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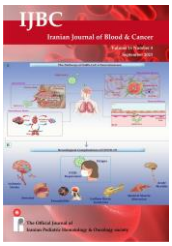

Review

Review of Endocrine Complications in Transfusion-Dependent Thalassemia

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Abstract

Acute Beta thalassemia is an inherited genetic disorder that often leads to transfusion dependence. One of the significant issues that these patients face is increased iron accumulation in their bodies due to the nature of the disease and regular blood transfusions. Iron overload can cause hemosiderosis and tissue damage in various organs, including the heart, liver, and endocrine systems. Endocrine problems are one of the most common complications in transfusion-dependent thalassemia, and addressing these complications can significantly improve patients' health-related quality of life. The prevalence of endocrinopathy is high, especially in patients with poor compliance with therapy. The most common endocrine disorders include hypogonadism, growth disturbances, short stature, delayed puberty, acquired hypothyroidism and hypoparathyroidism, adrenal dysfunction, osteoporosis, diabetes, fertility issues, and complications during pregnancy. Timely diagnosis and treatment of endocrine disorders can improve patient's quality of life and reduce social problems. This article reviews the literature on the various endocrine complications encountered in thalassemia.

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1. Introduction

Transfusion-dependent Beta-thalassemia (TDT) is a hereditary hemoglobinopathy characterized by abnormal synthesis of the beta chains of hemoglobin. Transfusion-dependent patients can present with variable phenotypes ranging from intermediate to major forms of the disease. The global prevalence of beta-thalassemia is approximately 1.5% to 3% (1, 2). Thalassemia major is a genetic disorder characterized by abnormal hemoglobin production, which leads to severe chronic anemia. Due to chronic anemia, individuals with thalassemia major often require frequent blood transfusions, which can lead to iron overload and subsequent organ damage (3, 4). According to a report from the Ministry of Health

of Iran, the prevalence of beta-thalassemia major in the country is 4%, with variable percentages observed in Kerman province and across different regions of Iran. The highest rates were observed in the Sistan, Baluchistan, and Mazandaran provinces. Of the approximately 24,000 thalassemia patients registered in Iran, nearly 19,000 have TDT, while the rest have intermediate thalassemia (5-8).

The current treatment for thalassemia major includes a regular blood transfusion program and iron chelators therapy. Iron overload disrupts the body's iron homeostasis, increasing extracellular non-transferrin-bound iron (NTBI) and intracellular labile iron pool. This increase in iron levels leads to the production of reactive oxygen species by the Fenton and Haber-Weiss reaction, which subsequently induces oxidative damage to vital components of the cells (9, 10). Iron overload can cause organ damage, particularly in the heart, liver, and endocrine glands. Chronic hypoxia due to anemia may facilitate the toxicity of iron deposition in these organs. Patients with good compliance to chelators therapy and good quality of care can reduce or prevent iron accumulation and its complications, decreasing morbidity and mortality (11-14).

There is a link between endocrinopathy and thalassemia; people with thalassemia may be at risk for endocrine disorders such as diabetes, hypothyroidism, and others. Individuals with thalassemia require regular medical care and monitoring to manage potential endocrine complications (15, 16).

Iran's comprehensive thalassemia care system has achieved proper quality care and a good quality of life for patients through an organized multidisciplinary team of specialists. Such a team should include a hematologist, endocrinologist, cardiologist, psychologist, blood banking specialist, gastroenterologist, social worker, and other specialists. Due to the increasing age of TDT patients, many endocrine problems are becoming more prevalent. However, the prevalence of these problems varies depending on the standard of care for thalassemia management worldwide.

2. Methods

A comprehensive search of electronic databases including PubMed, Medline, Embase, and Web of Science was conducted to identify articles related to endocrine complications in transfusion-dependent thalassemia. The investigation was performed using the following keywords: thalassemia, transfusion-dependent, endocrine complications, hypogonadism, hypothyroidism, diabetes, osteoporosis, and growth hormone deficiency. The search was limited to articles published in English till 2023. Data were extracted from the selected studies using a standardized data extraction form.

The following information was extracted from each study:

- Study design
- Patient characteristics (age, gender, and thalassemia genotype)
- Type and prevalence of endocrine complications
- Diagnostic criteria and methods used to diagnose endocrine complications
- Treatment options for endocrine complications.

The extracted data were synthesized using a narrative approach. The findings of the studies were summarized and presented in a structured manner, highlighting the prevalence, diagnosis, and management of endocrine complications in transfusion-dependent thalassemia. The data were organized according to the type of endocrine complication, and the results of each study were compared and contrasted to identify similarities and differences.

3. Endocrine Complications in Transfusion-Dependent Thalassemia

3.1. General Endocrine Complications

Endocrine glands, such as the pituitary, thyroid, parathyroid, adrenal, and gonads, are particularly vulnerable to iron overload and damage, leading to a high incidence of endocrine complications in individuals with thalassemia major (1, 17).

Routine endocrine screening accurately assesses height and weight at each visit. Evaluate growth based on standards charts. Annual endocrinology consultation and screening should be started at five years of age, after three years of transfusions, or as otherwise clinically indicated. The following tests are recommended annually or semiannually: TSH and free T4, PTH, serum calcium, ionized calcium, vitamin D, Fasting glucose, oral glucose tolerance testing as indicated by fasting glucose, IGF-1 and IGF BP-3 to screen for growth hormone deficiency, Trace elements: zinc, copper, selenium, Vitamins B1, B6, B12, C, E, A, pyridoxine, carnitine, methylmalonic acid, and homocysteine.

Figure 1 shows the mechanism of complications in thalassemia patients.

•Growth hormone deficiency: Growth hormone deficiency is a common complication in children with thalassemia major, occurring in up to 50% of cases. It can lead to growth failure, delayed puberty, and short stature. Growth hormone replacement therapy can be used to treat this condition (18).

•Hypogonadism: Hypogonadism refers to an underactive gonad, which can lead to delayed puberty, infertility, and osteoporosis. Hypogonadism is a common complication in male and female patients with thalassemia major, occurring in up to 70% of cases. Hormone replacement therapy can be used to treat this condition (19).

•Hypothyroidism: Hypothyroidism is when the thyroid gland does not produce enough thyroid hormone, leading to fatigue, weight gain, and cold intolerance. Hypothyroidism is a common complication in individuals with thalassemia major, occurring in up to 15% of cases. Thyroid hormone replacement therapy can be used to treat this condition (20).

•Diabetes: Individuals with thalassemia major are at increased risk of diabetes due to insulin resistance, iron overload, and chronic liver disease. The incidence of diabetes in thalassemia major varies depending on the population studied, with some studies reporting rates as high as 30% (21).

•Hypoparathyroidism: Hypoparathyroidism is a condition in which the parathyroid gland does not produce enough parathyroid hormone, leading to low calcium levels in the blood. Hypoparathyroidism is a rare complication of thalassemia major, occurring in less than 5% of cases, but it can cause significant morbidity if left untreated (22).

•Adrenal insufficiency: Adrenal insufficiency refers to a condition in which the adrenal gland does not produce enough cortisol, leading to symptoms such as fatigue, muscle weakness, and low blood pressure. Adrenal insufficiency is a rare complication of thalassemia major, occurring in less than 5% of cases (23).

The frequency of endocrine complications varies in different areas according to the standard of care and availability of iron chelators (**Table 1**). Here's an updated table with the frequency of incidence of endocrine complications in thalassemia major (21, 24-33).

3.2. Growth and development in thalassemia

Growth hormone (GH), also known as somatotropin, is a hormone produced by the pituitary gland that stimulates growth, cell reproduction, and regeneration in humans and other animals. GH is essential for normal growth

Table 1. **The frequency of endocrine complications in thalassemia major in different countries.** It can vary widely depending on the study and the patient population, and these estimates may not represent all patients with thalassemia major. Also, studies from some countries may not have been available for all endocrine complications.

