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Review

Thyroid disorders in thalassaemia: An update

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ABSTRACT

Over the course of past 2 to 3 decades, hypertransfusion therapy and chelation therapy have significantly increased the life expectancy and improved the life quality of patients with thalassaemia major (TM). Neverthless, even in carefully managed patients endocrine disturbances may develop. Stunted growth, delayed puberty/ hypogonadism, hypothyroidism, hypoparathyroidism and diabetes mellitus are well-recognized complications of iron overload. As the symptoms of hypothyroidism are non-specific, but the consequences affect virtually every organ system, an early systematic laboratory evaluation and control of thyroid function is recommended in all TM patients, annually. Different studies have revealed that several changes in thyroid hormone concentrations may occur with a wide spectrum of severity varying from sub-biochemical hypothyroidism to overt hypothyroidism. Central hypothyroidism is an uncommon clinical entity and its prevalence at different ages is unknown. Thyroid failure is expected to be more prevalent in older patients although in developing countries it may occur at younger age. The occurrence of malignancies in TM patients is an emerging concern for physicians. Recently, we observed three female TM patients with incidental papillary thyroid microcarcinoma. Overt hypothyroidism is classically treated by oral replacement with synthetic L-thyroxine. A close monitoring of TSH is recommended in hypothyroid TM patients with cardiac dysfunction and osteoporosis, as over-replacement with L-T4 may cause dysrhythmias and accelerated bone loss. In sub-clinical hypothyroidism the decision to treat depends on each individual case. In this review, we will highlight some recent aspects of diagnosis and treatment of thyroid disorders in patients with β-thalassaemia major.

KEYWORDS: thalassaemia, hypothyroidism, thyroid cancer, iron chelation therapy, treatment

INTRODUCTION

The haemoglobinopathies (thalassaemias and sickle-cell disease) are the most commonly inherited genetic disorders worldwide with some 240000 infants born annually with major haemoglobinopathies and at least 190 million carriers worldwide [1-3]. The recommended treatment of β-thalassaemia major consist of regular transfusions (every 2-4 weeks) and iron chelation therapy to remove the excess iron accumulation resulting from transfusions. Stunted growth, delayed puberty/hypogonadism, hypothyroidism, hypoparathyroidism and diabetes mellitus are well-recognized complications of iron overload [3, 4]. In this review, we will highlight some recent aspects of diagnosis and treatment of thyroid disorders in patients with β-thalassaemia major.

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Pathophysiology

The basic genetic defect results in the destruction of the thalassaemic red cells before the erythroblasts are well haemoglobinized; this is a consequence of the imbalance between the production of the α- and β-globin chains. This results in ineffective erythropoiesis leading to severe anaemia, increased production of erythropoietin and expansion of the bone marrow by 15 to 30 times the normal. This marrow expansion results in distortion and fragility of the bone and an increased blood volume. The reticuloendothelial cells become congested by these abnormal red cells and consequently hepatosplenomegaly develops [4, 5].

Relation of clinical phenotype to genotype

Patients with thalassemias (β-thal) can present with a broad spectrum of clinical severity, ranging from silent carriers to those with severe cases of iron overload. The severity of the clinical manifestations of these disorders relates to the amount of globin chain produced and the stability of residual chains present in excess [6]. Recently, molecular studies demonstrated that the clinical phenotypes of β-thal, are regulated by primary and secondary genetic modifiers. The primary modifies are related to genotype and mainly to the severity of β-thal mutations [7, 8]. The thalassemia minor syndromes are characterized clinically by mild anemia with persistent microcytosis. Thalassemia intermedia syndromes are defined by a moderate and variably compensated hemolytic anemia that may present clinically with symptoms only during episodes of exposure to physiological stressors such as infection, pregnancy, or surgery [1-4, 9]. Thalassemia major (TM) is the most common and severe type, which necessitates frequent transfusions for survival [1-5].

