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## Hypothyroidism in Thalassemia

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### 1. Introduction

Thalassemia major is an inherited hemoglobin disorder resulting in chronic hemolytic anemia. Chronic blood transfusion therapy caused excessive iron accumulation in different organs which was associated with high early fatalities. With the introduction of iron chelators, especially the oral ones during the last decade, rates of survival have improved (Tefler et al, 2009) but endocrine complications became more and more frequent in long-term survivors and substantially affect their quality of life. (De Sanctis et al, 2006).

The frequency of hypothyroidism in Thalassemia patients ranges from 6 to 30% among different countries depending on chelation regimens (De Sanctis et al, 2004). Lower prevalence was found in patients who had evidence of lower iron load as measured by ferritin levels (Borgna-Pignatti et al, 2004 ). The prognosis depends on the amount and the duration of iron overload.

Primary hypothyroidism that may affect thalassemic patients from the second decade of life is mainly due to gland infiltration by iron overload. Autoimmune thyroiditis is absent (Delvecchio & Cavallo, 2010). Central hypothyroidism caused by decreased secretion of thyrotropin stimulating hormone (TSH) from the anterior pituitary gland or by decreased secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus is less common. The thyroid gland appears to fail before the thyroid-pituitary axis, which is less sensitive than the gonadal axis to iron-induced damage (Landau et al, 1993).

A wide spectrum of pathogenic mechanisms is involved. Tissue chronic hypoxia (Magro et al, 1990) and iron overload have a direct toxic effect on the thyroid gland. High concentrations of labile plasma iron and labile cell iron which are considered responsible in the formation of free radicals and the production of reactive oxygen species (ROS) may lead to cell and organ damage (Esposito et al, 2003). In severe iron overloaded thalassemia patients the anterior pituitary may be damaged and regulatory hormonal secretion (LH, FSH, TRH) may be disrupted. (Cavallo et al, 1984). Organ siderosis (liver, cardiac and skeletal muscle, kidney) may affect specific receptors, which regulate thyroid hormone action and convert T4 to the bioactive T3. Recent studies have also demonstrated the incidence of Interferon induced thyroiditis in 40% of Thalassemia patients with Hepatitis C treated with IFN $\alpha$ , which seems to be induced by IFN $\alpha$  via both immune stimulatory and direct toxic effects on the thyroid. (Menconi et al, 2011).

Hypothyroidism may create major cardiovascular changes, such as a decrease in cardiac output because of decrease in oxygen and substrate utilization, a decrease in cardiac contractility, a reduction in heart rate and an increase in peripheral vascular resistance (Klein & Danzi, 2007). Thyroid hormones may also play a critical role in brain development in infants and in modulating brain metabolic activity in adults as shown by structural changes related to myelin, studied by brain imaging techniques (Bernal, 2002). Recent research aims to combine modern brain imaging techniques with years of experience in neuropsychological and clinical evaluations of thyroid dysfunctions. It is now clear that without optimal thyroid function, mood disturbance, cognitive impairment and other psychiatric symptoms can emerge.

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 TMp annually. Iron overload induced hypothyroidism may respond to adequate chelation therapy promoting prevention or/and reversal of the disease and other associated comorbidities. In one case of hereditary hemochromatosis, reversal of hypothyroidism was reported after iron depletion (Hudec et al, 2008). Also, a long-term follow-up study of Italian TMp demonstrated that regular iron chelation may prevent thyroid dysfunction and the development of clinically significant myocardial dysfunction. In addition, therapy with L-thyroxin should be considered in hypothyroidic, moderately and severely iron overloaded TMp (De Sanctis et al, 2008a).

The newer challenges of chelation therapy include the prevention and reversal of iron related morbidities by reducing and maintaining iron and free iron to very low levels (Kolnagou et al, 2009). With adequate chelation therapy, endocrinopathies may be stable or reversible in thalassemia major patients (TMp). (Gamberini et al, 2008). Each chelator has different properties influencing the clinical management of iron overload (Kalinowski et al, 2005). Additionally, each patient has a different safety and efficacy profile with regards to their response to chelation therapy. Iron excretion is dose dependent with wide subject-to-subject variability. A negative iron balance, which ensures prevention or/and reversal of iron overload complications, is difficult to achieve with monotherapy. Combined chelation treatment may be a better approach. It results in increased iron excretion compared to monotherapy alone, probably acting by a shuttle or/and additive effect and it was proved to increase overall survival (Telfer, 2009) and achieve treatment goals with manageable adverse reactions (Kontoghiorghes et al, 2010). Also with combined chelation, compliance to the daily lifelong commitment was improved as short-term results were readily evident to TMp themselves.