Endocrine Complication	Incidence in Thalassemia Major	Frequency in Studies	Frequency in Iran	Frequency in USA	Frequency in Italy	Frequency in Greece	Frequency in India	Frequency in Turkey
Hypogonadism	High	Up to 70%	Up to 70%	30% to 70%	Up to 70%	75.5% to 88%	Up to 50%	Up to 75%
Hypothyroidism	High	Up to 22.5%	Up to 22.5%	15% to 23%	11.9% to 23.2%	12% to 27%	Up to 14%	Up to 18%
Diabetes Mellitus	Moderate	Up to 8.7%	11.4%	Up to 8%	20.4% to 25%	Up to 8.7%	Up to 8%	Up to 4.9%
Hypoparathyroidism	Low	Up to 4.2%	Up to 4.2%	Not reported	Not reported	5.3%	Up to 1%	Up to 4.2%
Growth Hormone Deficiency	Low	Up to 6.7%	Up to 6.7%	17% to 22%	4.9% to 7.8%	8% to 10.6%	Up to7.8%	Up to 6.7%
Adrenal Insufficiency	Rare	Up to 3.5%	Up to 3.5%	Up to 3.3%	Up to 13.7%	3.2%	Up to 3.3%	Up to 3.5%
Hyperprolactinemia	Rare	Rare	13%	Up to 11.9%	Up to 13%	22%	Not reported	1.7% to 4%
Primary Hyperparathyroidism	Rare	Up to 5.7%	Up to 5.7%	Not reported	Not reported	Not reported	Up to 6.8%	Up to 4.2%
Osteoporosis	High	Up to 66%	39%	30.4% to 45.6%	Up to 50%	27.7% to 40.5%	Up to 70%	Up to 44%

and development during childhood and adolescence, and it also plays a critical role in maintaining bone density, muscle mass, and energy metabolism in adults. GH also plays a role in the maturation of various organs, including the brain, heart, and kidneys. It is essential to promote overall growth and development and regulate metabolism and body composition. In children, GH is necessary for normal growth and development. It stimulates the growth of bones, muscles, and organs and helps regulate body composition by promoting lean body mass growth and reducing fat accumulation. GH also plays a role in the maturation of various organs, including the brain, heart, and kidneys. GH continues to play a role in regulating metabolism and body composition in adults, but its effects are less pronounced than in children. GH deficiency in adults can lead to various symptoms, including decreased muscle mass, increased body fat, reduced bone density, and decreased energy and quality of life.

Chronic anemia and iron overload can lead to growth hormone deficiency (GHD), characterized by inadequate GH secretion from the pituitary gland in individuals with thalassemia major. GHD is a common complication in children with thalassemia major, occurring in up to 50% of cases. It can lead to growth failure, delayed puberty, and short stature (18-23, 34). All patients are required if there is a 5 percent or more falloff on the growth curve or poor growth velocity for the age.

A GH stimulation test should be performed if the patient presents with the following clinical and laboratory parameters: short stature (height standard deviation scores <−2.5), severe and/or prolonged iron overload, severe osteoporosis, and/or serum IGF-I level <−2 standard deviations. In patients with childhood-onset GHD, very low IGF-1 levels in the

presence of pituitary iron deposition and/or atrophy are highly suggestive of GHD. In adult TM patients with normal liver function, an IGF-I level <50th percentile should be considered a cut-off level for the GH assessment (18, 20).

The diagnosis of GHD in thalassemia major is typically based on clinical signs and symptoms, such as growth failure, delayed puberty, and low insulin-like growth factor 1 (IGF-1), a hormone produced in response to GH stimulation. GH stimulation tests may also be used to confirm the diagnosis (13, 17, 22). Growth hormone replacement therapy can be used to treat growth hormone deficiency in individuals with thalassemia major and has been shown to improve growth, bone density, and quality of life in these patients (34). Treatment for GHD in thalassemia major typically involves daily injections of synthetic GH, which can help to promote growth and development. GH therapy has been shown to be effective in improving growth velocity and final adult height in children with thalassemia major. However, long-term studies are needed to determine the safety and efficacy of GH therapy in this population (34, 35). It's important to note that diagnosing GHD in thalassemia major can be challenging, as iron overload and liver disease can also affect levels of IGF-1 and GH. Therefore, the diagnosis of GHD should be made by a healthcare professional with expertise in endocrinology and thalassemia major (36, 37). The treatment for growth hormone deficiency (GHD) in thalassemia major typically involves growth hormone replacement therapy. Growth hormone replacement therapy involves the administration of synthetic growth hormone (4, 36). Growth hormone replacement therapy aims to increase growth velocity and promote the development of lean body mass, bone density, and organ function. The treatment is usually started in children with a confirmed diagnosis of GHD. It is continued until the child reaches their final height or until growth velocity reaches a plateau. The dose of growth hormone replacement therapy is typically calculated based on the child's weight and is usually administered daily via subcutaneous injection. The treatment is generally well-tolerated, and potential side effects include fluid retention, joint pain, and the development of antibodies to the synthetic growth hormone (36-38). In addition to growth hormone replacement therapy, other treatments may be necessary to address other endocrine complications that are common in thalassemia major, such as hypothyroidism, hypogonadism, and diabetes (38-40). It's important to note that growth hormone replacement therapy is not without risks and should be used under the guidance of a healthcare professional with expertise in endocrinology and thalassemia major. Regular monitoring is required to ensure that the benefits of the treatment outweigh the risks and to adjust the dose as necessary to achieve optimal growth and development (41, 42).

The dose of growth hormone replacement therapy in individuals with thalassemia major should be adjusted based on several factors, including the individual's age, weight, and response to treatment. Growth hormone replacement therapy aims to promote optimal growth and development while minimizing the risk of side effects (43). The initial dosage of growth hormone ranging from 0.5–1.0 IU/kg/wk has significantly improved growth velocity in transfusion-dependent thalassemia children without any adverse effects on skeletal maturation, blood pressure, glucose tolerance, and serum lipids. During the initial phase of treatment, the dose of growth hormone replacement therapy is usually adjusted every three to six months based on the individual's growth velocity, bone age, and serum insulin-like growth factor 1 (IGF-1) levels. The goal is to achieve a growth velocity that is consistent with the individual's genetic potential while avoiding over-treatment (44).

Once a stable dose of growth hormone replacement therapy has been established, the individual should continue to be monitored regularly to ensure that the treatment is effective and well-tolerated. Follow-up visits should occur at least every six months and may

involve measurement of height, weight, bone age, and serum IGF-1 levels (1). If the individual does not respond to growth hormone replacement therapy, or if side effects occur, the dose of the treatment may need to be adjusted, or the treatment may need to be discontinued. It's important to note that growth hormone replacement therapy should be used under the guidance of a healthcare professional with expertise in endocrinology and thalassemia major and that regular monitoring is required to ensure that the treatment is safe and effective. Growth hormone replacement therapy is generally safe and well-tolerated in individuals with growth hormone deficiency (GHD) due to thalassemia major. However, like all medications, it can cause side effects in some individuals (36). Common side effects of growth hormone replacement therapy include:

- Injection site reactions: The most common side effect of growth hormone replacement therapy is pain, redness, or swelling at the injection site.
- Fluid retention: Growth hormone replacement therapy can cause water retention, leading to swelling in the hands and feet.
- Joint pain: Some individuals may experience joint pain or stiffness due to growth hormone replacement therapy.
- Headaches: Headaches are a common side effect of growth hormone replacement therapy, especially during the first few weeks of treatment.
- Hypoglycemia: Growth hormone replacement therapy can cause low blood sugar levels (hypoglycemia) in some individuals, particularly those with diabetes.
- Increased risk of cancer: There is some evidence to suggest that long-term use of growth hormone replacement therapy may increase the risk of certain types of cancer, such as leukemia and brain tumors. However, this risk is thought to be small (45, 46).

Notably, the risk of side effects from growth hormone replacement therapy is generally low, and most individuals tolerate the treatment well (44). However, like all hormone replacement therapies, growth hormone replacement therapy has potential risks and side effects and should be used under the guidance of a healthcare professional.

Overall, growth hormone is an important hormone that plays a critical role in growth and development. In individuals with thalassemia major, growth hormone deficiency is a common complication that can have significant morbidity if left untreated. Early diagnosis and treatment with GH therapy can help to prevent and manage this complication (7, 12).

