ENDOCRINE DISEASE

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Endocrine Disease

Introduction

- Endocrine abnormalities are the most common complications of TM
- Prevalence varies because of:

- The different levels of treatment
- The severity of the genetic defect
- The hemoglobin level
- The degree of iron load
- And increased survival to adulthood

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Prevalence of different endocrinopathies

- **Delayed puberty/hypogonadism:** Ranges 50-100%
- Prevalence of adult-onset ranges 8.3- 12%
- Genetic factors influence the susceptibility to hypogonadism, because of:

- Differences in transfusional iron input and
- Vulnerability to free iron damage

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Prevalence of different endocrinopathies

- **Hypothyroidism:** varies from 6 -35%
- **Impaired glucose tolerance and DM:** prevalence increases with age and varies from 10 - 24%
- **Hypoparathyroidism:** Varies from 1-19%
- **Adrenal insufficiency:** prevalence of 'biochemical adrenal insufficiency' varies up to 45%, but clinical adrenal insufficiency is rare

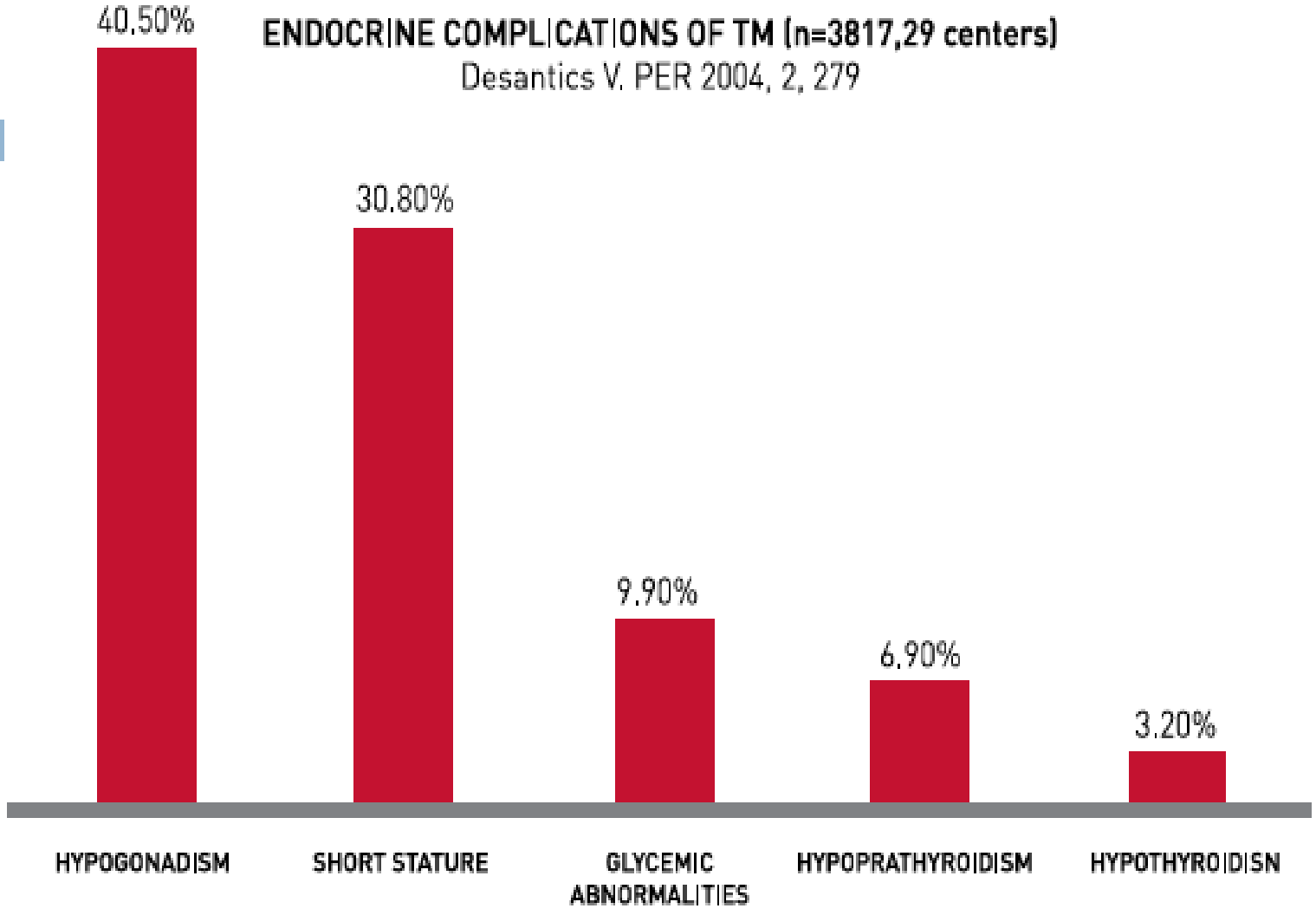

Figure 1. Growth and endocrine complications in thalassemia.Reproduced from Thalassaemia International Federation Study Group on Growth and Endocrine Complications in Thalassaemia (De Sanctis 2004).

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Delayed Puberty and Hypogonadism

- Delayed puberty and hypogonadism are the most obvious consequences of iron overload
- Delayed puberty is defined as the lack of pubertal development in girls by the age of 13, and in boys by age of 14
- Hypogonadism is defined in boys as the absence of testicular enlargement and in girls as the absence of breast development by the age of 16

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Delayed Puberty and Hypogonadism

- Arrested puberty is common in TM patients and is characterized by a lack of pubertal progression over a year or more
- In such cases, the testicular size remains 6-8 ml, and breast size at B3. And growth velocity is either reduced or absent
- Hypogonadism in adolescents and adults with TM has a prevalence of 38% in females and 43% in males

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Delayed Puberty and Hypogonadism

- Routine investigations include biochemical analysis,TSH and FT4, bone age and BMD
- Testing the hypothalamic-pituitary- gonadal axis as patients have:

- Lower basal FSH and LH secretion
- Low LH/FSH response to GnRH
- Low basal estradiol and testosterone
- Low testosterone secretion in response to HCG

• Pelvic ultrasound to assess ovarian and uterine size in females

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Treatment depends on factors such as

- Age,
- Severity of iron overload,
