment ratio may be seen not only in pre-pubertal but also in pubertal patients with TM leading to the conclusion that delayed puberty is not the only cause of relative truncal shortening. Furthermore, truncal shortening has been observed in children with good chelation therapy compliance and low ferritin levels due to platyspondylosis induced by DFO toxicity. In the severe form of DFO toxicity, there is significant slowing of linear growth with a short trunk, moderate sternal protrusion, swelling of wrist and knees, and genu valgum of variable severity. In some patients, back pain, bone pain, and limitations in movement are also present.<sup>[13,19]</sup>
2. The normal range of plasma zinc concentration using atomic absorption spectrophotometry is 11–19 μmol/L.



In mild deficiency, it is between 7 and 10  $\mu\text{mol/l}$  and in severe deficiency, it is less than 7  $\mu\text{mol/l}$ .

3. Pancreatic MRI may identify high-risk patients before irreversible pancreatic damage

## SPECIFIC ENDOCRINOPATHIES: TESTING AND EVALUATION

### GROWTH HORMONE DEFICIENCY

- Referral to endocrinologist for determination and treatment of growth hormone deficiency (GHD) is required if there is fall-off from the growth curve (slow GV), height  $<3^{\text{rd}}$  %ile or  $>2$  SD below the mean for age and sex in the reference population, or 1 SD below the mid-parental height SDS.
- Early diagnosis of GHD and judicious management before and during puberty is recommended to attain best results.

#### Investigations

The evaluation for patients with TM and short stature should include:

1. Dietary assessment preferably by a registered dietician.
2. Laboratory tests:
  - Biochemical: Urine analysis, serum albumin, serum glucose, complete and differential blood count, liver function tests, calcium and phosphate, alkaline phosphatase, creatinine, electrolytes, and ferritin concentrations.
  - Endocrine: Serum free T4, TSH, cortisol, and IGF-I concentrations
3. Bone age assessment (X-ray of wrist and hand)
4. Assessment of GH secretion: Significant GH insufficiency may be diagnosed by a reduced response of GH to two provocative tests (GH peak  $<10$  ng/ml) in children and adolescents and 3 ng/ml in adults<sup>[19-21]</sup> or reduced response of GH in one test plus low IGF-I and IGFBP3 concentrations.
5. In those with poor GH response, basal and IGF-1 generation test may be advised to exclude a partial GH insensitivity (GHI).<sup>[25]</sup>
6. Short children with normal GH secretion to stimulation tests and low IGF-I levels potentially may benefit from IGF1 or GH-IGF-I treatment. However, the treatment is expensive and the results in TM patients remain undetermined.
7. MRI of the hypothalamic–pituitary region is useful to evaluate pituitary iron overload as well as the size of pituitary gland (atrophy).

#### Notes

1. Refer to endocrinology for GH determination and

treatment of GHD.

2. Priming with sex steroids is necessary if the bone age is 10 years or greater. An intramuscular injection of testosterone ester (Sustanon) 100 mg is given 7 days before GH stimulation tests in boys. Ethinylo estradiol 50  $\mu\text{g}$  is given orally for 3 days before GH stimulation tests in girls with bone age of 9 years or greater. Girls whose bone age is less than 9 years and boys whose bone age is less than 10 years do not need priming.

#### Management

- Treat underlying cause (hypothyroidism, uncontrolled diabetes mellitus, chronic illnesses).
- For children suspected to be GHD, refer to pediatric endocrinologist for initiation of GH.
- Psychological support for non-treatable causes (genetic/familial short stature; constitutional delay of growth and puberty)

## GH TREATMENT

### Children and adolescents

- rhGH dose: 0.025-0.05 mg/kg/day (0.5-1.0 units/kg/wk) SC daily at night.
- rhGH treatment should start with low doses and be titrated according to clinical response (growth rate) and IGF-I levels. Side effects are uncommon, but should be monitored, especially glucose intolerance.