3.3 Hypogonadism and puberty in thalassemia

Thalassemia major is associated with an increased risk of hypogonadism, which is a condition where the body produces little or no sex hormones. This can lead to delayed puberty or absent puberty, resulting in incomplete sexual development. The exact mechanisms underlying hypogonadism in thalassemia major are not fully understood, but it is thought to be related to iron overload, chronic anemia, and endocrine dysfunction (11). Delayed or absent puberty is also common in individuals with thalassemia major, particularly those who receive frequent blood transfusions. Blood transfusions can lead to iron overload and damage to the pituitary gland, which can interfere with the normal production of the hormones that initiate puberty. Tanner staging should be assessed every six months. If girls show no evidence of advancing pubertal stage by 12 years or boys by 14 years, it is recommended to screen them using LH-ICMA, FSH, and estradiol levels, along with obtaining bone age films. The common symptoms of hypogonadism in thalassemia major can vary depending on the age of the individual but can include: Absent or delayed puberty, Lack of menstrual cycles in females, Decreased libido or sexual desire in both males and females, Erectile dysfunction in males, Infertility, Decreased muscle mass and strength, Decreased bone density, Hot flashes or night sweats, fatigue or decreased energy levels(45). It is important to note that some

individuals with hypogonadism may not experience any symptoms. Regular monitoring and screening for endocrine complications, including hypogonadism, are essential for individuals with major thalassemia to prevent further complications (16). To screen for hypogonadism in thalassemia major, healthcare providers may use the following tests:

- Hormone levels: Blood tests can be used to measure hormone levels such as testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Low levels of testosterone and gonadotropins (FSH and LH) may suggest hypogonadism.
- Bone density: Dual-energy X-ray absorptiometry (DXA) scans can be used to measure bone density, which can help detect osteoporosis and other bone-related complications of hypogonadism.
- Genetic testing: Genetic testing can be performed to identify mutations in genes that are associated with hypogonadism.
- Imaging studies: Imaging studies such as magnetic resonance imaging (MRI) or computed tomography (CT) scans can be used to evaluate the pituitary gland, which may be affected in cases of hypogonadism.
- Semen analysis: A semen analysis may be used to evaluate male fertility (47).

It is important to note that not all individuals with thalassemia major require screening for hypogonadism, and screening protocols may vary depending on the age and sex of the individual (14). Healthcare providers can advise on appropriate screening and follow-up care based on an individual's specific circumstances. Hypogonadism in thalassemia major can lead to a number of complications, including:

- Delayed or absent puberty: Hypogonadism can delay puberty or prevent it from occurring altogether, resulting in incomplete sexual development.
- Infertility: Hypogonadism can reduce or eliminate fertility in both males and females.
- Decreased bone density: Hypogonadism can lead to reduced bone density, increasing the risk of fractures and osteoporosis.
- Decreased muscle mass and strength: Hypogonadism can lead to reduced muscle mass and strength, which can affect physical performance and overall quality of life.
- Sexual dysfunction: Hypogonadism can cause sexual dysfunction such as erectile dysfunction, decreased libido, and vaginal dryness.
- Hot flashes and night sweats: Hypogonadism can sometimes cause hot flashes and night sweats (44).

If LH-ICMA and/or FSH levels are abnormal, a GnRH stimulation test should be performed. It is advisable to consider performing this test at age 12 in girls and age 14 in boys, with subsequent yearly assessments as clinically indicated. It's important to schedule this test on a different day than a blood transfusion and the oral glucose tolerance test.

Hypogonadism can lead to further complications, such as cardiovascular disease and metabolic disorders, if left untreated. However, with appropriate treatment and monitoring, many of these complications can be prevented or managed effectively. It is crucial for individuals with thalassemia major to receive regular monitoring and follow-up care to manage potential endocrine complications, including hypogonadism (22). Early diagnosis and treatment of hypogonadism are essential to prevent further complications such as decreased bone density and impaired fertility. Hormone replacement therapy (HRT) is often used to stimulate puberty and promote sexual development in individuals with thalassemia major (44). HRT may also help to improve bone density and reduce the risk of osteoporosis. It is essential for individuals with thalassemia major to receive regular monitoring and follow-up care to manage potential endocrine complications, including hypogonadism and delayed puberty. A multidisciplinary approach involving a hematologist, endocrinologist, and other specialists is often necessary to provide comprehensive care for individuals with thalassemia major. The treatment for hypogonadism in thalassemia major typically involves hormone replacement therapy (HRT), which is aimed

at restoring normal levels of sex hormones. The type of HRT used, and the duration of treatment may vary depending on the individual's age, sex, and the severity of the hypogonadism (44, 45).

In males, testosterone replacement therapy can be used to restore levels of testosterone, which can help improve sexual function, increase muscle mass and strength, and improve bone density. In females, estrogen and progesterone replacement therapy can be used to restore hormone levels and promote sexual development. HRT can also help to improve bone density and reduce the risk of osteoporosis. In addition to HRT, lifestyle modifications such as regular exercise and a healthy diet can help improve bone density and reduce the risk of complications related to hypogonadism (35). In boys, testosterone levels should be checked annually, starting in early adolescence (around 12 years old). If a patient's testosterone level is low, an endocrine consultation should be sought, and monthly testosterone treatment can be initiated. The typical starting dose is 50 to 100 mg, administered as a monthly intramuscular shot. The dosage will need periodic adjustments based on the patient's age, pubertal status, and sexual activity. It is important for individuals with thalassemia major to receive regular monitoring and follow-up care to manage potential endocrine complications, including hypogonadism. A multidisciplinary approach involving a hematologist, endocrinologist, and other specialists may be necessary to provide comprehensive care for individuals with thalassemia major (23).

In males, testosterone replacement therapy can be used to promote the development of secondary sex characteristics and improve bone density. Testosterone replacement therapy (TRT) is a medical treatment that involves administering testosterone to individuals with low hormone levels (44). Testosterone is a naturally occurring hormone that is primarily produced in the testicles in men and in the ovaries and adrenal glands in women. It plays a crucial role in the development of male sexual characteristics, such as muscle mass, bone density, and body hair, as well as in the regulation of libido and mood. TRT is typically prescribed to men who have low testosterone levels due to aging, injury, or disease. It can be administered in several forms, including injections, patches, gels, and pellets. TRT can help to improve symptoms associated with low testosterone levels, such as fatigue, decreased libido, erectile dysfunction, and depression. However, TRT is not without risks. Possible side effects of TRT include acne, fluid retention, breast enlargement, and sleep apnea. Long-term use of TRT can also increase the risk of heart attack, stroke, and prostate cancer. For this reason, TRT should only be prescribed and monitored by a qualified healthcare professional, and individuals considering TRT should undergo a thorough medical examination and hormone evaluation to determine if they are good candidates for the therapy (48, 49). In females, estrogen replacement therapy can be used to promote the development of secondary sex characteristics, regulate menstrual cycles, and improve bone density. There is limited research on the use of estrogen and progesterone replacement therapy (ERT/PRT), specifically in individuals with thalassemia. However, ERT/PRT is sometimes prescribed to women with thalassemia who experience menstrual irregularities or infertility due to low estrogen and/or progesterone levels. ERT can help to alleviate symptoms associated with low estrogen levels, such as hot flashes, vaginal dryness, and bone loss. PRT can help to support pregnancy in women undergoing fertility treatment. Estrogen replacement therapy is recommended for amenorrhoeic adolescent girls and adult women. A low dose of Premarin (0.0375 μg per day) is typically prescribed for six months. After this period, the dose can be increased for an additional six to twelve months. Subsequently, an oral contraceptive pill may replace Premarin. It is advisable for women on estrogen therapy to consult with a gynecologist and undergo fertility evaluation. However, ERT/PRT is not without risks as with any hormone replacement

