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REVIEW ARTICLE

Hypothyroidism and Levothyroxine, Review Article

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ABSTRACT

Hypothyroidism is a communal thyroid hormone deficit disorder. It affects ten percent of the general population and it is estimated that 5% go undiagnosed. If not treated properly, it can cause serious health problems and even death[1-2]. There is no great variability in the clinical picture or specificity of symptoms, therefore it is most often diagnosed mainly biochemically[3].

Levothyroxine (L-thyroxine, LT4) is the gold standard in the treatment of hypothyroidism. It was introduced in 1949 and has since improved the lives of millions of hypothyroid patients. As it is usually given for the patient's life, the dose can be affected by physiological changes. In addition, the dosage should be adjusted in the event of concomitant medical conditions, pregnancy and the elderly. Clinically significant interactions between levothyroxine and other drugs, food and dietary supplements may occur. This can change the safety and effectiveness of the treatment[4-5]. The physician should be aware of the use of thyroxine and its interactions with other medications and diet[6].

Hypothyroidism, levothyroxine uses and dose adjustments and their interactions will be discussed in this review.

Keywords: hypothyroidism, levothyroxine, dose adjustment, interaction

INTRODUCTION

Hypothyroidism is a state of deficiency in thyroid hormones. Because of the wide difference in the clinical picture and the general non-specificity of symptoms, hypothyroidism is mainly defined biochemically[7-8]. Manifest or clinical primary hypothyroidism is a condition in which the concentration of TSH is greater than the standard value and the concentration of thyroxine in free form is less than the standard value. The subclinical or mild hypothyroidism is definite as a TSH concentration greater than the standard value and a thyroxine in free form concentration within the standard value[9-10]. People with hypothyroidism may experience weight changes and feel weak, unhappy or tired, which can lower their life quality[11].

Epidemiology

Risk factors and Incidence: The pervasiveness of overt hypothyroidism in the US is about five percent. In European states; meta-analysis valued the incidence of un-identified hypothyroidism at around 5%, counting mild or overt cases[12]. The incidence of hypothyroidism is higher in women, the elderly (> 65 years old), and Caucasians. In addition, it is much communal in subjects with autoimmune diseases like type 1 diabetes, hypothyroidism, celiac disease, and autoimmune gastric atrophy and may transpire as part of many autoimmune endocrine pathologies[13]. Likewise, people with Down's or Turner syndrome have an augmented jeopardy of hypothyroidism. In disparity, moderate alcohol consumption and smoking are related with a lower danger of hypothyroidism[14].

The Causes of Hypothyroidism: Hypothyroidism is defined as a deficiency of the hormones T4 and T3. The T4 hormone is mainly produced by the thyroid gland, while the T3 hormone is produced in smaller amounts. Major T3 comes from the conversion of enzymes; T4 to T3 in target tissues. The inability of the thyroid gland to yield T3 and T4 arouses the pituitary gland to upsurge the thyroid stimulating hormone (TSH) production via negative feed-back mechanism[15]. In > 95% of patients, it is instigated by a lack of thyroid hormone production (primary hypothyroidism). The residual five percent of cases have hypothyroidism due to further reasons, counting 2^{ndry} hypothyroidism because of insufficient production of TSH by the pituitary gland, thyrotropin-releasing hormone deficiency causes tertiary hypothyroidism[16].

The utmost communal reason of hypothyroidism in zones without deficiency of iodine is chronic autoimmune thyroiditis (also known as Hashimoto's disease). Most autoimmune patients with thyroiditis have increase anti-thyroid antibodies levels (mainly anti-thyroglobulin and anti-thyroid peroxidase antibodies)[17]. Antibodies to thyroid peroxidase are too perceived in approximately 12% of the overall populace. The anti-thyroid peroxidase antibody also helps predict progression to overt disease in subclinical hypothyroidism[18-19].

The autoimmune thyroiditis underlying mechanisms are not well understood, but both environmental and genetic features may be tangled[20]. One finding is that smokers have lower levels of anti-thyroid peroxidase antibodies than nonsmokers, and the frequency rises later to cessation of smoking. Additional aspects that play a role include selenium and vitamin D deficiency, and moderate consumption of alcohol.