#### Notes

- rhGH treatment is not always as effective as expected in non thalassaemic children with GHD and may result in decreased insulin sensitivity and abnormal glucose tolerance.<sup>[13]</sup>
- During GH treatment, patients should be monitored at 3-monthly intervals with a clinical assessment (growth parameters, compliance) and an evaluation for parameters of GH response and adverse effects.
- Continue treatment until the child reaches near final height, defined as a height velocity  $<2$  cm/year over at least 9 months (or bone age  $>13$  years in girls and  $>14$  years in boys)
- Treat other pituitary hormone deficiencies such as hypothyroidism, hypogonadism, hypocortisolism.

### Adults

At present, there are no guidelines in the literature for the use of GH treatment in adult patients with TM and GHD. The American Association of Clinical Endocrinologists (AACE) recommends that one GH stimulation test is sufficient if clinical suspicion is high, such as in patients with at least one other pituitary hormone deficiency and low or low-normal IGF-1 level. However, in patients with

TM and chronic liver disease, IGF-1 levels are low and may have a low diagnostic sensitivity for GHD.<sup>[23]</sup>

## HYPOTHYROIDISM

Annual investigation of thyroid function is recommended beginning at the age of 9 years (unless symptomatic hypothyroidism is observed). Measuring serum T4 and TSH levels easily makes the diagnosis. The stages of hypothyroidism are presented in Table 2.

Symptoms and signs of primary hypothyroidism in children and adolescents, such as growth retardation and weight increase, may present.<sup>[13,23]</sup> The majority of patients have primary thyroid dysfunction. Secondary hypothyroidism (low-normal TSH, low FT4) is very rare.

Notes: Refer to endocrinology and start replacement therapy as indicated.

### Management

Good compliance with chelation therapy may prevent or improve hypothyroidism, Sub-clinical hypothyroidism—basal TSH 5 to 7 mIU/ml—requires regular follow-up and optimizing chelation therapy.<sup>[13,23]</sup> In patients with mild or overt hypothyroidism, L-thyroxine is given.<sup>[13,26]</sup>

Notes: In patients with TM, subclinical hypothyroidism, and cardiomyopathy, treatment with amiodarone may result in a rapid progression of severe thyroid disease and deterioration of cardiac function.<sup>[23]</sup>

## HYPOPARATHYROIDISM

This uncommon complication presents after the age of 16 years equally in both sexes. The majority of the patients present with mild hypocalcemia and rarely, with tetany and cardiac failure.<sup>[10,20]</sup> Hypoparathyroidism is thought to be the consequence of iron deposition in the parathyroid glands or due to suppression of parathyroid secretion induced by bone reabsorption resulting from increased hematopoiesis secondary to the chronic anemia.<sup>[10,20]</sup>

**Table 2: Primary hypothyroidism and its treatment**

Primary Hypothyroidism	Serum FT <sub>4</sub>	Serum TSH	Treatment
Preclinical	Normal	Marginally increased (basal TSH: <8 mIU/l)	Observation-Intensification of iron chelation therapy
Mild	Marginally low	High	L-thyroxin
Overt	Low	Elevated	L-thyroxin

A majority of patients have mild disease and present with only paraesthesia. However, severe cases may present with tetany, seizures, or cardiac failure.<sup>[21]</sup> The diagnosis is based on low serum calcium, high phosphate and low PTH levels.<sup>[26]</sup> If hypoparathyroidism is suspected, there is always a risk of hypocalcemia which must be treated without delay.<sup>[23]</sup>

Notes: Refer to endocrinology and start therapy with vitamin D

### Management

Calcitriol (0.25-2.0 µg/day) and calcium (1 g of calcium/day) are the treatment of choice, with frequent monitoring of serum and urine calcium levels. Diet rich in calcium and low in phosphorus is advised.<sup>[26]</sup>

Notes: Recently, abnormal cerebral CT findings (calcifications) have been reported in relation to hypoparathyroidism in patients with TM.<sup>[27]</sup>