Our group has had significant experience with the use of combined chelation regimen in TMp regarding the reversal of endocrine complications (Farmaki, 2008; 2010a; 2010b; 2011). Our results on hypothyroidism will be highlighted throughout this chapter. Controversies about exploration of thyroid function and regular follow up in TMp, adequate chelation and arguments for and against T4 treatment will be discussed.

## 2. Patients and methods

This was an open label, observational, single centre study conducted in the Thalassemia Unit, of the General Hospital of Corinth, Greece, for a period of seven years. The study was

approved by the hospital ethical committee and written informed consent was obtained from all patients.

- 2.1 All participants were transfusion-dependent thalassemia major patients (TMp), who presented with more than one iron-overload complication as defined by clinical and laboratory criteria.
- 2.2 Prior to initiation of this study, all patients received chelation monotherapy with DFO, 40 mg/kg; 8–12 h, subcutaneously, 3–5 days/week.
- 2.3 All participants were switched to an intensive combination scheme with DFO and Deferiprone (DFP) consisting of both daily oral administration of DFP 75–100 mg/kg/d in three divided doses and subcutaneous DFO (20–40 mg/kg; 8–12 h, 2–6 d/week. Individual dosing and frequency of DFO infusions were determined by patients' clinical and laboratory assessments, such as iron overload indices and comorbidities.
- 2.4 Although serum ferritin is not an accurate index, we estimated the trends of monthly serial measures of serum ferritin by Chemiluminescent Microparticle Immunoassay (CMIA) by Architect Abbott Diagnostics.
- 2.5 Quantification of heart and liver iron load was determined annually by Signa-MRI 1.5 Tesla, multi-echo T2\* and liver iron concentration (LIC) in mg/gr dry weight (g dw) derived from the T2\*L value by Ferriscan (St Pierre et al 2005, Wood et al, 2005).
- 2.6 A systematic control of thyroid function was performed annually by thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) screening. At baseline and after 5–7 years a thyroid releasing hormone TRH stimulation test was conducted. Following intravenous infusion of 200 mcg TRH, blood samples were taken at 0, 30, 60, 90 and 120 min for TSH measurements. The area under the curve (AUC) was also calculated for estimating integrated response during the test. All patients on hormone replacement therapy discontinued thyroxine at least 30 days before the test.
- 2.7 Cardiac function was assessed annually, with tissue 1Echo-Doppler TD (Philips ie33 system). Patients were classified according to the New York Heart Association (NYHA) criteria.
- 2.8 Gonadal function was assessed by peripheral hormone levels: testosterone and free testosterone or oestradiol and progesterone. In addition, serum basal levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were assayed. Gonadotrophin response was also assayed after intravenous infusion of 200 lg gonadotrophin-releasing hormone (GnRH). Samples were taken at 0, 30, 60, 90 and 120 for the measurement of FSH and LH. All analyses were performed by CMIA technology using the automatic immuno-analyzer ARCITECT, i2000SR,
- 2.9 Safety was evaluated by close clinical and laboratory monitoring of adverse reactions, according to each drug SPC. A full check up of each patient was implemented at baseline before protocol initiation and patients' records were thoroughly reviewed systematically in order to determine any changes.
- 2.10 All statistical analyses were carried out using the statistical package for the social sciences software (SPSS release 13.0, Chicago, IL, USA). All p values were two sided; the level of significance was  $< 0.05$ .

3. Results

Fifty-two patients, 25 males and 27 females, aged 10–49 years at baseline, were followed over a period of 5–7 years. The mean age at baseline was  $25.2 \pm 8.9$  years compared to  $32.9 \pm 9.8$  at the end of the study. Two patients discontinued the study after experiencing repeated episodes of neutropenia and withdrew their consent.