Since iodine is the main constituent of thyroid hormones, deficiency of iodine can lead to hypothyroidism, thyroid nodules and goiter[21]. Cretinism is the utmost severe outcome of deficiency of iodine (i.e., reduced physical and mental development in the womb and in infantile). Iodine supplementation plans are public health interventions designed to prevent cognitive and physical deterioration.

Table 1: Summary of Levothyroxine PK

Pharmacokinetic Characteristic	Description
Chief absorption site	Small intestine (jejunum and ileum)
Tmax	2–3 hours
Bioavailability	70–80 % in euthyroid person; may be slightly higher in hyperthyroid patients
Protein binding	T4 >99.9 % T3 = 99.8 %
Vd	11–15 L
CL	T4 = 0.055 and 0.038 L/h in euthyroid and hypothyroid patients, respectively
T1/2	T4 = 6.2 and 7.5 days in euthyroid and hypothyroid patients, respectively T3 = 1.0 and 1.4 days in euthyroid and hypothyroid patients, respectively

Burden of Hypothyroidism: Undiagnosed / untreated hypothyroidism has a significant economic impact, especially in terms of maternal and congenital hypothyroidism costs, and is most likely associated with decreased quality of life associated with weight changes such as fatigue, malaise and depression. It also plays a role in many other diseases, such as hypothyroidism and cardiovascular disorders[22]. In particular, it is related with a reduced contractility of the cardiovascular system and its connotation with CAD has been recognized for long. It donates to reversible dementia, infertility including musculoskeletal, gastrointestinal and neurosensory symptoms. A significant quantity of not-treated patients with subclinical or overt hypothyroidism displays signs of symptomless small fiber innervational neuropathy[23]. Severe thyroid dysfunction can cause menstrual disorders and infertility. The prevalence of thyroid disorders is high in women aged 20-45, so

infertility is also an issue. Fertility problems may persist even after thyroid function is restored to normal.

Treatment of Hypothyroidism: Hypothyroidism is treated with levothyroxine and a history of treatment and intervention goes back 2,000 years[24]. In 1890, attempts were made to transplant animal tissue of thyroid, resulting in a rapid response clinically in hypothyroidism, and in 1891 there were reports of injections of sheep's thyroid gland. After one-year, sheep fresh thyroid glands administration orally was tested and found to be operative. Over time, the recognition of the danger of overdosing the extracts has been questioned, and it has been suggested that the dosing regimens begin with a low dose based on symptoms and gradual titration as needed. Thyroxine was introduced in 1949[25].

The starting dose of levothyroxine may depend on the degree of remaining function of thyroid preserved by the patient's lean body mass or body weight, and the concentration of TSH[26].

As levothyroxine is usually administered for the lifetime of the patient, lifelong physiological changes will have an impact on the dose of levothyroxine. Conversely, hypothyroidism is instigated by medications and transitory forms of thyroiditis[23].

The initial dosage of thyroxine be contingent on the age of patient, concomitant heart disease, and the etiology and biochemical severity of hypothyroidism. The levothyroxine dose is titrated until the levels of TSH are stabilized to between 0.5 and 4.1 mIU / L. Healthy adult patients under 50 years of age diagnosed with overt hypothyroidism typically attain a full oral replacement dosage of levothyroxine (1.7 mcg / kg / day), whereas persons with CAD or those who were 50-60 years of age obtain the initial dose of levothyroxine (25-50 mcg once a day)[24].

The dose of thyroxine during pregnancy is aimed at achieving TSH in the 1st half trimester with precise range or less 2.6 mIU / L when possible.