## CALCIUM HOMEOSTASIS AND BONE DISEASE (OSTEOPENIA AND OSTEOPOROSIS)

Osteopenia and osteoporosis are the most common bone complications of TM, despite regular transfusions and iron chelation therapy.<sup>[28]</sup> The etiology of TM-induced bone mineral loss is multi-factorial.<sup>[28]</sup> Medullary expansion due to anemia, patient age, duration of the disease, chronic liver disease, vitamin D deficiency, hypogonadism, concurrent hypothyroidism, and other endocrine-associated complications are significant contributory factors.

### Investigations

- Serum calcium, phosphorus, alkaline phosphatase
- 25-hydroxy vitamin D
- Parathyroid hormone
- Osteocalcin
- C-terminal telopeptide
- 24-h urinary calcium
- Spinal radiograph (AP and lateral views)
- MRI scan of the spine may be considered for patients with severe back pain to exclude a intervertebral disc degeneration
- Currently, dual-energy X-ray absorptiometry (DEXA) scan is the method of choice to assess bone mineral density (BMD)

Notes: Annual evaluation of calcium metabolism and parathyroid function is recommended. If the patient has pubertal delay or failure, FSH, LH, testosterone, or estrogen should be measured.

## Definitions

The absolute value of bone density varies but the accepted definitions for adult patients are:

1. Bone density T-score >1.5 SD below the mean is diagnostic of osteopenia.
2. Bone density T-score >2.5 SD below the mean is diagnostic of osteoporosis.

The diagnosis of osteoporosis in children should not be made on the basis of densitometric criteria alone. The diagnosis of osteoporosis requires the presence of both a clinically significant fracture history and low bone mineral density. Terminology such as “low bone density for chronological age” may be used if the Z-score is below -2.0.

Notes: DEXA or other accepted methods of measurement should be performed at 10-12 years for girls and boys annually and every 2 years thereafter. BMD should be related to the age (and the height in short subjects) and sex.

The same method of bone density measurement should be used for subsequent evaluations.

## Treatment

- Supplement with calcium 500-1000 mg/day starting at age 12 years.
- Follow nutritional status and vitamin D levels. Supplement with vitamin D 400-800 units/day for patients with low levels or those at high risk to develop vitamin deficiency.
- For patients with established osteoporosis, treatment with bisphosphonates should be considered.
- Endocrine referral is recommended for hormone replacement (estrogen for females, testosterone for males), calcium supplementation, exercise program, and consideration of bisphosphonates.<sup>[28]</sup>

## DIABETES MELLITUS

Diabetes mellitus is seen after the age of 10 years.<sup>[18,20,21,26]</sup> The etiology of DM is multifactorial (genetic factors, insulin deficiency, insulin resistance, and liver dysfunction secondary to viral hepatitis).

Insulin-dependent diabetes in TM presents with some unusual characteristics<sup>[18,26]</sup> compared with type 1 diabetes:

- Ketoacidosis is a rare presenting symptom
- Renal glucose threshold is high
- Islet cell antibodies are negative
- There is no association with HLA haplotypes B8-DR3, BW15, and DR4.

Patients usually present with impaired glucose tolerance,

mostly due to Insulin resistance and subsequently develop insulin deficiency.<sup>[18,20,21,26]</sup>

A 2-h oral glucose tolerance testing (OGTT), preferably combined with insulin secretion determination, should be performed at 10, 12, 14, and 16 years of age and annually thereafter. If fasting serum glucose is >110 mg/dl, OGTT is indicated.