- Damage to the hypothalamic-pituitary-gonadal axis,
- Chronic liver disease and
- Presence psychological problems due to hypogonadism

- For girls, therapy may begin with ethinyl estradiol
- If breakthrough uterine bleeding does not occur, low estrogen-progesterone hormone replacement is recommended

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Treatment

- For delayed puberty in males, IM testosterone are given monthly for six months
- The same effects can be achieved with topical testosterone gel
- For pubertal arrest, the treatment consists of IM testosterone or topical testosterone gel

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Hypothyroidism

- Mainly attributed to iron overload and uncommon in optimally treated patients
- Central hypothyroidism is uncommon
- The frequency ranges from 6 to 30%
- The wide variations can be attributed to:

- Differences in patient genotypes,
- Differences in patients' ages,
- Ethnic variations and
- Different treatment protocols (transfusion and chelation)

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Laboratory tests

- TFT Should be performed annually, generally since 9 years
- FT4 and TSH are the key investigations but may include:
- Thyroid autoantibodies:
- Ultrasonography, to evaluate structure of thyroid gland
- Bone age, in selected cases
- Biochemistry including lipid profile
- Serum ferritin
- ECG and echocardiogram
- MRI of Hypothalamic-pituitary, in central hypothyroidism

Assessment of thyroid function

Grades of hypothyroidism

- Sub-clinical hypothyroidism is a combination of high TSH with normal FT4 levels

- Type A (normal FT4, TSH 5-10 μU/ml)

- Type B (normal FT4, TSH > 10 μU/ml)

- Overt hypothyroidism (high TSH with low FT4)

- Diagnosis of central hypothyroidism is based on low level of thyroid hormone with low TSH

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Clinical examination

- Signs of hypothyroidism are nonspecific and are attributed to anemia
- Patients with overt hypothyroidism exhibit:

- Stunted growth,
- Delayed puberty,
- Cardiac failure, and pericardial effusion
- They are shorter with more delayed bone age than euthyroid TM patients

Treatment

- Overt and central hypothyroidism: levothyroxine
- Subclinical hypothyroidism: intensification of chelation
- Subclinical hypothyroidism is treated when TSH > 8
  - Amiodarone may result in progression from subclinical to overt hypothyroidism

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Impaired Glucose Tolerance (IGT) and (IDDM)

- Common in patients who inadequately iron chelated
- Also have been observed in well transfused/ chelated patients, suggesting other cause may be involved:
  - Individual sensitivity to iron damage,
  - Chronic anemia,
  - Zinc deficiency and
  - Increased collagen deposition secondary to iron overload