3.1 After combined chelation (DFO & DFP) there was a statistically significant reduction of the total body iron load, as indicated by mean ferritin levels, MRI liver and heart iron quantification ( $T_2^*L$  &  $T_2^*H$ ) and LIC calculated by Ferriscan, shown in table 1.

Parameter	Baseline studies	End of study	p-value
Ferritin ( $\mu\text{g/L}$ )	$3421.6 \pm 882.0$	$87 \pm 25$	<.001
MRI $T_2^*H$ (ms)	$13.8 \pm 9.8$	$35.5 \pm 8.1$	<.001
MRI $T_2^*L$ (ms)	$1.5 \pm 8.2$	$34.4 \pm 5.4$	<.001
LIC (mg/g dwt)	$15.7 \pm 11.1$	$0.9 \pm 0.2$	<.001

Table 1. Results (mean  $\pm$  SD) of iron load assessments in Thalassemia patients

3.2 Euthyroid patients 32/50 demonstrated a significant increase in the mean  $FT_4$  ( $0.80 \pm 0.09$  vs.  $1.10 \pm 0.09$  ng/ml  $p < 0.001$ ) and  $FT_3$  levels ( $1.6 \pm 0.2$  vs.  $2.9 \pm 0.5$  pg/ml,  $p < 0.001$ ). No new cases of hypothyroidism were observed after combined chelation.

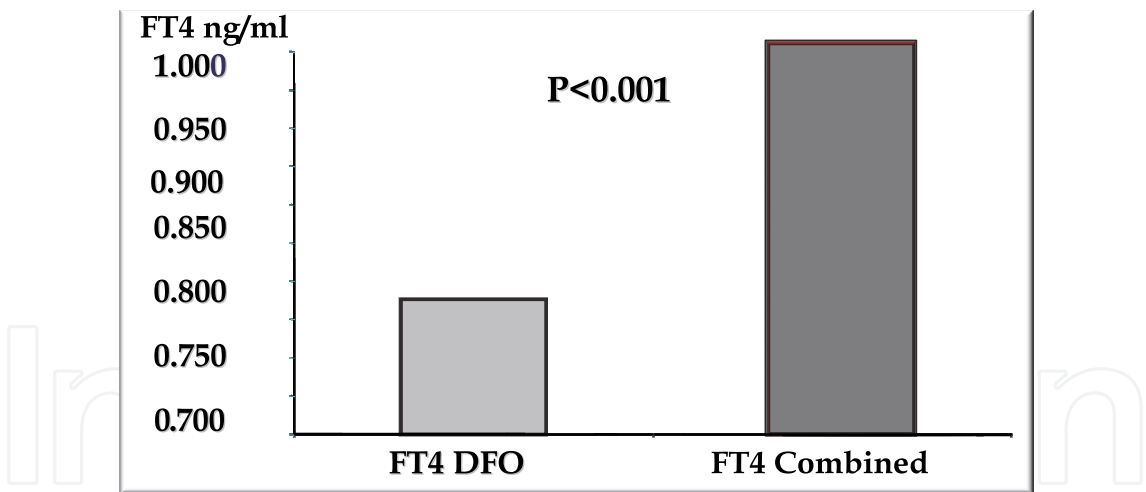


Fig. 1.  $FT_4$  levels at baseline (DFO monotherapy) and after combined chelation in euthyroid Thalassemia patients

3.3 At baseline, while on DFO monotherapy 18/50 patients were hypothyroid. After combined chelation 14/18 who had subclinical or compensated hypothyroidism presented a significant increase in mean  $FT_4$  ( $0.70 \pm 0.06$  vs.  $1.07 \pm 0.12$  ng/ml,  $p < 0.001$ ) and mean  $FT_3$  ( $1.30 \pm 0.3$  vs.  $2.50 \pm 0.6$  pg/ml,  $p < 0.001$ ). In addition, a significant decrease in the mean TSH ( $4.12 \pm 0.63$  vs.  $6.27 \pm 1.08 \mu\text{IU/ml}$   $p < 0.001$ ) and TSH quantitative secretion, calculated as the area under the curve ( $AUC = 2231 \pm 241$  vs.  $1332 \pm 131$   $p < 0.001$ ) in response to the TRH stimulation test were observed.