Treatment of TM

The recommended treatment for TM is regular blood transfusions (RBC) and chelation therapy, maintaining the overall mean haemoglobin level of about 12 g/dl. Pre-transfusion haemoglobin should be around 9.5 g/dl whereas post-transfusion haemoglobin should be a maximum of 14-15 g/dl [2, 4, 7]. The aim is to transfuse 10-20 ml/kg body weight of packed filtered red cells over a period of 2-3 hours throughout life. This ensures that erythroid marrow suppression preserves excellent health and normal development [2, 4, 7]. The frequency of transfusion is usually every two to five weeks. The amount of blood to be transfused depends on several factors including the weight of the patient, and the target increase in Hb level [2-5]. RBC transfusions eliminate the complications of anaemia, compensatory bone marrow expansion, permit normal growth throughout childhood, and extend survival. Today, in the developed world, the life expectancy of patients with thalassaemia varies between 25 and 55 years, mainly depending on compliance with medical treatment [2, 5].

Iron loading from blood transfusion

A unit processed from 420 ml of donor blood contains approximately 200 mg of iron (0.47 mg/ml of whole donor blood). If the mean hematocrit levels is approximately 60%, the accompanying iron content is about 0.7 mg/ml transfused [3]. In TM patients, the equivalent of 100-200 ml of pure erythrocytes/kg/year are transfused. This rate of iron loading adds approximately 116-232 mg of iron/kg bw/year or 0.32-0.64/kg/day in these patients [4]. In unsplenectomized thalassemia major patients, the transfusion requirements are generally higher [4].

Assessment of iron overload

Traditionally, iron overload has been assessed by serial serum ferritin measurements and liver biopsies. Although serum ferritin levels are much more conveniently and easily assessed, they can be influenced by inflammation, ascorbate levels, and intercurrent diseases, and therefore may not accurately reflect total body iron stores [10-13]. Also, serum ferritin measurements have poor reproducibility, as evidenced by the fluctuation in ferritin levels measured in an individual on consecutive days [14].

For many years, liver iron measurement by liver biopsy or magnetic measurements (SQUID) have been used as the gold standard for monitoring of haemosiderosis in TM. The latter method relies on the principle that ferritin and haemosiderin have

paramagnetic properties and has repeatedly been calibrated, validated and used in clinical studies. However, its complexity, high cost and limited access (available in approximately three centres worldwide so far) have restricted its general application [14].

Recently, cardiac and liver iron estimates by magnetic resonance imaging (MRI) have become the primary outcome measures for clinical studies of iron chelation therapy [15, 16]. MRI measures the tissue iron concentration indirectly by detecting the paramagnetic effect produced by the presence of storage iron (ferritin and haemosiderin) on proton resonance behaviour of tissue water [13-16].

Chronic packed RBC transfusion therapy increases liver iron by approximately 1 mg/mL (by dry weight) for every 15 mL/kg delivered. Therefore, patients receiving more than 10 transfusions (150 mL/kg), in the absence of significant losses, merit at least an initial scan. Iron measurements should be repeated on an annual basis unless there is a clinical indication for more frequent assessment [7].

Transfusional iron overload and iron toxicity

The most important consequence of these life saving transfusions is the inexorable accumulation of iron within tissues [13]. 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 able to redox cycle between Fe^{2+} and Fe^{3+}, thereby generating reactive oxygen species (ROS), leading to lipid peroxidation. The result of 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 dysfunctin, cytotoxicity and cell death [17-21]. Certain tissues are particularly susceptible to excess iron incorporation when NTBI is present.

L-type Ca^{2+} channels (LTCCs) are the front-runners for mediating NTBI transport in iron overload conditions [17]. LTCCs are highly expressed in pancreatic beta cells [22, 23] as well as have a moderate presence in thyrotrophs [24], osteoblasts [25], corticotrophs [26], gonadotrophs [27, 28] and in the parathyroid-hormone-producing cells of the parathyroid gland [29]. In addition, in presence of elevated oxidative stress, sarcoplasmic reticulum (SR) Ca^{2+} leak through ryanodine receptors (Ca^{2+} release channels) is increased [30], sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA) activity is inhibited [31], sodium-calcium exchanger (NCX) currents are enhanced [31], LTCCs are reduced [32, 33] and sodium and potassium currents can either be elevated or depressed, respectively [34]. The tissues at the greatest risk in iron overload for LTCC activity are the cardiomyocytes [16], anterior pituitary cells [35, 36], pancreatic beta cells [37, 38] and neurons [39].