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Impaired Glucose Tolerance (IGT) and (IDDM)

- Prevalence varies from 0 to 17%
- IDDM is uncommon during the first years of life and increases with age
- IGT may start early in the second decade of life in parallel with puberty

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Pathogenesis of IDDM in TM patients

- The initial abnormality is insulin resistance rather than defective insulin production, but :
- Insulin deficiency as a result of toxic damage from iron
- Pancreatic β-cell dysfunction characterized by:

- Insulin - resistance with normal OGTT
- IDDM

- Liver siderosis along with hep. C accelerates progression to IDDM
- Early recognition is essential
- The OGTT should be done after 10 yrs or earlier if needed

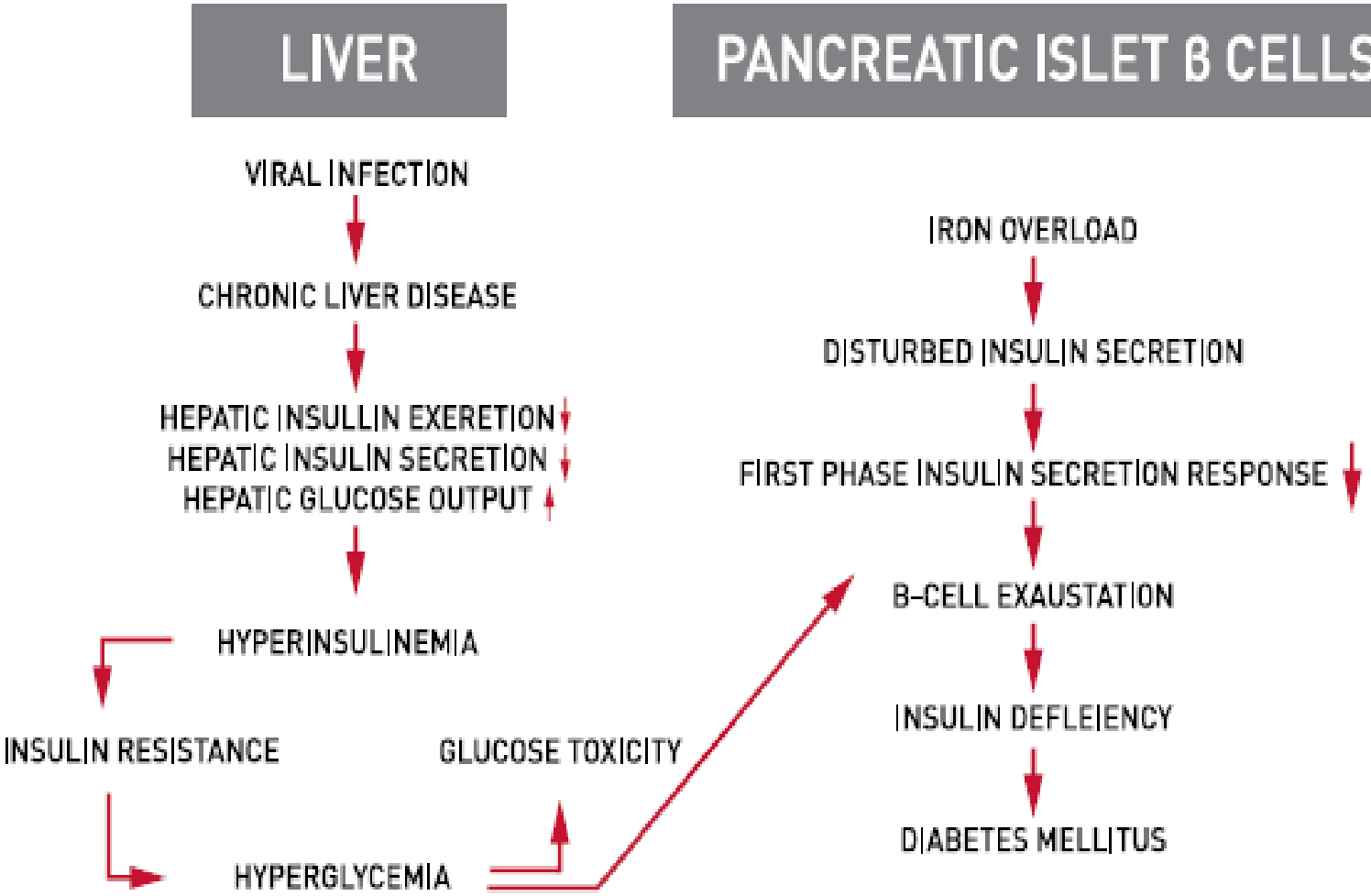

Figure 3. Pathogenesis of abnormal glucose homeostasis in thalassaemia. Reproduced with permission from (De Sanctis V. TIF Congress, Dubai – 2006).