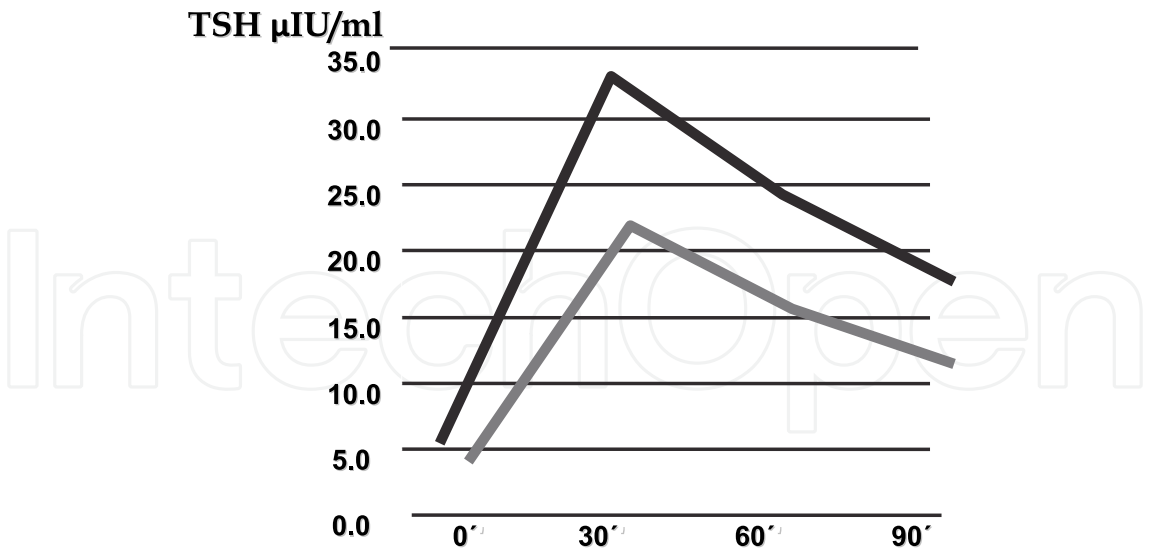


Fig. 2. TRH test at baseline (gray line) and during the reassessment (black line) after combined chelation in TMp with hypothyroidism. Basal TSH:  $4.12 \pm 0.63$  vs.  $6.27 \pm 1.08$ ,  $p=0.01$ . At 30' mins TSH:  $22.13 \pm 2.18$  vs.  $34.06 \pm 4.75$ ,  $p=0.005$ . At 60' mins TSH:  $15.89 \pm 1.13$  vs.  $25.69 \pm 3.72$ ,  $p=0.002$ . At 90' mins TSH:  $11.83 \pm 1.26$  vs.  $19.44 \pm 3.27$ ,  $p=0.001$ .

**3.4** Regarding safety, apart from the 2 patients who withdrew from the study, combined chelation was otherwise well tolerated. Adverse events like joint symptoms (5%), gastrointestinal upset (8%) were managed with symptomatic treatment and an increase in liver enzymes (11%) with a temporarily dose reduction of DFP. One case of tinnitus and one with ocular problems required a transient interruption of DFO for 1-2 months after which were reversed, in both cases.

**4. Discussion**

**4.1** An early systematic laboratory evaluation and control of thyroid function is recommended in all TMp annually because thyroid hormones may affect the function of virtually every organ system.

**4.1.1** Hypothyroidism symptoms are not typical (fatigue, cold intolerance, weight gain). Criteria for the diagnosis of subclinical hypothyroidism (SH) was an elevated basal TSH concentration ( $>5$  TSH  $\mu$ IU/ml) or an increase of the TSH levels during the test more than 20  $\mu$ IU/ml from the basal value or additional low levels of FT4 and FT3 respectively.

**4.1.2** In case of borderline TSH and FT4 levels a TRH stimulation test has to be performed. An exaggerated TSH response ( $>$  or  $=$  21 microIU/Ml) to TRH may occur in 20%-33% of thalassemia patients with normal FT4 levels (Zervas et al, 2002; De Sanctis et al, 2008c). Also, a 15-year longitudinal study has demonstrated that more than 30% of TMp had an abnormal response to TRH test and that 14% change from normal to uncompensated hypothyroidism (Landau et al, 1993). Moreover, TRH stimulation test can also differentiate primary from central hypothyroidism.