## The diagnostic criteria for glucose tolerance are as follows

- Fasting blood glucose >126 mg/dl is diagnostic of diabetes mellitus
- OGTT serum glucose at 2 h >140 <200 mg/dl indicates glucose intolerance
- OGTT serum glucose at 2 h > 200 mg/dl is diagnostic of diabetes mellitus

## Therapeutic approaches

The patient should be referred to an endocrinologist for management of diabetes mellitus or glucose intolerance.<sup>[18,20,21,26]</sup>

- In cases where impaired glucose tolerance is present the patients are advised to follow a proper diet and lose weight if they are obese.
- Intensive iron chelation therapy with deferoxamine and deferiprone seems to be associated with an improvement in glucose intolerance in terms of glucose and insulin secretion, particularly in patients in early stages of glucose intolerance.<sup>[29]</sup>
- The use of oral anti-diabetic agents in DM (metformin and glibenclamide) remains undetermined.
- Insulin therapy is considered in the stage of insulin deficiency, where all other measures fail. Insulin dose is adjusted based on frequent glucose monitoring.

Patients with DM require periodical monitoring of metabolic control and possible complications.

## Notes

1. Metabolic control may be difficult to achieve. Insulin requirements (0.15-1.72 U/kg) differ due to a wide variation in pancreatic beta-cell function as determined by C-peptide level
2. Because the HbA1C test is based on normal hemoglobin, hemoglobinopathies can affect the reliability of the test in three ways:<sup>[30]</sup>
  - Altering the normal process of glycation of HbA to HbA1C
  - Causing an abnormal peak on chromatography, making estimation of A1C unreliable,
  - Making the red blood cell more prone to hemolysis, thereby decreasing the time for glycosylation to occur and producing a falsely low A1C result.

3. Fructosamine testing may be used as a target for metabolic control
4. Investigation of kidney function and imaging of the fundi should be carried out to evaluate the presence and degree of diabetic complications. However, the incidence of retinopathy and nephropathy in thalassemic patients with diabetes is lower than in patients affected by juvenile diabetes. It is suggested that this may be due to normal or below normal serum levels of cholesterol and triglycerides and to the frequent presence of hypogonadism in TM.<sup>[29]</sup>

## ADRENAL INSUFFICIENCY

Secondary hemochromatosis due to excess iron has the potential to disrupt adrenal function by affecting the hypothalamic-pituitary adrenal axis at the hypothalamic or pituitary and/or adrenal level.<sup>[30]</sup>

Several studies reported a significant prevalence of “biochemical” adrenal insufficiency, ranging from 0% to 45%, in patients with TM, due to different patient characteristics and different diagnostic tests used. Clinical adrenal insufficiency, i.e., adrenal crisis, on the other hand, is extremely rare.<sup>[30,31]</sup>

In primary adrenal insufficiency, cortisol, aldosterone, and androgen secretion are affected. Secondary or tertiary adrenal insufficiency (pituitary or hypothalamic affected) causes no mineralocorticoid defect.<sup>[32]</sup>

Patients are usually asymptomatic. Adrenal androgen levels might be decreased explaining the poor development of pubic and axillary hair observed in thalassemic adolescents.<sup>[30,31]</sup> Manifestations of mild adrenal hypofunction might be masked by symptoms commonly complained of by thalassemic patients, such as asthenia, muscle weakness, arthralgias, and weight loss.

### Investigations

Measurement of both basal serum cortisol level and cortisol response to stimulation by ACTH or insulin stimulation (ITT) can be used for assessment of adrenal function.

Baseline cortisol [morning baseline cortisol level (at 8-9 AM)] can be used to detect subtle adrenal insufficiency. Patients with abnormal screening are referred to the endocrinologist for further evaluation and replacement therapy.

ACTH stimulation test should be done in patients with an abnormal baseline cortisol level. A peak cortisol level of <500 nmol/L (18 µg/dL) 30-60 min after ACTH stimulation is abnormal.

Even though the insulin tolerance test (ITT) has been considered the gold standard to disclose impaired adrenal function, the ACTH stimulation test has been used for many years as an acceptable alternative with the advantage of lacking relevant adverse effects.<sup>[30,31,33]</sup> Either the low-dose (1 µg) or the standard high dose (250 µg/1.75 m<sup>2</sup> surface area) cosyntropin are used.<sup>[30,31]</sup>

### Treatment

It is advised to test adrenal function every 1-2 years, especially in GHD patients during rhGH therapy.