therapy. Possible side effects of ERT/PRT include bloating, breast tenderness, mood changes, headaches, and an increased risk of blood clots, stroke, and breast cancer. The timing and duration of hormone replacement therapy depends on the individual's age, sex, and specific endocrine complications. Progesterone replacement therapy (PRT) is a medical treatment that involves administering progesterone to individuals who have low levels of the hormone. Progesterone is a naturally occurring hormone that is primarily produced in the ovaries in women and in the testes and adrenal glands in men. It plays a crucial role in regulating the menstrual cycle and preparing the uterus for pregnancy (22, 50, 51). PRT is typically prescribed to women who have low progesterone levels due to menopause, infertility, or other medical conditions. It can be administered in several forms, including oral capsules, creams, gels, and injections (23). PRT can help to alleviate symptoms associated with low progesterone levels, such as irregular menstrual cycles, hot flashes, and sleep disturbances. It may also be used to support pregnancy in women undergoing fertility treatment. However, PRT is not without risks. Possible side effects of PRT include bloating, breast tenderness, mood changes, and headaches. Long-term use of PRT can also increase the risk of blood clots, stroke, and breast cancer. For this reason, PRT should only be prescribed and monitored by a qualified healthcare professional, and individuals considering PRT should undergo a thorough medical examination and hormone evaluation to determine if they are good candidates for the therapy. It's important to note that hormone replacement therapy should be used under the guidance of a healthcare professional with expertise in endocrinology and thalassemia major, as there are potential risks and side effects associated with this treatment. In addition to hormone replacement therapy, other treatments may be necessary to address other endocrine complications that are common in thalassemia major, such as hypothyroidism, diabetes, and growth hormone deficiency (50, 52).

Hormone replacement therapy (HRT) for hypogonadism in thalassemia major can have potential side effects, which may vary depending on the type of hormone replacement used and the individual's specific circumstances. Some potential side effects of HRT include Acne, Fluid retention, Breast tenderness or enlargement, Mood changes, Headaches, Nausea, Vaginal bleeding, or spotting (in females) (35). In addition, long-term use of HRT can increase the risk of certain health conditions, such as blood clots, stroke, and breast cancer. However, the risks associated with HRT may be lower in individuals with thalassemia major than in the general population since the condition is often associated with iron overload, which can have a protective effect against hormone-related cancers. It is essential for individuals receiving HRT to receive regular monitoring and follow-up care to manage potential side effects and evaluate the effectiveness of the treatment. Monitoring and follow-up care for hormone replacement therapy (HRT) for hypogonadism in thalassemia major typically involves regular blood tests to monitor hormone levels and evaluate the effectiveness of the treatment. The frequency of monitoring may vary depending on the type of HRT used and the individual's specific circumstances but may include:

- Periodic measurement of hormone levels such as testosterone, estrogen, and progesterone
- Evaluation of bone density using dual-energy X-ray absorptiometry (DXA) scans
- Regular check-ups with a healthcare provider to monitor for potential side effects of the treatment (48, 50).

In addition, individuals receiving HRT should receive regular follow-up care to monitor for potential complications such as blood clots, stroke, and breast cancer. The frequency of follow-up care may vary depending on the individual's specific circumstances but may include regular check-ups with a healthcare

provider and periodic imaging studies such as mammograms.

3.4. Hypothyroidism

Some evidence suggests that individuals with thalassemia may be at increased risk for hypothyroidism. This may be due to a combination of factors, including iron overload from frequent blood transfusions and autoimmune disorders that can affect the thyroid gland. The prevalence of thyroid dysfunction in thalassemia may vary depending on factors such as the region, iron chelation management, and diet. The frequency of hypothyroidism is ranging from 13% to 60% (1, 8).

Symptoms of hypothyroidism can include fatigue, weight gain, cold intolerance, dry skin and hair, and constipation. Hypothyroidism can lead to more serious complications, such as heart disease, infertility, and nerve damage, if left untreated. The frequency of thyroid function tests for individuals with thalassemia may vary depending on factors such as age, medical history, and the severity of their thalassemia (18). TSH and free T4 should be measured at five years of age or after three years of transfusion. However, in general, it is recommended that individuals with thalassemia undergo thyroid function tests at least once a year. Thyroid function tests typically involve a blood test to measure the levels of thyroid-stimulating hormone (TSH) and thyroid hormones, such as thyroxine (T4) and triiodothyronine (T3). These tests can help to identify early signs of hypothyroidism or hyperthyroidism, which can affect individuals with thalassemia due to factors such as iron overload and autoimmune disorders. In addition to annual thyroid function tests, individuals with thalassemia should also undergo regular monitoring of their iron levels through blood tests and other medical evaluations. This can help prevent complications associated with iron overload, including damage to the heart, liver, and other organs (39, 53). Treatment for hypothyroidism usually involves taking a daily dose of synthetic thyroid hormone, such as levothyroxine, to replace the missing thyroid hormone. Regular blood tests are used to monitor thyroid hormone levels and adjust the medication dosage as needed. In addition to regular monitoring of thyroid function, individuals with thalassemia should also undergo regular monitoring of their iron levels, as iron overload can contribute to the development of thyroid dysfunction. Close collaboration between healthcare providers and individuals with thalassemia can help to ensure the timely detection and optimal management of thyroid dysfunction and other medical conditions associated with thalassemia (54).

3.5. Diabetes Mellitus and impaired glucose tolerance

The incidence of diabetes mellitus in thalassemia major is relatively high compared to the general population. Studies have reported that up to 25-30% of patients with thalassemia major may develop diabetes mellitus over their lifetime. Impaired glucose tolerance (IGT) is a well-known complication of thalassemia major. Studies have reported that up to 30% of patients with thalassemia major may have impaired glucose tolerance (1, 55). Disturbances of glucose homeostasis in thalassemia major can range from mild glucose intolerance and increased insulin resistance to overt diabetes mellitus. Patients with mild glucose disorders may not experience any symptoms, but close monitoring of blood sugar levels is still necessary. Impaired glucose tolerance (IGT) is common in patients with thalassemia major, occurring in up to 24.1% of cases. IGT is a precursor to diabetes mellitus and can increase the risk of cardiovascular disease, which is already a concern for patients with thalassemia major (12). The exact mechanisms underlying the increased risk of diabetes mellitus in thalassemia major are not fully understood, but several factors may contribute. For example, iron overload resulting from repeated blood transfusions, which are often necessary to treat thalassemia major, can lead to insulin resistance and

impaired glucose tolerance. Additionally, chronic inflammation associated with thalassemia major may also contribute to the development of diabetes mellitus (13). Iron overload-induced diabetes mellitus (DM) in patients with thalassemia major shares some characteristics with both type 1 diabetes and type 2 diabetes, but it is considered a separate entity with a unique pathophysiology. Insulin deficiency is a primary defect in iron overload-induced DM, similar to type 1 DM. This means that patients with this condition still produce some insulin but cannot use it effectively to regulate blood sugar levels. The onset of iron overload-induced DM is usually gradual and insidious, similar to type 2 DM. Insulin resistance, which is a hallmark of type 2 DM, is also detected in some patients with iron overload-induced DM. Insulin resistance refers to the body's reduced sensitivity to the effects of insulin, which can contribute to elevated blood sugar levels(22, 23). The unique pathophysiology of iron overload-induced DM is thought to be related to the accumulation of excess iron in pancreatic beta cells, which are responsible for producing insulin. Excess iron can damage these cells and impair their ability to produce insulin, leading to relative insulin deficiency. Overall, iron overload induced DM is a distinct entity with a unique pathophysiology that shares some characteristics with both type 1 and type 2 DM. Understanding the underlying mechanisms of this condition is essential for its early detection and appropriate management in patients with thalassemia major (40).

Isolated impaired fasting plasma glucose (FPG) is considered in 25% of thalassemia major, a pre-diabetic state, and is associated with an increased risk of developing diabetes mellitus and cardiovascular disease (56). Impaired FPG is typically diagnosed through a blood test that measures the glucose level in the blood after a fasting period. Patients with isolated impaired FPG may not experience any symptoms, but regular monitoring of blood glucose levels is necessary to detect progression to diabetes mellitus. Impaired FPG is also associated with other glycemic indices, such as fasting insulin, insulin resistance index, and beta cell function index. These indices can provide additional information about glucose metabolism and may be helpful in predicting the risk of future diabetes mellitus (57).