**4.1.3** In our study, while on DFO monotherapy 18/50 (36%) patients presented with laboratory findings of hypothyroidism. Classification of hypothyroidism in TMp



according to laboratory tests is shown in table 2. Among them 14/18 (78%) had subclinical or compensated hypothyroidism and 4/18 (22%), mostly older patients, had overt hypothyroidism.

	FT4	T3	TSH	TSH response to TRH Test
Subclinical Hypothyroidism	normal	normal	Increased > 5-10 mU/L	increased
Compensate Hypothyroidism	slight decrease	slight decrease	normal or increased	exaggerated
Overt Hypothyroidism	decreased	normal or decreased	Increased >10 mU/L	exaggerated

Table 2. Classification of hypothyroidism in TMp according to laboratory tests

- 4.1.4** Although ultrasonography is one of the techniques most frequently used to evaluate the volume and structure of thyroid gland, it is not ubiquitous in TMp as autoimmune thyroiditis is absent (Mariotti et al, 2011) and most echogenicity patterns are not specific. However, Pitrolo et al, 2004 reported a reduced echogenicity in 47% of TMp and a diffuse spotty echogenicity in 33% of them, indicative of thyroid dysfunction. Also, Filosa et al, 2006 reported features of dyshomogeneity of the parenchyma with different degrees of severity in TMp, which were in accordance with the criteria of Sostre and Reyes and also a slow worsening of thyroid function in 25% of TMp during a 12 year-period of follow up.
- 4.1.5** Magnetic resonance imaging (MRI) plays an adjunctive role in the further investigation of primary hypothyroidism or/and central hypothyroidism with pituitary dysfunction. Hekmatnia et al, 2010 demonstrated that signal reduction may precede pituitary volume loss and could be expected first on MRI especially in hypogonadic thalassemia patients. Additionally the use of pituitary R2, have allowed to define age-specific norms for pituitary volume allowing earlier recognition of relevant iron deposition and damage and prevention of pan-hypopituitarism (Wood et al, 2010).

**4.2 Hypothyroidism & total body iron overload**

- 4.2.1** Serum ferritin levels of approximately 3,000 ng/ml in TMp were found to correlate with hypothyroidism according to Gamberini et al, 2008. De Sanctis et al, 2008c, reported that TSH peak values correlated directly with ferritin levels, ALT, and the compliance index to chelation therapy. In our study, the intensification of chelation with combined therapy and the achievement of normal serum ferritin levels, led to an amelioration of thyroid function with significant increase in the secretion of FT<sub>4</sub> and FT<sub>3</sub> levels both in euthyroid as well as in hypothyroid TMp. While on DFO monotherapy, there were safety concerns with low ferritin levels ( Piga et al, 1988), with combined chelation, no significant adverse effects associated with lowering patients’ body iron load to normal levels were observed. In some TMp, thyroid impairment was transient, and their secretory capacity improved. In the elderly TMp, with a late onset of chelation therapy, the detrimental effect of iron accumulation led to a permanent impairment of thyroid function suggesting that iron-induced toxicity is mainly time dependent.

**4.2.2** Liver iron concentration (LIC) has been regarded as the reference standard for estimating body iron loading and has been shown to accurately predict total body iron stores (Angelucci et al, 2000). R2 and R2\* magnetic resonance imaging (MRI) relaxation time techniques allow for non-invasive estimation of LIC in patients with hemoglobinopathies. The LIC cut-off points of 7 and 15 mg Fe/g dw have been used to categorize iron overload status, predict morbidity and mortality, and tailor iron chelation therapy in TMp for the past two decades. However, LIC  $\geq 6$  mg Fe/g dw was found to be the best threshold for discriminating the presence and absence of endocrine/bone morbidity (hypothyroidism, osteoporosis, or hypogonadism). According to Musallam et al, 2011, Thalassemia patients with a LIC  $\geq 6$  mg Fe/g dw were 4.05 times more likely to have endocrine morbidity compared with patients with a LIC  $< 6$  mg Fe/g dw. Liver iron overload also seems to influence hormonal peripheral metabolism (Maggiolini et al, 1995). In our study at baseline, 98% of patients had hepatic iron overload (LIC  $\geq 1.5$  mg/g dw), and among them 64% had severe iron overload (LIC  $> 12$  mg/g dw). After 5 to 7 years of intensive combined chelation, TMp had a normal mean LIC:  $0.9 \pm 0.2$  vs.  $15.7 \pm 11.1$  mg/g dw and this was correlated  $r = -0.679$   $p < 0.03$  with a significant increase of FT4 levels in all TMp. This provides clear evidence that iron-induced tissue damage is reversible, suggesting that such reductions may prevent or reverse thyroid dysfunction.