Thus, iron overload constitutes the most important complication in thalassaemia major and is the major focus of clinical management. Apart from iron overload, other factors responsible for organ damage have been previously pointed out including chronic hypoxia due to anaemia that may potentiate the toxicity of iron deposition in endocrine glands [40]. Also viral infections as well as individual susceptibility have been implicated in causing endocrine dysfunctions [41].

Iron chelation therapy

Current practice is to begin iron chelation with desferrioxamine when the serum ferritin levels reach 1000 ng/ml or when child reaches three years of age or has received about 10-20 transfusions [4, 5, 42-44]. Iron chelators in current clinical use include subcutaneous or intravenous desferrioxamine, oral deferiprone and oral deferasirox. Desferrioxamine is most commonly self administered as a subcutaneous infusion over 8-10 hours, 3-7 nights weekly, while oral deferiprone and deferasirox are mainly used for patients in whom chelation with desferrioxamine has been inadequate or intolerable [42-44]. Effective chelation reduces or prevents iron accumulation and iron-mediated organ damage, resulting in a consistent decrease of morbidity and mortality [4, 5]. Patients who administer

subcutaneous desferrioxamine infusion about five times a week (250 times a year) have 95% survival to 30 years of age, whereas survival is only 12% in patients who fail to achieve this target [5]. It has been shown that prognosis for survival is best for those thalassemia patients in whom serum ferritin levels can be maintained below 2500 mcg/L, but at the same time some patients who receive ideal management in terms of present standards do develop significant endocrine damage [45]. Poor compliance with chelation regimens is common even in countries where standard recommended treatment is available and affordable. This constitutes the most important threat to the occurrence of complications leading to increased morbidity and mortality in these patients [46].

Hypothyroidism in TM

This complication is mainly attributed to iron overload [47-49] and is uncommon in optimally treated patients [50]. Central hypothyroidism is uncommon. Hystologically, deposition of iron in the follicular epithelium and iron-loaden macrophages of the interstitium with consequent fibrosis have been observed [47-49]. The anterior pituitary gland is particularly sensitive to free radical oxidative stresses and MRI shows that even a modest amount of iron deposition within the anterior pituitary can interfere with its function [51, 52].

Laboratory tests

The most common conventional way for the diagnosis is with an ultra-sensitive TSH and FT4 estimations [53]. Rindang *et al.* [54] studied 179 subjects (male: female ratio of 1:1.6). The prevalence of primary hypothyroidism in thalassemia major patients with severe iron overload was 26.8% (48/179). Of those 48, 45 had compensated hypothyroidism and 3 had decompensated hypothyroidism, 25.1% and 1.7% of the total subjects, respectively. Based on multivariate analysis, only age of < 10 year-old was significantly associated with primary hypothyroidism (P = 0.029, OR 0.469; 95% CI 0.23 to 0.93). Further analysis using receiver operator curve (ROroC) technique found that age of 8.5 year-old was the cutoff value to predict the risk of hypothyroidism.

Additional tests may include the following:

- Thyroid autoantibodies-anti-thyroid peroxidase and antithyroglobulin autoantibodies
- Ultrasonography, to evaluate structural thyroid abnormalities
- Bone age, in selected cases
- Routine blood tests
- Serum ferritin
- ECG and EcoCG (especially in severe cases)
- Hypothalamic-pituitary magnetic resonance imaging (MRI), in selected cases

Thyroid antibodies are usually negative [48]. Thyroid ultrasonography may show different echo patterns. Pitrolo *et al*. [55] observed a reduced echogenicity in 47% of TM patients and a diffuse spotty echogenicity in 33% of them, indicative of thyroid dysfunction. Filosa *et al*. [56] reported features of dyshomogeneity of the parenchyma with different degrees of severity, which were in accordance with the Sostre and Reyes criteria [57]. The thyroid gland appears to fail before the thyroid-pituitary axis, which is less sensitive than the gonadal axis to iron-induced damage [58-61].

Grades of thyroid dysfunction

The advent of more precise diagnostic techniques, which enable different aspects of thyroid function to be measured, have shown that hypothyroidism is a graded phenomenon. Therefore, several definitions have been used in the literature to define different aspects of impaired thyroid function in TM as well. The following grades have been identified [47, 48, 51, 52, 59]:

1. Sub-biochemical hypothyroidism, consist of an exaggerated TSH response to TRH test in presence of normal TSH and FT4.

2. Sub-clinical hypothyroidism is a combination of high TSH with normal FT4 levels. Two types of sub-clinical hypothyroidism have been reported: Type A (normal FT4, TSH 5-10 microU/ml) and Type B (normal FT4, basal TSH > 10 microU/ml).