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Diagnosis

- FBS >126 mg/dl is diagnostic of diabetes mellitus
- 2hpp>200 mg/dl is diagnostic of diabetes mellitus
- 2hpp >140 <200 mg/dl indicates IGT
- Pancreatic iron can be evaluated by MRI
- MRI and fasting glucose/insulin are complementary
- OGTT remains the gold standard
- Screening for viral hepatitis and regular chelation therapy are important in preventing of diabetes

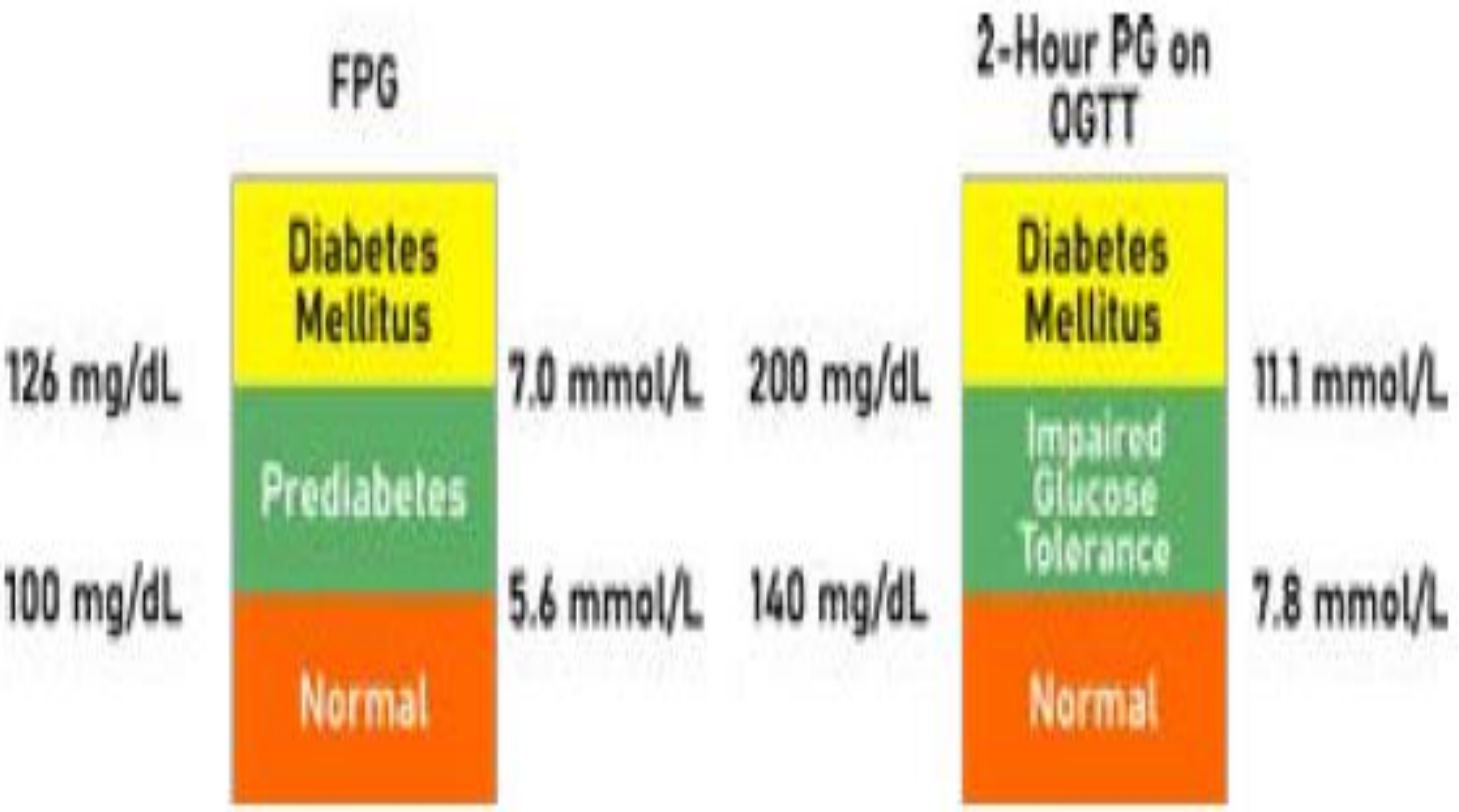

Figure 6. **The diagnostic criteria for the glucose tolerance.** FPG: fasting plasma glucose; OGTT, oral glucose tolerance test; PG, plasma glucose.