**4.2.3** Extrahepatic tissues have different kinetics of iron uptake and clearance than the liver, because they selectively, or almost selectively, load circulating non-transferrin bound iron (NTBI) (Glickstein et al, 2005). Long periods of unprotected exposure to NTBI could predispose to increased iron uptake in endocrine glands. The cellular labile iron (LIP) expansion in iron overload conditions poses a threat to cell integrity. Iron-mediated oxidative stress triggers apoptosis, volume loss, and fatty replacement in the organs leading to their dysfunction over time.

### 4.3 Hypothyroidism and iron chelators

**4.3.1** With DFO monotherapy the incidence of primary hypothyroidism in TMp was approximately 30%. In some retrospective studies this incidence was shown to decrease over time according to compliance, but in most cases there was a progression from subclinical to overt hypothyroidism (De Sanctis, 2008c). In our study, at baseline while on DFO monotherapy, 18/50 TMp (36%), were treated with thyroxin replacement therapy. Among them 14/18 (78%) had subclinical or compensated hypothyroidism and 4/18 (22%), mostly older patients had overt hypothyroidism. The incidence was high possibly because of inadequate dosing, poor compliance, or relative poor thyroid protection from DFO-specific properties. Monotherapy usually maintains iron balance but does not decrease iron that has accumulated over an extensive period. As TMp require transfusions indefinitely, a negative iron balance is difficult to achieve. Besides, chelator efficacy depend on their availability in plasma or interstitial fluids and their membrane-crossing ability in accessing and neutralizing intracellular LIP which pose a threat to cell integrity. DFO contrary to oral chelators, is a large positively charged, lipophobic molecule with low membrane permeation abilities and thereby low cell iron extraction capacity.

**4.3.2** Combined chelation with DFO and DFP because of an additive or synergistic effect on iron excretion, seems to be the treatment of choice in achieving a negative iron balance,



normalizing body iron load and reversing clinical and subclinical iron overload complications. Of the 50 patients completing the study, 18 (36%) were treated with thyroxin replacement therapy at baseline while on DFO monotherapy. After combined chelation and an important decrease in total body iron overload 14/18 who had subclinical or compensated hypothyroidism presented a significant increase in mean FT4, FT3 ( $p < 0.001$ ) and an decrease in TSH (reflected by the AUC calculation). Among them, 10/18 (56%) discontinued thyroxin therapy (Fisher's exact test  $p < 0.001$ ) and 4/18 (22%) reduced their thyroxin dose. The remaining 4 (8% of the total study group) who had biochemical overt hypothyroidism, while they all improved their TRH stimulation test, only 2 converted to compensated hypothyroidism with TSH levels 5-10 mIU/ml and normal FT4 & FT3 levels. The time needed to reverse hypothyroidism with combined chelation varies according to the patient age and iron load status. Besides combined chelation may prevent hypothyroidism as no new-onset nor worsening of thyroid dysfunction was observed during the study period. Whether the overall improvement in thyroid function that was achieved in our patients can be solely attributed to the intensification of chelation therapy and better compliance or if there is a tissue-specific effectiveness of DFP in iron removal from thyroid gland is debatable.

- 4.3.3** To our knowledge, this is the first report that documents, the beneficial effect of long-term combined therapy in normalizing total body iron load and reversing most of the cases of subclinical and compensate hypothyroidism in TMp.

