Chapter

Hypothyroidism Therapy

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Abstract

Hypothyroidism refers to the common pathological disorder of thyroid hormone deficiency. The successful therapy for hypothyroidism is levothyroxine (LT4) administration, which is the same as thyroxine but produced synthetically. Serum thyrotropin (TSH) normalization with LT4 replacement therapy in hypothyroidism is generally needed to restore a euthyroid state. The daily dose of thyroxine therapy depends on various factors, such as body weight, age, and severity. It also differs from hypothyroidism during pregnancy to congenital hypothyroidism. The presence of various comorbidities may exist such as myxoedema coma, coronary artery disease, obesity, anemia and COVID-19 which necessitate individualized treatment. LT4 intolerance manifested with sympathetic hyperactivity may appear during the first hours after the LT4 administration. It requires starting with very low doses of LT4 that should be increased gradually, and reaching normal TSH may take several months. The sympathetic hyperactivity may be attributable to the presence of uncorrected iron-deficiency anemia that worsens by the use of thyroid hormone.

Keywords: Levothyroxine, dose, hypothyroidism, anemia, myxoedema coma, treatement

1. Introduction

Hypothyroidism refers to the common disorder of thyroid hormone deficiency. According to the time of onset, it may be present at birth (congenital) or develop later in life (acquired). Treatment of hypothyroidism consists of replacing the deficiency of thyroid hormone to improve symptoms and prevent the adverse consequences of hypothyroidism. Levothyroxine (LT4) that is identical to thyroxine but synthetically produced, is the most effective way to treat hypothyroidism. Treating hypothyroidism strategies are based on adopting an adequate dose of LT4, selecting a patient-appropriate serum thyrotropin (TSH) goal, and ensuring maintenance of that desired goal [1, 2]. The serum TSH normalization with LT4 replacement is generally needed to restore a euthyroid state. The daily LT4 dose must be individualized taking into account various factors such as body weight, age and severity of disease. Special situations may be coexisting requiring special treatement [2]. The purpose of this chapter is to provide the different therapeutic strategies of hypothyroidism management in various circumstances.

2. Congenital hypothyroidism

The guidelines of the American Academy of Pediatrics [3] and the European Society of Pediatric Endocrinology [4] recommends keeping TSH values below 5

μU/dl (optimally 0.5–2.0 μU/dl) for the first 3 years of life. LT4 is the treatment for hypothyroidism in children. Infants with suspected hypothyroidism require rapid evaluation and treatment, ideally within the first 2 weeks of life since delays in treatment of congenital hypothyroidism are correlated with poorer outcomes. Congenital hypothyroidism treatment should be initiated with 10–15 lg/kg of LT4 daily. Early starting treatment and adequate LT4 initial doses are associated with rapid normalization of thyroid function and improved neurodevelopmental outcomes [5].

Tablets might be crushed, suspended in a small amount of water, breast milk, or non–soy-based formula, and administered orally via a syringe. LT4 should not be administered with substances that may interfere with its absorption such as multivitamins containing calcium or iron, aluminum hydroxide and soy formula. The medication is administered once a day. The same dose should be repeated if there is immediate vomiting. If a dose is missed, it may be doubled the following day [6].

Serum thyroid function testing should be checked every 1–2 weeks until normal, and then every 1–2 months during the first year of life and every 2–4 months during the 2nd and 3rd years of life with an appropriate adjustment of LT4 dose [7]. The needed dose of LT4 to restore euthyroidism varied with the age and the hypothyroidism severity. The dose required per kilogram body mass to fully replace thyroid function is significantly higher in children than in adults and decreases with age (**Table 1**). Early and adequate prenatal treatment with LT4 prevents severe neurocognitive deficits and results in normal brain development [1].

3. Acquired hypothyroidism

The approach to treat acquired hypothyroidism is similar to that of congenital, consisting of replacing the deficiency of thyroid hormones to improve symptoms and prevent the adverse consequences of hypothyroidism. The target is to keep serum TSH <5 mIU/L (optimally 0.5–2 mIU/L) [8].

The recommended treatment is LT4 in tablets form administered once daily. Adherence to LT4 may be influenced by multiple factors such as the time of day when the medication is administered. Although the majority of experts recommend administration of LT4 prior to food consumption, but bedtime administration may be more convenient and does not appear to be associated with worse control of hypothyroidism in children and adolescents [9].