TSH must be evaluated 4-6 weeks later to the starting treatment or changing the dose. Subsequently, subjects with normal and stable serum levels of TSH must be observed every one-year. The aim of levothyroxine therapy is to decrease signs and avert long-term problems. Over the years, the replacement dose of levothyroxine may need to be adjusted as the patient progresses additional situations or disease progresses that disturb the metabolism of thyroid hormones. Features that may require modification of the dose of levothyroxine comprise drug incompatibility, concomitant use of drugs or dietary supplements such as iron or calcium, and variations in eating habits and body weight[25].

When serum TSH levels exceed the standard value related with normal free thyroxine levels, it is termed subclinical hypothyroidism[26].

There is controversy over the subclinical hypothyroidism treatment with levothyroxine. There is now agreement on the treatment of hypothyroidism in subclinical form with levothyroxine in gravid females and those considering gravidness. This will help decrease the jeopardy of complications in pregnancy and affect the intellectual growth of the infant. On the other hand, the treatment of non-pregnant adults is controversial[27].

Table 2: Pharmacokinetics of Levothyroxine in Special Populations

	Bioavailability	Metabolism (T4 to T3)	Protein Binding	Elimination	TT4	TT3	fT4	fT3
Hepatic impairment (cirrhosis)		↓	↓		↑	↓	↑	↑↓
Renal impairment		↓	↓			↓		↓
Children				↑	↓			
Elderly	↓	↓		↓		↓		↓
Pregnancy				↓			↓	
Obesity					↑↓	↑↓		
Food	↓							
Gastrointestinal disorders	↓							

It is supposed that subclinical hypothyroidism treatment with levothyroxine may delay overt hypothyroidism progression while reducing the incidence of CAD and improving the musculoskeletal and neuropsychiatric signs related with hypothyroidism[24-25].

The necessity for the amalgamation of LT3 and levothyroxine in the treatment of hypothyroidism has recently been reconsidered in several clinical guidelines. As more than a third of patients continue to receive inadequate treatment despite levothyroxine treatment, they have high levels of TSH or insistent symptoms. This may be related to changes in people attitudes, the co-occurrence of additional autoimmune diseases, and the lack of adequate T4 to T3 conversion with decrease T3 / T4 ratio in levothyroxine therapy. There is an ongoing debate as to whether addition of artificial LT3 to standard therapy of LT4 in such cases would represent natural treatment plan[26]. However, most clinical guidelines address this issue and recommend that combination therapy not be routinely used. However, only in some cases the European, ATA and British strategies endorse amalgamation treatment as an individual investigational method.

Table 3: Drugs Interfering with Thyroid Function or with Levothyroxine Pharmacokinetics

Drug or Drug Class	Relative Bioavailability	Synthesis	Metabolism	Protein Binding	Thyroid stimulating Hormone	Overall Effect on Thyroid Hormones Total T4	Free T4	Clinical Recommendation
Amiodarone	↑↓	↑↓	↓			↔↑↓		Monitor thyroid function
Aluminium hydroxide	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Androgens				↓		↔	↔	Lower dose may be necessary
Anabolic steroids				↓		↓	↔	Lower dose may be necessary
Calcium carbonate/citrate/ acetate	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Beta blockers	↓a	↓a	↓a	↓b		↓ (transientb)		Monitor thyroid function
Cholestyramine	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Carbamazepine			↑	↓		↓	↓↔	Monitor thyroid function
Colsevelam	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Cimetidine	↓					↓		Increase levothyroxine dosage
Ethinyl oestradiol				↑		↑		Higher dose may be necessary

Dopamine (≥0.4 mcg/kg/min)					↓	↓ (transient)		Dose modification unnecessary
Fluorouracil				↑		↑	↔	Dose modification unnecessary
Ferrous sulphate	↓					↓		Avoid concomitant use (separate intake by 4 to 6 hours)
Glucocorticoids (dexamethasone ≥0.5 mg/day or hydrocortisone ≥100 mg/day)			↓ (initial)	↓	↓ (transient)	↓ (transient)		Lower dose may be necessary
Furosemide (high dose)				↓		↓ (transient)	↑ (transient)	Dose modification unnecessary
Heroin				↑		↑	↔	Monitor thyroid function
Heparin				↓		↓ (transient)		Dose modification unnecessary
Lithium		↓				↓		Monitor thyroid function
Iodide		↑↓				↓		Monitor thyroid function
Methadone				↑		↑	↔	Dose modification unnecessary
Nicotinic acid				↓		↓		Dose modification unnecessary
Mitotane				↑		↑	↔	Dose modification unnecessary