3. Overt hypothyroidism is a combination of high TSH with low FT4.

Central hypothyroidism is defined as a reduction in circulating thyroid hormone as a result of inadequate stimulation of a normal thyroid gland

by TSH (low free T4 and a low or "inappropriately normal" TSH).

Sick euthyroid syndrome may be observed in non-thyroidal illness. The abnormalities are more likely with increasing severity of such diseases. The earliest change is a decreased concentration of free triiodothyronine and a TSH in the normal or even low-normal range. This condition is not due to pituitary or hypothalamic problems but the presence of chronic liver disease or the basic disease itself [42].

Clinical examination

The classical clinical signs of hypothyroidism in TM patients are not easy because most of the symptoms, especially in mild cases, are non-specific and are frequently attributed to anaemia or associated diseases [42, 48]. Thalassemic patients with overt hypothyroidism have been reported to exhibit stunted growth, delayed puberty, cardiac failure and pericardial effusion [42, 48, 52, 62]. They are shorter with more delayed bone age than euthyroid thalassemic patients.

Prevalence of thyroid dysfunction in subjects with TM

Different studies have revealed that several changes in thyroid hormone concentrations may occur with a wide spectrum of severity between sub-biochemical hypothyroidism and overt hypothyroidism. Central hypothyroidism is an uncommon clinical entity and its prevalence at different ages is unknown. Tatò *et al*. [60] found a poor response of the free α-subunit both to thyreotrophin releasing hormone stimulation tests in 14 euthyroid TM patients (8 females and 6 males, aged 15-24 years) suggesting central involvement, and Hekmatnia *et al*. [61] found a signal reduction and a pituitary volume using an assessment with MRI. The frequency of hypothyroidism in thalassemia patients ranges from 6 to 30% [47]. Lower prevalence is found in patients who had evidence of lower iron load as measured by ferritin levels [63]. These wide variations in different reports can be attributed to different patients genotype, differences in patients' ages, ethnic variations and different treatment protocols, including differing transfusion rates and chelation therapies [64].

Thyroid failure is expected to be more prevalent in older patients (as it is true for other endocrine deficits) although in developing countries it may occur at younger ages as reported by Rindang *et al.* [54] and Malik *et al.* [65]. Thalassaemic patients having thyroid dysfunction have shown a greater incidence of other complications including multiendocrine dysfunction, worsening of growrh retardation, liver disease and need for splenectomy during the course of the disease [42].

Several studies have reported a lack of concordance of ferritin concentrations with the thyroid function status [59, 66, 67]. This may be, in part, due to the fact that serum ferritin levels increase linearly with the transfusion load up to 100 units of transfused blood, but thereafter there is no simple relationship [68]. Also, misleading ferritin levels can occur with chronic inflammatory disease [69] as well as vitamin C deficiency [70].

Risk factors for the development of thyroid dysfunctions

A. Rhythm disturbances and amiodarone treatment

Cardiac dysfunction is common in patients with thalassaemia and is the leading cause of mortality. The main cardiac abnormalities reported in patients with TM and iron overload are left ventricular systolic and diastolic dysfunction, pulmonary hypertension, valvulopathies, arrhythmias and pericarditis. Rhythm disturbances begin with the characteristic prolongation of the PR interval, then first degree heart block, premature atrial beats, and, later, ST segment depression and ventricular ectopy [71-75]. Amiodarone is an iodine-rich drug that has been tested in many clinical trials to control cardiac arrhythmias and is now widely used [75]. In usual doses, it may generate 6 mg iodine a day, much higher than the optimal iodine intake recommended by the World Health Organization, which is 0.15 to 0.3 mg/day. These pharmacological doses of iodine may affect thyroid hormone production and secretion, and may induce hyper- or hypothyroidism [75].

Thyroid disorders may occur in patients with pre-existing thyroid abnormalities and in subjects with apparently normal thyroid glands. Clinicians should keep in mind the possibility of development of thyroid disorders in patients on treatment with amiodarone even after several years of use [75].