The presence of diabetes mellitus in thalassemia major has important implications for patient management. Patients with thalassemia major may require close monitoring of their blood sugar levels, and in some cases, treatment with insulin or other medications may be necessary to manage hyperglycemia. Additionally, lifestyle modifications such as a healthy diet and regular exercise may help improve glucose regulation in patients with thalassemia major. Managing glucose abnormalities in patients with thalassemia major typically involves a combination of lifestyle modifications and medications (58). Here are some ways to manage glucose abnormalities in patients with thalassemia major:

- Lifestyle modifications: Patients with thalassemia major should follow a healthy diet and exercise regularly to help manage their glucose levels. A diet that is low in simple sugars and high in fiber, whole grains, fruits, and vegetables can help regulate blood sugar levels. Regular exercise like brisk walking or cycling can also help improve glucose metabolism.
- Medications: Medications may be necessary to help manage glucose abnormalities in patients with thalassemia major. Metformin, a medication that helps improve insulin sensitivity, is commonly used to treat glucose abnormalities in patients with thalassemia major. In some cases, other drugs, such as sulfonylureas or insulin, may also be used to manage hyperglycemia.
- Blood transfusions: Regular blood transfusions can help reduce the risk of iron overload, which can contribute to the development of glucose abnormalities in patients with thalassemia major.
- Close monitoring: Patients with thalassemia major should have regular blood tests to monitor their

glucose levels. This can help detect glucose abnormalities early and allow for appropriate management.

•Education and support: Patients with thalassemia major and their families should receive education and support to help them manage their condition. This may include information about healthy eating and exercise habits, medication management, and regular monitoring of glucose levels (59).

Overall, managing glucose abnormalities in patients with thalassemia major requires a comprehensive approach that includes lifestyle modifications, medication management, regular monitoring, and education and support. Close collaboration between the patient, their healthcare provider, and their family is essential to help manage this condition effectively (56).

The frequency of blood tests for patients with thalassemia major may vary depending on their individual needs and the recommendations of their healthcare provider. However, in general, patients with thalassemia major require frequent blood tests to monitor their health and detect any complications early. Patients with thalassemia major typically require regular blood transfusions to manage their anemia, which can lead to iron overload over time. Iron overload can cause damage to organs such as the liver, heart, and endocrine glands, which can result in complications such as diabetes mellitus. Therefore, patients with thalassemia major should have regular blood tests to monitor their iron levels and other markers of organ function (58). In addition to monitoring iron levels, patients with thalassemia major should also have regular blood tests to monitor their glucose levels and detect any glucose abnormalities early. The frequency of glucose monitoring may vary depending on the patient's individual needs and the severity of their glucose abnormalities (22).

Overall, the frequency of blood tests for patients with thalassemia major should be determined by their healthcare provider based on their individual needs and the recommendations of the relevant medical guidelines. Regular monitoring is essential to detect and manage complications early and improve outcomes for patients with thalassemia major. The prevalence of diabetes mellitus (DM) and impaired glucose tolerance (IGT) in adolescents and young adults with thalassemia major (TM) conventionally treated with deferoxamine (DFO) can vary widely in different series. Some studies have reported a prevalence of up to 10.5% for DM and 24% for IGT in this population. The variation in the occurrence of glycemic abnormalities can be partially explained by several factors, including:

•Age composition of cohorts: The prevalence of DM and IGT tends to increase with age, so cohorts with a higher proportion of older patients may have a higher prevalence of glycemic abnormalities.

•Genetic background: Genetic factors can influence the risk of developing DM and IGT in patients with TM.

•Transfusion regimens: The frequency and duration of blood transfusions can affect the risk of developing iron overload and subsequent glycemic abnormalities.

•Degree of chelation: The effectiveness of iron chelation therapy in reducing iron overload can also affect the risk of developing glycemic abnormalities.

•Screening method used: The sensitivity and specificity of the screening method used to detect DM and IGT can also influence the reported prevalence of these conditions (56).

The occurrence of glycemic abnormalities in patients with TM is a complex issue that depends on multiple factors. Regular monitoring of blood glucose levels and appropriate management of glycemic abnormalities is essential for improving outcomes in patients with TM (57).

Overall, the increased risk of diabetes mellitus in thalassemia major highlights the importance of regular monitoring and appropriate management of glucose abnormalities in patients with this disorder. Early detection and treatment of diabetes mellitus can

help improve outcomes and prevent complications in patients with thalassemia major (8, 58).

3.6. Hypoparathyroidism

Hypoparathyroidism is a rare complication of thalassemia major, but it can occur. The exact incidence of hypoparathyroidism in individuals with thalassemia major is not well established in the medical literature, but some studies suggest that it may occur in up to 5% of individuals with thalassemia major (1).

The prevalence of overt hypoparathyroidism (HPT) in individuals with thalassemia major (TM) varies depending on the study and population being evaluated. The Italian Working Group on Endocrine Complications in Non-Endocrine Diseases reported a prevalence of 3.6% for overt HPT in 1661 TM patients. It is also worth noting that subclinical HPT, which is characterized by normal morning serum calcium levels but abnormal levels during other times of the day, may be more common in individuals with TM, and almost 100% of 13 TM patients were found to have subclinical HPT when measured using nocturnal serum mineral measurements. It is important to note that the prevalence of HPT in individuals with TM may be influenced by factors such as age, disease severity, and the use of chelation therapy. Regular monitoring of calcium, phosphorus, and parathyroid hormone levels is essential in individuals with TM to detect and manage any endocrine complications, including HPT (1, 8, 42). The risk of developing hypoparathyroidism in thalassemia major may be related to factors such as chronic iron overload, which can damage the parathyroid glands, or to the use of chelation therapy, which is used to remove excess iron from the body. Additionally, certain genetic factors may contribute to the risk of developing hypoparathyroidism in individuals with thalassemia major. The clinical sign and symptoms are muscle cramps, tingling or numbness in the fingers and toes, or seizures (22).

Hypoparathyroidism can lead to several complications in individuals with thalassemia major, including:

- Hypocalcemia: Hypoparathyroidism can cause low levels of calcium in the blood, leading to muscle cramps, spasms, and seizures. In severe cases, hypocalcemia can be life-threatening.
- Osteoporosis: Calcium and vitamin D deficiency can contribute to the development of osteoporosis, a condition in which bones become weak and brittle.
- Dental problems: Low calcium levels in the body can also affect the development and maintenance of teeth, leading to dental problems such as tooth decay and gum disease.
- Neuropsychological symptoms: Hypoparathyroidism can cause a range of neuropsychological symptoms, including anxiety, depression, memory problems, and difficulty concentrating.
- Cardiac complications: Hypoparathyroidism can increase the risk of cardiac arrhythmias and heart failure.
- Seizures: Repeated seizures can occur in severe cases of hypoparathyroidism (42).

Diagnosing hypoparathyroidism in thalassemia major involves a combination of clinical evaluation, laboratory tests, and imaging studies (60).

- Clinical evaluation: A healthcare provider will typically perform a physical exam and take a medical history to assess for symptoms of hypoparathyroidism, such as muscle cramps, tingling or numbness in the fingers and toes, and seizures. They may also ask about any prior treatments for thalassemia major, such as blood transfusions or chelation therapy, which may increase the risk of hypoparathyroidism (61).
- Laboratory tests: Blood tests can help to assess calcium and phosphorus levels in the blood, as well as levels of parathyroid hormone (PTH). In hypoparathyroidism, PTH levels are typically low or undetectable. Additional tests, such as 25-hydroxyvitamin D levels, may also be ordered to

assess for vitamin D deficiency, which can contribute to hypocalcemia (60).

• Imaging studies: Imaging studies, such as ultrasound or MRI, may be used to examine the parathyroid glands and assess for any structural abnormalities or damage (59).

Treatment may involve a combination of medications, supplements, and other supportive measures and will be tailored to the individual's specific needs and symptoms (42).