#### **4.4 Hypothyroidism & cardiac dysfunction**

- 4.4.1** Thyroid hormones control several enzymes involved in regulating calcium fluxes in the heart including the calcium-dependent adenosine triphosphatase and phospholamban. In case of hypothyroidism, the decreases in the expression and activity of these enzymes could potentially impair systolic performance and diastolic relaxation of the ventricles, leading to a reduction in cardiac output (Klein & Danzi, 2007). Additionally thyroid hormones play a role in reducing peripheral vascular resistance by relaxing vascular smooth muscle cells. Thus, in case of hypothyroidism there is an increase in peripheral vascular resistance and a reduction in tissue perfusion and oxygen utilization. Symptoms of cardiovascular dysfunction are not common or prominent but may include dyspnea, exercise intolerance, and edema. Findings on physical examination may include bradycardia, hypertension, nonpitting edema, and pleural or pericardial effusion. Laboratory indices like dyslipidemia with high serum total and low-density-lipoprotein (LDL) cholesterol concentrations are common in hypothyroidism.

- 4.4.2** In a recent long-term follow-up study (De Sanctis, 2008a), was mentioned that cardiac involvement may be present in 50% of hypothyroid TMp 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. The changes in cardiovascular function in hypothyroidism respond to replacement therapy with L-thyroxine and an adequate chelation regimen (De Sanctis, 2008b).

- 4.4.3** In our study, all hypothyroid TMp were presented at baseline with moderate to severe cardiac iron overload (mean MRI T2\*H:  $13.8 \pm 9.8$  msec) and 16/18 (88,8%) with a cardiac dysfunction (mean LVEF of  $54 \pm 1.5\%$ ) and classified according to their symptoms 4/16

(25%) NYHA Class I, 7/16 (44%) Class II, 3/16 (19%) Class III and 2/16 (12%) Class IV. Twelve of them were on cardiac medications (angiotensin-converting enzyme [ACE] inhibitors, anti-arrhythmics, digoxin or diuretics). After combined chelation therapy, the overall change from cardiac iron loaded to non-iron loaded was significant (Fisher's exact test  $p < 0.001$ ) with mean MRI T2\*H increased to normal levels  $35.5 \pm 8.1$ ms and mean LVEF:  $65 \pm 2.8\%$ , respectively. Only in 2/16 less compliant TMp, although ameliorated cardiac dysfunction (one of Class IV and one of Class III improved to Class II) kept on cardiac medication. None of our TMp died during the follow-up interval, from heart failure or arrhythmia. No new cases of cardiac dysfunction were observed suggesting that combined chelation may prevent or reverse cardiac complications. A considerable body of data now exists confirming that DFP is superior to DFO in reducing iron in the heart (Pennell et al, 2006) and reversing cardiac complications and that combined chelation (DFP-DFO) can have a more marked effect in purging cardiac iron (Anderson et al, 2002; Tanner et al, 2007, 2008), as it was observed in this study. Maggio et al, 2009 speculated that DFP had a protective effect on the heart even before cardiac iron declined significantly, most likely because of the clearance of cellular toxic labile iron. In any case, reversal of cardiac complications and discontinuation of cardiac medication, as documented here, is a significant achievement. Reversal of hypothyroidism, in the same TMp, possibly sustained cardiac amelioration.

#### 4.5 Hypothyroidism & hypogonadism

- 4.5.1** Subclinical hypothyroidism may be associated with male and female gonad dysfunction and interferes with their reproductive ability (Trokoudes et al 2006). The awareness of the thyroid status in any infertile couple is crucial, because of its significant, frequent and often reversible or preventable effect on infertility.
- 4.5.2** Indeed, among our hypothyroid TMp one female with secondary amenorrhea, after 5 years of combined chelation, the normalization of her total body iron load and the improvement of her overall hormonal profile, gave birth to 2 healthy children after normal conception.