A higher prevalence of overt hypothyroidism (22.7%) as compared to controls (4.1%, p = 0.02) was found in TM patients < or = 3 months after starting amiodarone, while the prevalence of subclinical hypothyroidism was similar in amiodarone-treated (18.2%) and untreated (15%) TM patients [76].

Overt hypothyroidism resolved spontaneously after amiodarone withdrawal in one case, while the remaining TM patients were maintained euthyroid on amiodarone by L-thyroxine administration. After 21-47 months of amiodarone therapy, three patients (13.6%) developed thyrotoxicosis (2 overt and 1 subclinical), which remitted shortly after amiodarone withdrawal. No case of hyperthyroidism was observed TM controls (p = 0.012 vs amiodarone-treated patients) [76].

B. Chronic viral hepatitis and antiviral treatment

Blood transfusion exposes the patient to a number of risks, adverse events associated with transfusion, including infectious agents such as viruses, bacteria and parasites [77]. Chronic liver inflammation is not rare in patients with thalassaemia, since over 40% of them have positive anti-hepatitis C virus (HCV) antibodies and more than 50% have chronic (persistent or active) hepatitis [78-84].

The diagnosis of hepatitis B virus- or hepatitis C virus-related chronic hepatitis is required to detect patients who have a high risk of developing liver complications and who may benefit by antiviral therapy [85]. Combination therapy with Peg-interferon plus ribavirin is suggested to patients with HCV chronic hepatitis or compensated cirrhosis. The main goals of antiviral treatment are the eradication of virus C, the control of liver inflammation and the prevention of cirrhosis [85].

Two distinct mechanisms are described in the development of thyroid disorder during interferon alpha (IFNα) therapy: autoimmune and nonautoimmune- induced thyroid dysfunction. The autoimmune form seems to have more severe consequences and longer evolution. The prevalence of thyroid disease during IFNα treatment is extremely variable, ranging between 1 and 35% [86-88].

Women are more susceptible than men to develop related thyroid disease, having a relative risk 3 to 7-fold higher as reported in some [86-88] but not in all studies [86-88]. Combined treatment with IFNα and ribavirin seems to be associated with a higher percentage of overt hypothyroidism than monotherapy [89]. Patients who developed overt hypothyroidism during therapy were treated with levothyroxin and hyperthyroidism with propranolol.

Long-term follow-up of the pituitary-thyroid axis and cardiac function

Landau *et al*. [59] studied the course of thyroid disease in thalassaemia major patients in a 15-year longitudinal study. The Authors found that more than 30% of TM patients had an abnormal response to TRH test and 14% changed from normal to uncompensated hypothyroidism.

Similar results were also observed in 25% of the patients (27 females and 23 males, mean age 25.7+/-1.4) by Filosa *et al*. [56] during a 12 year-period of follow up and in 37.5% of TM patients with sub-biochemical by De Sanctis *et al*. during a period follow-up of 3-11 years [74]. We have also observed that cardiac involvement may be present in 50% of hypothyroid TM patients with moderate or severe iron overload. Among them, 16.6% died during the follow-up from heart failure and arrhythmia, in a 4-year interval [90].

Thyroid cancer

The occurrence of malignancies in thalassaemic patients is an emerging concern for physicians. In the last five years, in a single Thalassaemia Unit following 195 thalassaemic patients, eleven cases of carcinoma were diagnosed: 4 cases of liver, 1 of lung, 1 of adrenal gland and 5 cases of papillary thyroid carcinoma (patient mean age 42.6 years) [91].

Recently we observed three female thalassaemia patients (2 with TM and 1 with thalassaemia intermedia) with incidental papillary thyroid microcarcinoma and addressed the possible pathogenic role of iron in cancer development and/or progression. In brief, a) iron can promote the growth of some cancer cells probably through its role in the activation of ribonucleotide reductase; b) iron may promote the formation of mutagenic hydroxyl radicals; c) iron excess diminishes host defences through inhibition of the

activity of CD4 lymphocytes and through the suppression of the tumoricidal action of macrophages; d) iron can enhance host cell production of viral nucleic acids which may be involved in the development of some human tumors [92].