Clinical adrenal insufficiency and adrenal crisis are very rare. On the other hand, subclinical impairment of adrenocortical function in patients with TM is not uncommon, but of little or no clinical impact under basal conditions; however, it may have relevance during stressful events. Accordingly, glucocorticoid treatment coverage might be advised only for stressful conditions.<sup>[30,31]</sup>

## HYPAGONADISM

Delayed puberty and hypogonadism are the most obvious clinical consequences of iron overload.<sup>[13,18]</sup> Iron deposition in the pituitary gonadotrophic cells leads to disruption of gonadotropin (LH and FSH) production. In the majority of well-chelated patients, the function of gonads is normal; however, gonadal iron deposition occasionally occurs. TM patients with a favorable genotype manifest less severe gonadal dysfunction, due to less iron loading.<sup>[34]</sup>

Delayed puberty is defined as the complete lack of pubertal development in girls by the age of 13 years and in boys by the age of 14 years. Hypogonadism is defined by the absence of testicular enlargement (less than 4 ml) in boys, and by the absence of breast development in girls by the age of 16 years.<sup>[35]</sup>

Adolescent patients with TM may present with delayed puberty or slowly progressive puberty. Arrested puberty is a relatively common complication in moderately or grossly iron overloaded patients with TM. This is characterized by the lack of pubertal progression over a year or longer. In such cases, the yearly GV is either markedly reduced or completely stops.<sup>[13,18]</sup>

Most women with TM present with primary amenorrhea (PA), whereas secondary amenorrhea (SA) will invariably develop with time, especially in patients poorly compliant to chelation therapy. Ovarian function of these women is normal as they produce the expected number of ova after stimulation therapy. Damage of the ovaries by iron deposition is rare and is more likely to appear in women of 25-30 years of age because of high vascular activity in the ovaries at this age.<sup>[36]</sup>



## Investigations

Tanner staging should be determined every 6 months starting from the age of 12 years.

- Girls without evidence of puberty by 13 years and boys by 14 years require screening with measured serum levels of LH, FSH, and estradiol/testosterone:
  1. Low FSH and LH for age infer hypogonadotropic hypogonadism (HH) (hypothalamic-pituitary lesion) and MRI of the pituitary (T2\*) is recommended.
  2. Elevated FSH and LH suggests primary hypogonadism (very rare)
- If LH and/or FSH are low, performing GnRH stimulation with poor or flat LH and FSH responses confirms the diagnosis of HH.
- Bone age evaluation is useful for prediction of the final adult height of these patients.
- Pelvic ultrasound is useful in assessing ovarian and uterine maturation.

## Induction of puberty in boys: At 14 years or BA >12 years

The treatment of delayed or arrested puberty and HH depends on factors such as age, severity of iron overload, degree of damage to the hypothalamic-pituitary-gonadal axis, presence of chronic liver disease, and the psychological problems resulting from hypogonadism in these patients. The treatment of pubertal disorders in TM is a complex issue. Collaboration between endocrinologists and other physicians, nurses, psychologists, dieticians, and social workers is critical due to the many associated hematological, cardiac, hepatic, skeletal, and psychological disorders in these patients. Therefore, each patient has to be assessed individually.<sup>[18,20,21,20]</sup>

In boys, treatment is usually initiated with IM depot testosterone in doses of 50-100 mg per month. This is followed by hormonal re-assessment. In patients with HH, low dose testosterone therapy (50 mg) can be continued until the growth rate wanes. The fully virilizing dose is 75-100 mg of depot-testosterone esters every 10 days administered intramuscularly. The same effects can be achieved with topical testosterone gel.

For pubertal arrest, the treatment is similar to that of delayed puberty if growth potential is present or to that of HH when growth is completed.