The treatment of hypoparathyroidism in thalassemia major is similar to the treatment of hypoparathyroidism that occurs in other settings. The goal of treatment is to restore normal levels of calcium and phosphorus in the body and to manage any associated symptoms. The mainstay of treatment for hypoparathyroidism is calcium and vitamin D supplementation. Calcium supplements can help to raise blood calcium levels, while vitamin D supplements help the body absorb calcium. The doses of calcium and vitamin D supplements will depend on the severity of the hypoparathyroidism and the individual's calcium and vitamin D levels (61). In addition to calcium and vitamin D supplementation, some individuals with hypoparathyroidism require medications to raise blood calcium levels. These medications may include calcium-sensing receptor agonists, which stimulate the body's production of PTH, or active vitamin D analogs, which increase calcium absorption from the intestine and help regulate calcium and phosphorus levels in the blood. The recommended dosage for calcium and vitamin D supplements in individuals with hypoparathyroidism may vary depending on the severity of the condition and the individual's calcium and vitamin D levels. Working with a healthcare provider to determine the appropriate dosage for your specific needs is essential. Generally, the recommended daily calcium intake for adults is 1,000-1,200 mg per day. The recommended daily vitamin D intake for adults is 800-1,000 IU per day. However, individuals with hypoparathyroidism may require higher doses of calcium and vitamin D to maintain normal levels in the blood. Calcium supplements are available in different forms, including calcium carbonate and calcium citrate. The amount of elemental calcium in different calcium supplements can vary, so it is essential to check the label to determine the appropriate dosage (42). Vitamin D supplements are available in vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) types. Vitamin D3 is the preferred form for supplementation, as it is more effective at raising vitamin D levels in the blood (60). It is essential to take calcium and vitamin D supplements as directed by a healthcare provider, as excessive intake of these nutrients can lead to complications such as hypercalcemia (high levels of calcium in the blood) and kidney stones. Regular monitoring of calcium and vitamin D levels and kidney function may be necessary to ensure that the supplements are well-tolerated and effective at managing the condition (61).

Treating subclinical hypoparathyroidism (HPT) in individuals with thalassemia major (TM) may not always be necessary, as it typically does not cause symptoms or complications. However, if subclinical HPT is associated with low levels of calcium or high levels of phosphorus in the blood, treatment may be necessary to prevent the development of overt HPT and associated complications. The treatment of subclinical HPT in TM is similar to the treatment of overt HPT and involves calcium and vitamin D supplementation. The goal of treatment is to maintain calcium and phosphorus levels within the normal range and to prevent bone loss. The dosage of calcium and vitamin D supplements may vary depending on the individual's calcium and vitamin D levels and the severity of the subclinical HPT. Regular monitoring can help detect changes in calcium or phosphorus levels and ensure that the condition is well-managed. In some cases, additional medications or interventions may be necessary to manage subclinical HPT and prevent the development of complications (34, 60).

Surgical intervention may be necessary in severe cases of hypoparathyroidism that are not responsive to medical treatment and may involve the transplantation of parathyroid tissue or the removal of the parathyroid glands.

There is no guaranteed way to prevent the development of hypoparathyroidism in individuals with thalassemia major (35). However, several strategies may help to reduce the risk of developing this condition:

- Regular medical check-ups: Regular check-ups with a healthcare provider can help identify and manage potential medical problems, including hypoparathyroidism. Routine blood tests can help to identify changes in calcium, phosphorus, and PTH levels that may indicate the development of hypoparathyroidism.
- Adequate iron chelation therapy: Thalassemia major is typically treated with blood transfusions, which can lead to iron overload in the body. Iron chelation therapy removes excess iron from the body and prevents complications such as organ damage. Adequate iron chelation therapy may help to reduce the risk of developing hypoparathyroidism.
- Calcium and vitamin D supplementation: Calcium and vitamin D are essential for bone health and can help to prevent hypocalcemia and other complications associated with hypoparathyroidism. Individuals with thalassemia major may be advised to take calcium and vitamin D supplements as part of their routine care.
- Genetic counseling: Thalassemia major is a genetic condition that is inherited from parents. Genetic counseling can help individuals and their families to understand the risk of passing on the condition to future generations and to make informed decisions about family planning.

In addition to medication and supplementation, some lifestyle changes may help manage subclinical hypoparathyroidism (HPT) in individuals with thalassemia major (TM). These lifestyle changes may help to support bone health, improve overall health, and reduce the risk of complications associated with HPT (60, 61).

- Exercise: Regular exercise can help to improve bone density, muscle strength, and overall health. Weight-bearing exercises such as walking, jogging, or strength training may be particularly beneficial for individuals with TM and subclinical HPT.
- Diet: A well-balanced diet that is rich in calcium and vitamin D can help to support bone health and prevent complications associated with HPT. Foods that are high in calcium include dairy products, leafy green vegetables, and fortified cereals. Foods that are high in vitamin D include fatty fish, egg yolks, and fortified foods such as milk and cereal.
- Sun exposure: Vitamin D can also be obtained through exposure to sunlight. Individuals with subclinical HPT may benefit from spending time outdoors in the sun, particularly during the summer months.
- Smoking cessation: Smoking has been linked to reduced bone density and increased risk of fractures. Quitting smoking may help to improve bone health and reduce the risk of complications associated with HPT.
- Limiting alcohol consumption: Excessive alcohol consumption has been linked to reduced bone density and increased risk of fractures. Limiting alcohol consumption may help to improve bone health and reduce the risk of complications associated with HPT(42).

Treating hypoparathyroidism (HPT) in individuals with thalassemia major (TM) typically involves lifelong therapy with vitamin D or its metabolites and calcium supplements as needed. However, it is important to closely monitor calcium, phosphorus, and parathyroid hormone levels to prevent under and overtreatment (60). Under-treatment of HPT can lead to chronic hypocalcemia and hyperphosphatemia, which can cause ectopic calcifications in organs such as the kidneys, lungs, and heart. These calcifications can be irreversible and may lead to organ dysfunction. On the other hand, over-treatment of HPT can lead to

hypercalcemia, which can increase the risk of kidney stones and nephrocalcinosis, a condition in which calcium deposits form in the kidneys and can cause kidney damage (61). Therefore, it is essential to work closely with a healthcare provider to monitor calcium, phosphorus, and parathyroid hormone levels and adjust treatment as needed to maintain calcium and phosphorus levels within the normal range. Regular monitoring can help to prevent both under and overtreatment and detect and manage any potential complications associated with HPT in TM (42).

3.7. Adrenal insufficiency

Adrenal insufficiency is a rare but potentially significant complication that can occur in individuals with thalassemia major. In individuals with thalassemia major, adrenal insufficiency may occur due to iron overload in the adrenal glands, leading to damage and dysfunction of the glandular tissue. Adrenal insufficiency may also occur due to an autoimmune disease that affects the adrenal glands, although this is less common (38). Symptoms of adrenal insufficiency may include fatigue, weakness, weight loss, nausea, vomiting, and low blood pressure. In severe cases, an adrenal crisis may occur, which can be life-threatening and requires immediate medical attention (39).

Diagnosing adrenal insufficiency in individuals with thalassemia major typically involves a combination of clinical evaluation, blood tests, and imaging studies (62).

- Clinical evaluation: The healthcare provider may ask about symptoms such as fatigue, weakness, abdominal pain, and low blood pressure, which can indicate adrenal insufficiency. Physical examination may also reveal dehydration or electrolyte imbalances (37).
- Blood tests: Blood tests can measure cortisol and aldosterone levels in the blood. In individuals with adrenal insufficiency, cortisol levels are typically low, and aldosterone levels may also be low (21).
- ACTH stimulation test: The ACTH stimulation test involves measuring cortisol levels before and after receiving a synthetic form of ACTH, which stimulates the adrenal glands to produce cortisol. In individuals with adrenal insufficiency, cortisol levels will not increase appropriately in response to ACTH.
- Imaging studies: Imaging studies such as ultrasound or CT scan may be performed to evaluate the adrenal glands and detect any structural abnormalities or damage (63).