The dose of LT4 required to restore euthyroidism depends on patient age, body surface area, weight and severity of hypothyroidism (**Table 1**) [1]. The dose required to fully replace thyroid function is significantly higher in children than in

Age	LT4 dose (lg/kg/day)
0–3 months	10–15
3–12 months	6–10
1–3 years	4–6
3–10 years	3–5
10–16 years	2–4
16 years	1.6

Modified from reference [1].

Table 1.
Levothyroxine (LT4) weight-based dose in pediatric hypothyroidism.

adults and decreases with age. Thyroid function should be controlled 6 to 8 weeks after initiating therapy and then every 4 to 6 months until the child achieves final height or every 6 to 8 weeks following a change in LT4 dose [10].

4. Subclinical hypothyroidism

Subclinical hypothyroidism (SCH) is considered in two categories according to the elevation in serum TSH level: mildly increased TSH levels (4.0–10.0 mU/l), and more severely increased TSH value (>10 mU/l) [11]. For the American Thyroid Association recommendation, the goal of therapy is to normalize TSH levels within 0.5–3.5 mIU/L. The starting thyroid hormone treatment is recommended when the serum TSH is above 10 mIU/L. The treatment is generally not recommended when the TSH is 5–10 mIU/L except in patients with increased cardiovascular risk.

These guidelines suggest that LT4 is the treatment of choice with a daily dose of 25–75 mcg, depending on the degree of TSH elevation and to be adjusted based on clinical response and serum thyroid function test monitoring. Addition with liothyronine (T3) is not routinely recommended [1, 12].

For the European Thyroid Association, even in the absence of symptoms, replacement therapy with LT4 is recommended for younger patients (<65–70 years) who have serum TSH levels greater than 10 mIU/L and in younger SCH patients (serum TSH <10 mU/l) with symptoms suggestive of hypothyroidism. For older individuals (>80–85 years) with elevated serum TSH ≤ 10 mU/l, observation without hormonal treatment should be the strategy of choice. The aim is to reach a stable serum TSH in the lower half of the reference range (0.4–2.5 mU/l). A daily dose of LT4 between 50 and 100 μg for most SCH patients and between 25 and 50 mcg for those with cardiac disease and/or older age has been advised to normalize serum TSH. The use of T3 or combined LT4/T3 is no supported in the treatment [11].

According to the Latin American Thyroid Society, LT4 is started in individuals with a serum TSH greater than 10 mIU/L and considered to start in those with a serum TSH 4.5–10 mIU/L especially greater than 7 mIU/L, who are younger than 65 years with increased cardiovascular risk. Patients with persistent mild elevations in TSH with positive serum thyroid peroxidase (TPO) antibodies and ultrasound findings consistent with autoimmune thyroiditis could be considered for treatment. These guidelines recommends against treatment of elderly (65–80 years) patients with TSH levels less than 10 mIU/L [13].

The British Thyroid Association recommends starting treatment in patients with positive antibodies or serum TSH >10 mU/L. The guideline advise to start with LT4 doses between 50 and 125 mcg/day. Treatment should aim for TSH levels within the normal reference range. Older individuals or with cardiac disease, require smaller starting doses to avoid inducing cardiac ischaemia. Combined therapy with LT4 and liothyronine (LT3) is not routinely recommended [14].

The American Association of Clinical Endocrinology recommends starting treatment with LT4 in patients with TSH > 10 mIU / L or those with symptoms, cardiovascular risk factors or positive TPO antibody. The goal of LT4 therapy is to normalize TSH. The starting dose of LT4 is 1.5 mcg/kg in the absence of cardiovascular disease. In patients with cardiovascular disease, the starting dose of LT4 is 25 mcg and is up-titrated as needed [12]. The American Endocrine Society recommends against routine treatment of SCH patients with serum TSH levels of 4.5–10 mU/liter, but indicated that treatment was reasonable for patients with TSH levels greater than 10 mU/liter [15].

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5. Myxoedema coma

Myxedema coma is the most extreme, life-threatening expression of severe hypothyroidism. Usual precipitating factors are discontinuation of therapy, infections and exposure to cold. Its clinical manifestations include hypothermia, respiratory depression, cardiovascular instability and altered mental status [1]. According to the American Thyroid Association guidelines, patients with myxedema coma should first receive empiric glucocorticoid coverage with intravenous glucocorticoid administration (at appropriate doses for the stressed state). These guidelines recommends a daily intravenous dose of 200 to 400 mcg of LT4, with lower doses given for patients who are of smaller stature, older, or who have a history of coronary disease or arrhythmia. Subsequently, daily dosing of 1.6 mcg/kg/day reduced to 75%, should be given.