#### 4.6 The decision to treat TMp with L-thyroxin

- 4.6.1** Although the course of thyroid disease in TMp is a slow process and it might take years to progress from normal to uncompensated hypothyroidism, the decision to treat with L-thyroxin is crucial. 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 (Gharib et al, 2005; De Sanctis et al, 2008b). It is particularly recommended in TMp with cardiac dysfunction because of the potential for reducing the risk of cardiac problems (Biondi & Cooper, 2008). The therapeutic use of thyroid hormones in the clinical treatment of mood disorders or memory impairment is taking on a new dimension even in patients with euthyroid hormonal state (Bauer et al, 2008). Additionally, thyroxine treatment in subclinical hypothyroidism may restore ovulatory dysfunction and adverse pregnancy outcome. Trokoudes et al, 2006 underlined that awareness of the thyroid status in the infertile couple is crucial, because of its significant, frequent and often reversible or preventable effect on infertility.

- 4.6.2** Therefore in our group of TMp the decision to treat was individualized and based on patients' clinical history and aggravating factors (hyperlipidaemia, cardiac dysfunction, diabetes, pregnancy, depression). For this reason, the overall prevalence in our group (18/50 36%) was higher than that reported by others (Cunningham et al, 2004; Borgna-Pignatti et al, 2005). After the use of combined chelation and the reversal of cardiac, glucose metabolism abnormalities and hypogonadism and other aggravating factors, thyroxine treatment was reconsidered according to thyroid investigation of each individual patient. Thereby 56% of TMp with subclinical or compensated hypothyroidism discontinued thyroxin therapy and 22% reduced their thyroxin dose.
- 4.6.3** Special attention has to be paid in hypothyroid children and adolescents presenting clinical features that include declining growth velocity, short stature and pubertal delay. Replacement therapy with T4 should be installed in order to restore normal growth and development. Once growth and pubertal development are complete, thyroid hormone treatment can be discontinued and thyroid function re-evaluated. Patients and families should be aware that treatment may sometimes cause temporary behavior symptoms, poorer school achievement, and may not restore full growth potential.
- 4.6.4** After initiation of T4 therapy, the patient should be reevaluated and serum TSH should be measured in six weeks, and the dose adjusted accordingly. A systematic follow-up biochemical monitoring (TSH) should be performed every six months to determine if re-titration of the dose is necessary. For patients whose serum TSH is confirmed to be at the upper limits or above the normal reference range, is recommended to increase the dose of T4 with the aim of lowering the serum TSH value into the lower half of the normal range.
- 4.6.5** As T4 should be taken once per day, on an empty stomach (one hour before eating or two hours after), sometimes compliance is difficult to achieve, considering that TMp take many medications. Also some of them may interfere with T4 absorption and should be taken several hours after the T4 dose. Additionally a high-fiber diet or coffee uptake can interfere with the absorption of T4.
- 4.6.6** A close monitoring of TSH is recommended in hypothyroid TMp with cardiac dysfunction and osteoporosis, as over-replacement with T4 may cause atrial fibrillation and accelerated bone loss with risk of fractures.

## 5. Conclusion

This study demonstrated that hypothyroidism in Thalassemia, is a frequent iron overload complication. In most TMp there are no obvious clinical signs of hypothyroidism, so a regular follow-up for early detection and a timely replacement treatment should be implemented especially in children and adolescents with growth failure and pubertal delay. The use of intensive combined chelation and the reduction of total body iron load to normal levels may play a leading role in the prevention or/and reversal of hypothyroidism in Thalassemia. As shown in our study there was a reversal of most cases of subclinical and compensated hypothyroidism. Additionally this treatment regimen may prevent the progression from subclinical to overt hypothyroidism or may improve some cases of overt hypothyroidism, suggesting that even iron-induced damage of the thyroid pituitary axis might be reversed. Combined chelation was well tolerated and had

a positive impact on patient quality of life. It remains to be established, possibly through clinical trials in the future, whether other chelation regimens, will offer comparable benefits.

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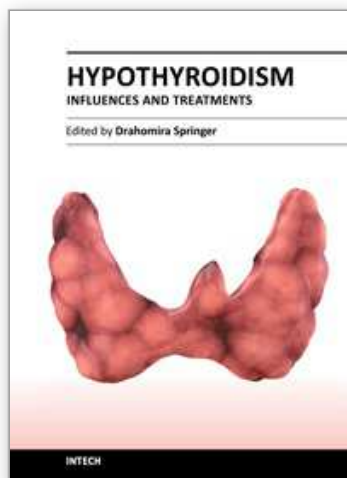
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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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