Working with a healthcare provider familiar with diagnosing and managing adrenal insufficiency in individuals with thalassemia major is essential. Treatment typically involves hormone replacement therapy and close monitoring of symptoms, electrolyte levels, and response to treatment. In most cases, treatment involves using glucocorticoids such as hydrocortisone, prednisone, or dexamethasone to replace the deficient cortisol production. The dosage and frequency of administration may vary depending on the severity of the adrenal insufficiency. In addition, mineralocorticoids such as fludrocortisone may be prescribed to replace aldosterone, which regulates salt and water balance in the body. Regular monitoring of electrolytes and blood pressure is essential to ensure proper dosing of mineralocorticoids. It is important to note that treating adrenal insufficiency in thalassemia major should be individualized and closely monitored by a healthcare professional experienced in managing these conditions. Regular monitoring of adrenal function is essential in individuals with thalassemia major to detect and manage adrenal insufficiency early and to prevent complications such as adrenal crisis. This may involve routine blood tests to evaluate cortisol and aldosterone levels and imaging studies to evaluate the adrenal glands (12, 21, 62) (**Figure 1**).

3.8. Osteoporosis

Osteoporosis is a condition characterized by low bone mass and deterioration of bone tissue, which can lead to an increased risk of fractures. Individuals with thalassemia major are at an increased risk of developing osteoporosis due to chronic anemia, iron

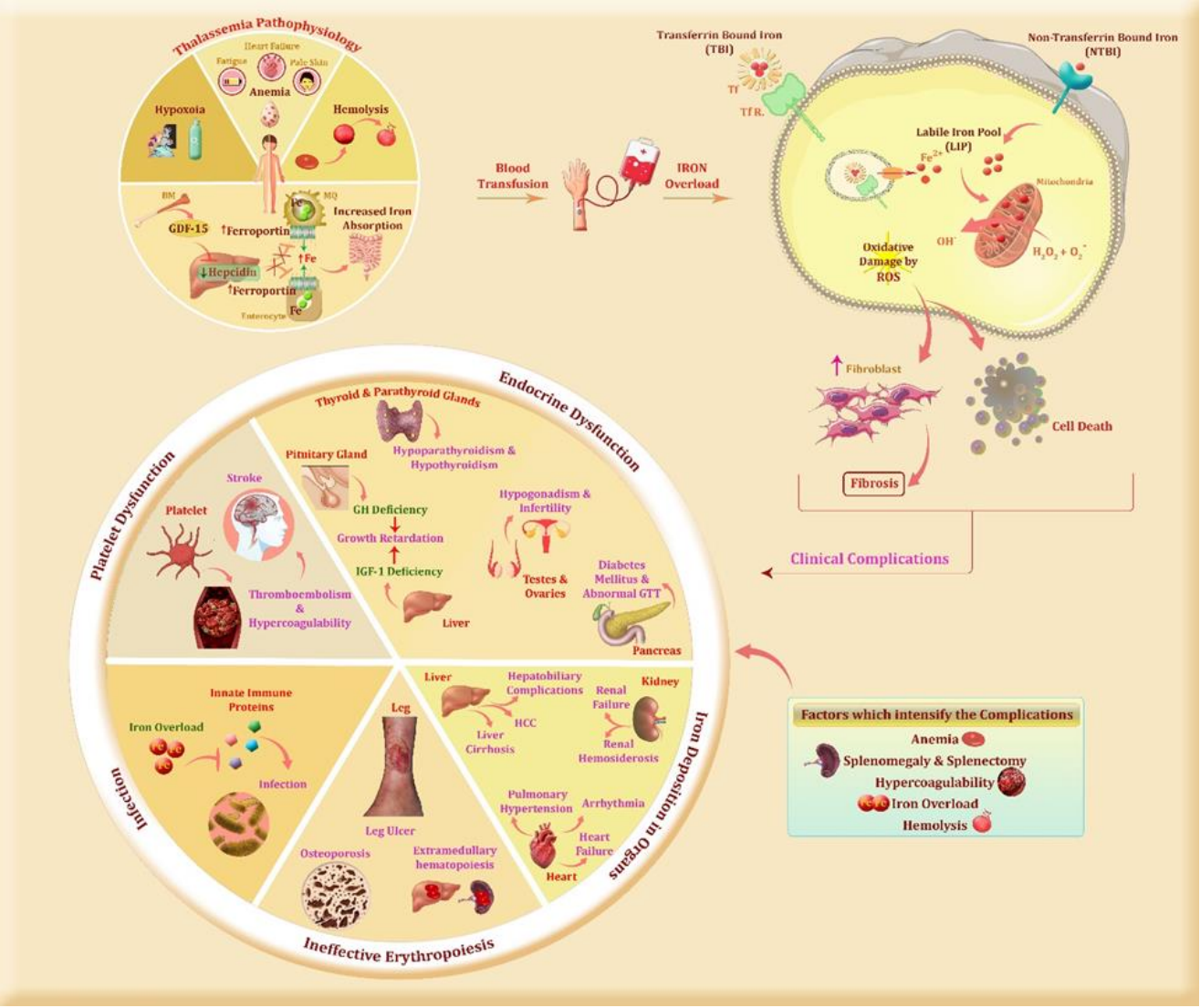

Figure 1. **The mechanism of endocrine complications in thalassemia patients**

overload, hormonal imbalances, and vitamin D deficiency (64). The exact incidence of osteoporosis in thalassemia major is not well established, and studies have reported varying rates depending on the population and diagnostic criteria used. However, some studies have reported a prevalence of osteoporosis in up to 50% of patients with thalassemia major, particularly in older individuals (65, 66). The diagnosis of osteoporosis in thalassemia major is typically made through a combination of clinical evaluation, laboratory tests, and imaging studies.

•Clinical evaluation: A healthcare professional will typically evaluate an individual's medical history, including any history of fractures or risk factors for osteoporosis, such as low body weight or a family history of osteoporosis.

•Laboratory tests: Blood tests may be performed to evaluate calcium, vitamin D, and hormone levels. Elevated levels of parathyroid hormone (PTH) and low vitamin D levels are commonly seen in individuals with osteoporosis.

•Imaging studies: Dual-energy X-ray absorptiometry (DXA) is the most commonly used imaging study to diagnose osteoporosis. This test measures bone mineral density (BMD) and compares it to the BMD of a healthy young adult of the same gender. A (Z-score) of -2 or lower indicates osteoporosis below the age of 55 years with (T score) below -2.5(65).

In individuals with thalassemia major, DXA scans may need to be interpreted cautiously, as iron overload can affect the accuracy of the test. Additional imaging studies such as quantitative computed tomography (QCT) or magnetic resonance imaging (MRI) may be necessary to evaluate these individuals' bone density accurately. Iron overload can affect the accuracy of DXA (dual-energy X-ray absorptiometry) scans, which are commonly used to measure bone density and diagnose osteoporosis. The presence of excess iron in the bone can cause a false elevation in the BMD (bone mineral density) measurements, leading to an overestimation of the actual bone density (66). Iron deposition in the bone can also cause bone marrow hyperplasia, which can lead to an increase in the measured BMD. This is because DXA scans measure both the mineral content of the bone and the soft tissue surrounding it, including the bone marrow (21). Iron overload is a common complication in patients with thalassemia major due to the frequent blood transfusions required for treatment. Therefore, it is essential to interpret DXA scans with caution in these individuals. Additional imaging studies such as quantitative computed tomography (QCT) or magnetic resonance imaging (MRI) may be necessary to accurately evaluate bone density in individuals with thalassemia major and iron overload (64).

In summary, iron overload can affect the accuracy of DXA scans by causing a false elevation in the measured BMD due to iron deposition in the bone and bone marrow hyperplasia. Healthcare professionals should interpret DXA scans with caution in individuals with thalassemia major and consider using additional imaging studies to evaluate bone density accurately (28, 54). Early detection and regular monitoring of bone density are essential for preventing and managing osteoporosis in individuals with thalassemia major. Individuals with thalassemia major should work closely with their healthcare team to identify and manage risk factors for osteoporosis and other associated complications (65, 66).

There are several medical therapies available to treat osteoporosis in thalassemia major patients, including:

- Bisphosphonates: These medications are the most commonly used drugs for osteoporosis treatment and work by reducing bone resorption. Examples of bisphosphonates include alendronate, risedronate, and zoledronic acid.
- Hormonal therapy: Hormone replacement therapy (HRT) or selective estrogen receptor modulators (SERMs) may be used in postmenopausal women with osteoporosis. Testosterone replacement therapy may be used in men with low testosterone levels.
- Parathyroid hormone (PTH) analogs: Teriparatide is a synthetic form of PTH that is used to treat severe osteoporosis. It stimulates the formation of new bone tissue.
- Denosumab: This medication is a monoclonal antibody that inhibits osteoclasts, which are the cells that break down bone tissue. It is given as a subcutaneous injection every six months.
- Calcium and Vitamin D supplementation: Adequate calcium and vitamin D intake is essential for maintaining bone health. Supplements may be prescribed to individuals with thalassemia major who are at risk of developing osteoporosis.