Additional administration of intravenous T3 in a loading dose of 5–20 μg, followed by a maintenance dose of 2.5 to 10 mcg every 8 hours is recommended [1, 16–18]. For the Latin American Thyroid Society guidelines, LT4 replacement is the backbone of myxedema coma therapy. The daily starting dose is 300–500 μg/day followed by maintenance dose 50–100 μg/day. T3 can be added to therapy at 10–20 mg bolus followed by 10 μg every 4–6 hours [19]. The necessity of intravenous LT4 replacement is apparent, but administering LT4 alone or with a combination of LT4 and LT3 remains controversial [1, 16–18]. Carter et al. [20] prouved that combinated treatment with LT3 and LT4 are more beneficial than LT4 monotherapy to improve symptoms and to reverse the biochemical abnormalities in patients with myxedema coma. At the same Ono et al. [21] showed that patients receiving LT4 combined with LT3 had a lower mortality rate than those who received LT4 alone. T3 is an active hormone in the body with an immediate onset of action, whereas LT4 has a slow onset of action with relatively few adverse events. Also T3 affinity for the nuclear receptor is 10- to 20- fold higher than that of T4 and it reaches a peak level in 2–4 h after administration [22]. The beneficial effect of this combined treatment on neuropsychiatric symptoms has been confirmed because of the capacity of T3 to cross the blood brain barrier [23].

6. Pregnancy

6.1 Treatment of overt hypothyroidism in pregnancy

Women with overt hypothyroidism who contemplate pregnancy must first normalize TSH and thyroid hormone levels. LT4 is the first choice of treatment. American Thyroid Association guidelines specifies a goal of TSH less than 2·5 mIU/L in women planning to become pregnant [24]. Women with a previous diagnosis of hypothyroidism, should checked their serum TSH concentration and increased LT4 dose made as soon as possible after pregnancy is confirmed [25]. The LT4 replacement dose may be as high as 2.0–2.4 μg/kg body weight per day, which

is 25–50% higher than levels used in the general population (1.6–1.8 μg/kg body weight) [26].

Once pregnant, women should increased the dose of LT4 by about 30–50%, beginning in the first 4–8 weeks of gestation and gradually increasing the dose through 16–20 weeks of gestation [27]. After initiation of therapy, thyroid function should be retested within 30–40 days, and then every 4–6 weeks. Maternal TSH concentrations should be maintained between 0·1–2·5 mIU/L in the first trimester, 0·2–3·0 mIU/L in the second, and 0·3–3·0 mIU/L in the third [27, 28].

6.2 Treatment of SCH in pregnancy

According to the American Thyroid Association guidelines, TSH levels should be keept below 2.5 mU/L and 3.0 mU/L in the first and second/third trimesters, respectively [28]. Autoantibodies to TPO should be mesured in women with SCH, since TPO positivity acts in synergy with SCH and it is an independent risk factor for pregnancy outcomes [29–31]. The rise of maternal TSH level increase the risk of miscarriage. This risk becomes even greater at a TSH level > 2.5 mU/L, accompanied by TPO positivity [24]. Pregnant women with SCH have a higher risk of several side effects such as pregnancy loss and premature birth [32]. In women receiving LT4 treatment for SCH, the risk of miscarriage in early pregnancy increases at a TSH level > 4.5 mU/L.

It was showed that LT4 treatment is capable to reduce the rate of pregnancy loss in TPO positive euthyroid women, therefore starting treatment with low doses of LT4 may be considered in TPO positive women with a history of recurrent pregnancy loss [33, 34]. Starting doses of LT4 were based on TSH levels, either 1 μg/kg/day (TSH 1.5–2.5 mU/L) or 0.5 μg/kg/day (TSH 0.5–1.5 mU/L), raising or lowering amounts by 0.5 μg/day at TSH levels >3 mU/L or < 0.5 mU/L, respectively [34].

7. Coronary artery disease

If untreated, hypothyroidism in patients with coronary heart disease might lead to ventricular arrhythmias, congestive heart failure or acute myocardial infarction.