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Management

- Intensive iron-chelation and prevention and treatment of hepatitis C are most important issues
- Intensive chelation can normalise β-cell function and may improve insulin secretion and glucose tolerance
- Healthy diet suitable for IDDM
- Regular physical activity
- Drugs used with good effect: Metformin, acarbose glibenclamide, sitagliptin
- When overt IDDM develops, patients require insulin

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Management

- Diabetic patients should be seen by a multidisciplinary team. The team should include an endocrinologist and dietician
- Monitoring glycemic control in thalassemia patients is the same as with nonthalassemic patients with IDDM
- Urine ketones if blood sugar >250 mg/dl
- Fructosamine determination is useful
- Periodic assessment of renal function
- Microalbumin test to detect early signs of kidney damage (once a year)
- Evaluation of retinopathy

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Hypoparathyroidism is complication of second decade of life in TM

- The incidence varies from 1.2- 19% and seen more in men

Signs and symptoms

- Most patients show paresthesia and prolonged QTC
- Severe cases demonstrate tetany, seizures or cardiac failure

Investigations should begin from the age of 16 years and include serum Ca, phosphate and ALP

- In cases with low calcium and high phosphate levels, PTH should also be measured

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Management **:** To prevent complications of hypocalcemia

- Control of symptoms,
- Maintaining serum calcium in the low to normal range
- Maintaining serum phosphorus within normal limits,
- Maintaining 24-hour urine calcium < 300 mg/day
- Maintaining calcium-phosphate product < 55 for prevention of nephrolithiasis, nephrocalcinosis and soft-tissue calcification

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Treatment includes Oral vitamin D. Some patients require high doses

- Calcitriol, 0.25-1.0 μg, twice daily, is usually sufficient
- Phosphate binder in patients with high phosphate level
- Tetany and cardiac failure require IV calcium, followed by oral vitamin D
- In some patien treated with calcium and vitamin D, hypercalciuria is a potential unwanted effect
- In these cases restriction of Na, thiazide diuretics or reduction of calcium or calcitriol may be required

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Dietary steps

- No special diet is required, but some dietician is likely to advise a diet that is:
- Rich in calcium. This includes
  - dairy products,
  - green leafy vegetables,
  - broccoli,
  - kale
  - Fortified orange juice and breakfast cereals
- Low in phosphorus-rich items
  - Avoiding carbonated soft drinks
  - Eggs and meats also tend to be high in phosphorus

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Adrenal Insufficiency

- There is a significant prevalence of 'biochemical' adrenal insufficiency in patients with TM (0 to 45%)
- But Clinical adrenal insufficiency (adrenal crisis) is extremely rare

Diagnosis

- Mild forms might be masked by other complications of TM, such as:
- Asthenia, muscle weakness,
- Arthralgia and
- Weight loss

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Laboratory tests

- Cortisol levels both basal and 30-60 minutes after ACTH or insulin stimulation
- It is advised that adrenal function be tested every 1–2 years, especially in GH deficient patients during rhGH therapy

Treatment

- In Subclinical impairment, Glucocorticoid treatment might be advised only for stressful conditions
- Clinical adrenal insufficiency are rare

Short statements

- Endocrine complications are very common in TM
- Periodic evaluation of these problems advised, particularly after the age of 11 years
- Delayed puberty and hypogonadism are the most obvious clinical consequences of iron overload
- The etiology of IDDM is multifactorial (genetic factors, insulin deficiency, insulin resistance and liver dysfunction secondary to viral hepatitis)
- Sub-clinical hypothyroidism (TSH 5 to 8) requires regular follow-up and optimizing chelation therapy

Short statements

- Subclinical impairment of adrenocortical function is common, but clinical adrenal crisis are rare
- Most patients with hypoparathyroidism show a mild form of the disease
- Intensive chelation reverses cardiac and endocrine complications of TM
- Monitoring of growth, puberty, reproductive ability and endocrine functions are essential to achieve a good quality of life in TM

THANK YOU