The choice of therapy will depend on the severity of the osteoporosis, the patient's age and gender, and other underlying medical conditions. It is crucial for individuals with thalassemia major to work closely with their healthcare team to determine the most appropriate treatment plan for their specific needs. Regularly monitoring bone density and response to therapy is also vital to ensure optimal outcomes (64, 65).

3.9. Nutritional Deficiency

Patients with thalassemia are at risk for various nutritional deficiencies due to a combination of factors such as increased iron overload, chronic blood transfusions, and malabsorption. The incidence of nutritional deficiencies in thalassemia major is relatively high due to several factors, including

malabsorption, increased nutrient requirements, and iron overload (67, 68). Here are some estimates of the incidence of nutritional deficiencies in patients with thalassemia major:

- Vitamin D deficiency: The incidence of vitamin D deficiency in patients with thalassemia major ranges from 50% to 90%, depending on the population studied and the diagnostic criteria used. Vitamin D deficiency can lead to bone disorders, muscle weakness, exacerbate iron overload, and other complications. Vitamin D supplementation is often recommended for patients with thalassemia.
- Calcium deficiency: The incidence of calcium deficiency in patients with thalassemia major ranges from 30% to 60%. Calcium deficiency can contribute to bone disorders and other complications. Calcium supplementation may be necessary to prevent or correct this deficiency.
- Folate deficiency: Folate deficiency is common in patients with thalassemia due to increased folate requirements and malabsorption. The incidence of folate deficiency in patients with thalassemia major ranges from 20% to 70%. Folate deficiency can lead to anemia and other complications. Folate supplementation may be necessary to prevent or correct this deficiency.
- Vitamin B12 deficiency: Vitamin B12 deficiency can also occur in patients with thalassemia, likely due to malabsorption. The incidence of vitamin B12 deficiency in patients with thalassemia major ranges from 10% to 70%. Vitamin B12 deficiency can lead to anemia, neurologic symptoms, and other complications. Vitamin B12 supplementation may be necessary to prevent or correct this deficiency.
- Zinc deficiency: The incidence of zinc deficiency in patients with thalassemia major ranges from 35% to 50%. Zinc deficiency can contribute to growth retardation, immune dysfunction, and other complications. Zinc supplementation may be necessary to prevent or correct this deficiency (41, 69).

It is important to note that the incidence of nutritional deficiencies in thalassemia major may vary depending on the population studied, the severity of the disease, and other factors. Regular monitoring of nutritional status and appropriate nutritional support, including vitamin and mineral supplementation, can help prevent or correct these deficiencies and improve long-term health outcomes in patients with thalassemia major (67-69).

3.10. Appropriate monitoring and management of patients

Patients with thalassemia major can ensure they receive appropriate monitoring and management by following these steps:

- Establish a relationship with a healthcare professional who is experienced in the management of thalassemia major. This may include a hematologist, endocrinologist, and other specialists as needed.
- Attend regular appointments with the healthcare team to monitor conditions and receive appropriate treatment. This may include regular blood tests to monitor iron levels, liver function, and hormone levels.
- Follow the recommended treatment plan, including regular chelation therapy to manage iron overload. It is essential to take chelation therapy for patients.
- Be aware of the signs and symptoms of endocrine complications, such as adrenal insufficiency, diabetes, and hypothyroidism, and promptly report any changes in patients' health.
- Adopt a healthy lifestyle, including a balanced diet, regular exercise, and avoiding smoking and excessive alcohol consumption.

By following these steps, patients with thalassemia major can work with their healthcare team to manage their condition effectively and improve their quality of life (40, 69).

3.11. Strategic plan

Management of endocrine complications in thalassemia requires a multidisciplinary approach involving specialists in endocrinology, hematology, and other relevant fields. The goal of management is

Table 2 Routine timetable for laboratory and clinical assessment

Parameter	Pediatric	Adults
Baseline and General Data	Growth assessment • Weight monthly in infants, every three months in older children and adolescents • Head circumference every other month in infants till two years • Annual growth velocity in children • The Tanner stage occurs every six months in older children and adolescents after 10 years	• Weight every 3 months • Standing height every 6 months
Endocrine survey	• T3, free T4, TSH annually starting at age five years every 12 months • PTH, calcium, and ionized calcium annually starting at age five years every 12 months • Fasting glucose start in at age 55 years every 12 months • Oral glucose tolerance test* at ages 10, 12, 14, and 16 years if clinically indicated • IGF-1 and IGFBP-3 as clinically indicated (for growth delay) • LH-ICMA, FSH, and estradiol as clinically indicated (for delayed puberty,12 years in girls and 14 years in boys) • Testosterone as clinically indicated (for delayed puberty in males after 14 years) • Zinc levels annually • Bone density testing each two years after 12 years (if normal result)	• T3, free T4, TSH annually • PTH, calcium, and ionized calcium annually • Fasting glucose, HbA1c, or oral glucose tolerance test* annually • IGF-1 and IGFBP-3 as clinically indicated (for growth delay) • Bone densitometry testing every two years (if normal result)
Hematology	• CBC at any transfusion • Blood type and antibody screen monthly in TDT • Direct antiglobulin test (DAT; direct Coombs) as clinically indicated • Serum ferritin – Every three months • Blood group and immunophenotype at diagnosis	• CBC at any transfusion • Blood type and antibody screen monthly in TDT • Direct antiglobulin test (DAT; direct Coombs) as clinically indicated • Serum ferritin – Every three months

to prevent or minimize the impact of endocrine complications on long-term health outcomes.

Some common management strategies for endocrine complications in thalassemia include:

• Regular monitoring of endocrine function: Patients with thalassemia should undergo regular monitoring of their endocrine function, including tests for growth hormone deficiency, hypogonadism, thyroid and adrenal function, and glucose metabolism.

• Hormone replacement therapy: Hormone replacement therapy, such as growth hormone replacement, testosterone replacement, and thyroid hormone replacement, may be necessary for patients with hormone deficiencies.

• Iron chelation therapy: Iron overload due to frequent blood transfusions can lead to endocrine complications in thalassemia. Iron chelation therapy, such as deferoxamine, deferasirox, or deferiprone, can help reduce iron overload and prevent endocrine complications.

• Nutritional support: Nutritional deficiencies, such as vitamin D, are common in thalassemia and can

contribute to endocrine complications. Nutritional support, including vitamin and mineral supplementation, may be necessary to prevent or correct these deficiencies.

•Lifestyle modification: Lifestyle modifications, such as regular exercise and a healthy diet, can help prevent or manage endocrine complications in thalassemia. Patients should also avoid smoking and excessive alcohol consumption.

•Psychological support: Endocrine complications in thalassemia can significantly impact patients' quality of life and mental health. Psychological support, including counseling and support groups, can help patients cope with the challenges of living with thalassemia and its associated complications.

These management strategies may vary depending on the type and severity of the endocrine complication, the patient's needs, and medical history. A comprehensive approach to managing endocrine complications in thalassemia is essential to ensure optimal long-term health outcomes (39, 40).

3.12. General timetable for clinical and laboratory investigation for endocrine complications in transfusion-dependent thalassemia

The checklist for routine monitoring in individuals with transfusion-dependent thalassemia (TDT) for endocrine complications is in **Table 2.**

4. Conclusions

In summary, endocrine complications are common in individuals with thalassemia major and can have significant morbidity if left untreated. Regular monitoring and early intervention are essential to prevent and manage endocrine complications in individuals with thalassemia major. Timely and standard chelation therapy is crucial for enhancing the quality of life. Iron overload remains a significant issue, and early and regular chelation therapy is vital for preventing and managing associated complications. It is essential to work closely with healthcare professionals experienced in managing thalassemia major to ensure appropriate monitoring and management of the condition and related complications.

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