Therefore, patients with coronary artery disease and hypothyroidism should be treated cautiously with thyroid hormone replacement [35]. Therapy is performed with the administration of LT4,that induced significant improvement in myocardial function, cardiac pump function and resting cardiac output [36]. However, in subjects with an already compromised myocardial blood supply due to coronary atherosclerosis, LT4 treatment may lead to anginal symptoms. A previous study showed that 2% among 1503 hypothyroid subjects presented new onset angina during LT4 therapy [37]. The recommended initial therapeutic dose for patients with pre-existing angina is 25 mg / day or even less and it should not be increased faster than at 4 week intervals [38].

8. Elderly

The serum TSH levels reference range is 4–5 mIU/L in the elderly patients. The hormone replacement with LT4 is the specific therapy for old individuals with hypothyroidism [39]. A normal starting dose of LT4 in an elderly subject is around 1 mg/kg/day, which is maintained for 4–6 weeks [40]. Dosage adjustments are guided by the TSH response and the clinical state, with emphasis on possible cardiac adverse effects [38]. Some experts recommended to increase the dosage by 25 μg in

accordance with the patient's complaints [41]. While this therapeutic dose should be reduced of about 50 μg/day, or 25 μg/day when the patient was underweight or developed cardiovascular disease [39].

Hormone replacement with LT4 in patients with hypothyroidism requires specific therapy. LT4 is available in the form of tablets at various doses, but also in liquid form as an oral solution, thus enabling a customized dose titration [41]. The European Thyroid Association recommends treatment in patients above 70 years old who have a TSH >10 mUI/L and signs and/or symptoms of hypothyroidism [11]. However, the LT4 dose needs to be tailored, aiming for a TSH level between 4 and 10 mIU/L, while the patient's health condition and the potential presence of dyslipidemia and other metabolic derangements should be considered [42].

Likewise, van den Beld et al. [43] showed that low serum FT4 levels are associated with a longer 4-year survival, reflecting a possible adaptive mechanism to prevent excessive catabolism in the elderly. Hypothyroidism is prevalent among the elderly population, that's why efforts should be made to maintain optimal thyroid function with individualized treatment based on severity and comorbidities [43].

9. COVID-19

Hypothyroidism is not a risk factor associated with worse outcomes in COVID-19 positive patients, therefore no particular changes or consultations are envisaged relating to the diagnosis and treatment of hypothyroidism during the COVID-19 crisis [44]. It is recommended to pursue the same form, frequence and dosage of thyroid hormone replacement therapy. No particular therapeutic dosage was addressed. Regular blood test monitoring may be difficult, but when patients on thyroid hormone replacement feel significantly unwell or if there are significant weight changes, thyroid function testing with measurement of serum TSH and free thyroxine, is recommended to adjust medication if needed [45].

10. Obesity

LT4 is the treatment of patients developed SCH associated with hyperlipidae. T3 can be added for patients with adequately substituted hypothyroidism with obesity resistant to a lifestyle intervention or suspected of thyroid hormone conversion disorders [46].

An individual approach of treatment is necessary for obese patients with higher TSH levels. The clinical condition of elevated TSH without symptoms, thyroid antibodies, goiter, or associated thyroidal illness, was defined as obesity-associated hyperthyrotropinemia. The efficacy of thyroid hormone therapy in obese subjects with hyperthyrotropinemia has not yet been evaluated [47]. LT4 treatment of obese with hyperthyrotropinemia were performed only in children demonstrating that the increase TSH levels causes impaired glucose metabolism and dyslipidemia [48].

However, no evidence regarding a favorable effect of LT4 treatment on body weight in obese subjects with TSH < 10 mU/L and normal free thyroxine level has been demonstrated, so such treatment is not recommended. In such subjects dietary-behavioral intervention contributed to weight loss irrespective of LT4 use. However, in normal-weight patients with hypothyroidism LT4 treatment is an effective strategy to decrease total and LDL cholesterol, this effect is more pronounced in patients with TSH > 10 mU/L [11]. Obese individuals with isolated hyperthyrotropinemia without symptoms or other signs of thyroid disease should not be treated with thyroid hormone replacement [47].

The role of thyroid hormone in treating obesity was confirmed. So that T3 and T4 administration at varying doses and durations has been shown to enhance weight loss in obese euthyroid subjects [49]. Such therapy increased fat loss without decreasing skeletal muscle mass and strength or inducing cardiac dysfunction [50]. However, a systematic review by Kaptein et al. [51] describing the effects of T3 or T3/T4 treatment on weight loss in euthyroid individuals during caloric deprivation showed that T3 is associated with decreases in serum T4 concentrations, indicating pituitary suppression of TSH, resulting in subclinical hyperthyroidism.