Prevention of endocrine complications

Gamberini *et al*. [93] reported a decline of thyroid dysfunction from 6.5% (in 1981) to 0.9% (in 2007). The main risk factors observed in these patients were high serum ferritin levels, poor compliance with desferioxamine (DFO) therapy and splenectomy. Combined chelation with DFO and deferiprone, because of an additive or synergistic effect on iron excretion, seems to be the treatment of choice in achieving a negative iron balance and reversing clinical and sub-clinical iron overload complications. Similar result have been reported by Farmaki *et al*. [94, 95]. The Authors showed that regular and intensive combined chelation therapy reduce or improve the thyroid function in TM patients with iron overload. The time needed to reverse hypothyroidism with combined chelation varied according to the patient age and iron load status.

Treatment of overt hypothyroidism

In the normal population, experts recommend treatment with thyroid hormone if TSH levels >10 mU/l. In thalassaemic patients more criteria are taken into consideration [48, 90]. Overt hypothyroidism is classically treated by oral replacement with synthetic L-thyroxine. L-thyroxine is peripherally converted to FT3, the active form of thyroid hormone; it has a half-life of 6 days and is typically administered as a once-daily dose of 1.6 ug/kg, although the appropriate dosage may vary among patients. Because levothyroxine has a narrow therapeutic range, small differences in absorption can result in subclinical or clinical hypothyroidism or hyperthyroidism [96-99].

The initial levothyroxine dosage may range from 12.5 ug daily to a full replacement replacement dose based on the age, weight, cardiac status of the patient and the severity and duration of the hypothyroidism. It should be noted that there is considerable variation in patient response to thyroxine because of differential thyroid hormone receptor isoform tissue concentration. Adjustment of the dose can then be made based on clinical and laboratory data. A close monitoring of TSH is recommended in hypothyroid TM patients with cardiac dysfunction [96, 100, 101] and osteoporosis, as over-replacement with T4 may cause arrhythmias and accelerated bone loss [102, 103].

Certain medications, supplements and even some foods may affect the levothyroxine absorption, such as: iron supplements, aluminum hydroxide, which is found in some antacids, and calcium supplements. Therefore, the physician must make the appropriate adjustments in levothyroxine dosage in the face of absorption variability and drug interactions.

Treatment of sub-clinical hypothyroidism

Transient serum TSH abnormalities are common in hospitalized and especially in severely ill patients, and in the period after recovery. Sub-clinical thyroid disease should not be diagnosed and therapy not initiated under such circumstances [97].

The following checklist is recommended when dealing with a patient with sub-clinical hypothyroidism [97]:

1. Verification of the diagnosis by repeated testing after for example 1-2 months.

2. The subtype of disease (Type A or B) should be established.

3. Status on clinical symptoms and signs of the disorder.

4. Status on other risk factors and diseases.

5. Information of the patient about the disease, and on the possibility of therapy or wait and see control.

6. Follow the patient’s decision.

7. Follow-up control.

If treatment is started, an initial dose of 25-50 mcg/d of LT4 can be used and can be titrated every 6-8 weeks.The T4 dose is adjusted to normalize serum TSH.

Patients with cardiovascular disease should receive smaller doses per day of L thyroxine [98-99].

A recovery of sub-clinical hypothyroidism has been observed in some iron overloaded TM

patients after an intensive iron chelation therapy [90, 94, 95].

FUTURE PERSPECTIVES AND OPEN PROBLEMS

Over the course of past 2 to 3 decades, hypertransfusion therapy and chelation therapy has significantly increased the life expectancy and improved the life quality of these patients. Three chelators are currently available worldwide, deferoxamine, deferasirox and deferiprone. Several factors, including chelator availability and its properties, drug tolerability, degree of organ-specific iron loading, ongoing transfusional iron burden, and patient preference, must be considered in the design of optimal, individualized chelation regimens, and these factors must periodically be reviewed and chelation adjusted accordingly [104].

Several aspects remain to be elucidated in these patiens, such us the existence of a relationship between thyroid dysfunction, cardiovascular diseases and the components of the metabolic syndrome (insulin resistance) [105, 106], and hypercoagulable and hypocoagulable states [107]. Therefore, further studies are needed to explain these emerging issues also in TM patients.

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