## Induction of puberty in girls: At 13 years or BA >11 years

For girls, therapy may begin with the oral administration of ethinyl estradiol (EE) 2.5-5 µg daily for 6 months, followed by hormonal reassessment. If spontaneous puberty does not occur within 6 months after stopping the treatment, oral estrogen is re-introduced with gradually increasing dosages of EE from 5 to 10 µg daily for another 12 months and to 20 µg for additional 12 months. Norethisterone or

medroxyprogesterone acetate 5 mg/day 10-21 day and E2 for 21 days, once EE reaches 20 µg/day or if breakthrough bleeding occurs.

Transdermal administration of estrogens can also be used.<sup>[18,20,24,26]</sup>

The transdermal use of estradiol and norethisterone is the ideal substitution treatment in the hypogonadal female, because of its proven beneficial effect on bones and its fewer side effects.

## Management of fertility and pregnancy in β-thalassemia

The desire of the thalassaemic woman to become a mother is always viewed with special caution and sensitivity. Ambitions of this sort pose numerous medicolegal and ethical issues that need to be addressed prudently if the patients' quality of life is to be optimized.<sup>[37-47]</sup> Therefore, the desire of the female thalassaemic to procreate should be viewed with special caution and sensitivity by all physicians who are involved in her medical care.

Gynecological consultation is recommended in women for fertility evaluation.

Each patient should be assessed regarding suitability to embark on pregnancy with optimum outcome both for the mother and the fetus.<sup>[37-47]</sup>

Cardiac and liver functions are important issues, as well as the risk of vertical transmission of viruses. Ascertaining the hemoglobinopathy status of the partner is important.<sup>[37-39]</sup>

Women with TM, who are regularly transfused and are well chelated, can become pregnant either spontaneously or by inducing ovulation. The presence of gonadal dysfunction can be overcome with proper combination treatment. It is necessary that all pregnant women with TM be followed up very closely.<sup>[37-39]</sup>

Apart from the routine pregnancy follow-up, the thalassaemic pregnant woman needs additional medical care. Hemoglobin levels should be maintained at 10 g/dL and careful monitoring of vital signs during transfusion is required. Ferritin levels should also be measured and observed to avoid iron overload. Careful monitoring of the transfusion regime and regular evaluation of cardiac function should be done in all pregnant thalassaemic women to prevent fluid overload. Cardiac function should be evaluated periodically by a cardiologist.<sup>[37-39]</sup>

Iron chelation therapy, due to its possible teratogenic effects, is withheld as soon as the pregnancy is planned

or identified. It has been assumed that pregnancy is an efficient chelator of iron due to its hemodilution effect and the fetal consumption of free iron. Although therapy with DFO and deferasirox has not been implicated in any deleterious effect on the fetus, the current recommendation is its discontinuation, both once pregnancy is identified<sup>[39]</sup> and during the induction period.

Chronic maternal anemia in the thalassemic pregnant woman may result in fetal hypoxia, which predisposes to premature labor, intrauterine growth retardation (IUGR), and death.<sup>[39]</sup>

Induction of spermatogenesis in males by HCG/HMG should only be undertaken by a specialist. Cryopreservation of sperm should be recommended for all thalassemic patients after induction of spermatogenesis.<sup>[39,40]</sup>

## CONCLUSION

The practical objectives of I-CET are to encourage and guide endocrinological follow up of multi-transfused patients in developing countries, to promote and help collaborative research in this field, and to educate and train more endocrinologists and other pediatricians/physicians to prevent and improve management of the growth and endocrine complications in these patients.<sup>[41]</sup>

The following recommendations are an effort, based on current evidence and existing guidelines,<sup>[23,42-47]</sup> to bring uniform, consistently good care to patients affected by TM. Such comprehensive care is best provided in by coordinated, multidisciplinary teams working in expert centers. Physical, emotional, educational, and vocational aspects must be addressed.

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