11. Adrenal insufficiency

Glucocorticoid deficiency can accompany hypothyroidism and if it is not detected, it may be exacerbated by thyroid hormone replacement, raising the risk of adrenal crisis that can be fatal. The signs and symptoms of coexisting adrenal insufficiency are manifold and can be summarized as hypoglycemia, anemia, nausea, vomiting, alopecia areata, weight loss, abdominal pain, hypotension and hyperpigmentation [52]. If so, it is important to start with replacing glucocorticoids first before starting LT4 and then approaching LT4 replacement 5–7 days later. Starting by LT4 therapy can contribuate to an increased metabolism which raise demand of cortisol, leading then to an increased risk of an adrenal crisis [38, 53].

Not to be confused, the modest increase of serum TSH levels in cases of untreated adrenal insufficiency, might return to normal without for thyroid hormone replacement but only by the correct hydrocortisone replacement treatment. The diurnal variation in TSH levels is influenced by cortisol, it manifests higher concentrations at night and lower in the morning, which explains the increase in TSH levels in untreated adrenal insufficiency [54].

12. Differentiated thyroid cancer

Differentiated thyroid cancer should be treated with an appropriate expertise in order to ensure an optimal long-term treatment quality. The therapeutic approach is individualized and risk-adapted. Surgery and radioiodine therapy followed by LT4 substitution is the established therapeutic procedures. For widely invasive follicular thyroid carcinomas and follicular thyroid carcinoma with vascular infiltration, thyreoidectomy is recommended. Radioiodine therapy has been established for more than 60 years, consisted on systemic administration of radioiodine (I-131) to irradiate thyroid remnants as well as non-resectable or incompletely resected differentiated thyroid cancer.

The benefit of I-131 therapy was confirmed in individuals with differentiated thyroid cancer at high risk for recurrence, however in subjects with very low-risk differentiated thyroid cancer the positive effect of radioiodine on tumor-free and overall survival has not been proven [55]. Patients who undergone thyroidectomy for differentiated thyroid cancer, with or without additional treatment with I-131, need to take LT4 not only for treatment of hypothyroidism but also to minimize potential TSH stimulation of tumor growth [56]. The recommended levels of thyroid-stimulating hormone (mIU/L) targets in patients with differentiated thyroid cancer by American Thyroid Association are;<0.1 for high and intermediate risk (initial therapy) and persistent disease, 0.1–0.5 for high-risk disease free (follow-up) and low risk (initial therapy) and 0.3–2.0 for low-risk disease free (follow-up) [57].

13. Anemia

Anemia seems to be associated with thyroid dysfunction particularly hypothyroidism. Anemia was found in 65% of children and adolescents with hypothyroidism [58]. At the same, 10% of the individuals with thyroiditis manifested anemia. These patients may be particularly sensitive at the beginning of LT4 replacement therapy [59]. Lack of stimulation of erythroid colony development by thyroid hormones, reduction in oxygen distribution to tissues and diminution of erythropoietin level in the absence of thyroid hormones leads to anemia [60]. The correction of hypothyroidism promotes an adequate therapeutic response to iron salts. Iron may interfere with the absorption of the thyroid hormone, that's why LT4 should be taken at least four hours apart from the iron intake [52].

14. LT4 intolerance

A sympathetic hyperactivity may appear during the first hours after the LT4 administration manifested by precordialgia or palpitations. This condition requires starting with very low doses of LT4 that should be increased gradually, and reaching normal TSH may took several months. The sympathetic hyperactivity may be attributable to the presence of uncorrected iron-deficiency anemia that worsens by the use of thyroid hormone. The anemia should be corrected and thyroid hormone therapy should be stoped temporarily and then restarted at low doses. Occasionally, beta blockers can be used in these cases to control the symptoms during the first few weeks of thyroid replacement treatment [59, 61].

15. Conclusion

Hypothyroidism is a common disorder, diagnosed by the measurement of blood levels of thyroid hormones. In the face of this challenge, efforts should be made to maintain optimal thyroid function. Therapy of choise is the administration of LT4. Treatment should be individualized in accordance with the subject's age, weight, severity and comorbidities. Special situations can coexist such as adrenal insufficiency, pregnant women, elderly patients and patients with differentiated thyroid cancer, needing special considerations to ensure the patient's welfare and prevent therapeutic complications. Under- or over-treatment is common in clinical practice and should be avoided and lifelong follow-up is strongly indicated.

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