Table 4:

Drug or Drug Class	Relative Bioavailability	Synthesis	Metabolism	Protein Binding	Thyroidstimulating Hormone	Overall Effect on Thyroid Hormones Total T4	Free T4	Clinical Recommendation
Phenobarbital			↑			↓		Increase levothyroxine dosage
Orlistat	↓					↓		Monitor thyroid function
Phosphate binders	↓					↓	↓	Separate intake by four or more hours
Phenytoin			↑	↓		↓	↔↓	Monitor thyroid function
Rifampin			↑			↓		Increase levothyroxine dosage
Proton pump inhibitors (omeprazole, lansoprazole)	↓					↓		Increase levothyroxine dosage
Sucralphate	↓					↓		Separate intake by four or more hours
Salicylates (>2 g/day)				↓		↓ (transient)	↓ (long-term use)	Dose modification unnecessary
Tamoxifen				↑		↑	↔	Higher dose may be necessary
Sulphonamides		↓				↓		Monitor thyroid function
Tolbutamide		↓				↓		Monitor thyroid function

Treatment Of Hypothyroids With Levothyroxine And Interactions With Drugs, Diet And Food Supplements: It is essential that clinicians using thyroxine to treat hypothyroidism be aware of the interaction of thyroxine. In a study by McMillan et al. studied patients with hypothyroidism to identify various factors influencing L-T4 therapy. Of the 926 participants, 52.1% used dietary supplements acknowledged to interrelate with L-T4, such as iron, calcium and often (more than twice a week) high-fiber foods and drinks (, bar fiber, bran flakes, broccoli or fiber drinks), iodine (blueberries, dried seaweed, cod or plain yogurt) or soybeans. They found that 124 patients (13.4%) had difficulty controlling symptoms of hypothyroidism. Therefore, it is concluded that the treatment of patients with hypothyroidism should take into account the interaction of L-T4 with food, drink and dietary supplements[27].

It is known that patients with increased gastric pH also impair L-T4 absorption. Studies have established that subjects with reduced secretion of gastric acid because of disease or the use of PPIs may require augmented dosages of levothyroxine to attain the wanted level of TSH[28].

Consuming L-T4 with diet influences not solitary the drug pharmacokinetics, but correspondingly increases the effectiveness of treatment (as restrained by variations in fT3, fT4 and TSH levels). Seechurn et al. Support the endorsement to delay eating for minimum 30-60 minutes later taking L-T4 tablets[27-28].

Because patients with hypothyroidism are overweight or obese. Some people have constipation symptoms. Patients sometimes eat a high-fiber diet or use supplements containing fibers deprived of accessing by the physician[29]. However, the category of diet can significantly affect the L-T4 bioavailability. Since L-T4 is un-specifically adsorbed to the fiber, this results in malabsorption of the drugs. In addition, products containing insoluble dietary fiber increase movements in the bowel and enhance the absorption of L-T4 in the intestines may be changed as a result. Liel et al. In their study, they described 13 cases of patients with hypothyroidism, in which the intake of products enriched with fiber resulted in a substantial reduction in the effectiveness of L-T4 drugs. They recommended TSH levels monitoring in subjects succeeding dietary changes and enhancing the dosage of L-T4 as needed[30].

One study found that milk had an effect on absorption of L-T4. Chon et al. L-T4 drugs administered unaided or with cow's milk. They observed that shared milk consumption reduces the absorption of levothyroxine.

Several studies have also shown that coffee may reduce the safety and effectiveness of L-T4 therapy. A possible cause for this interface is coffee appropriation of L-T4 and the consequent transformed intestinal absorption of drugs[30].

Campbell et al. showed that the effectiveness of L-T4 decreased after the administration of 300 mg of ferrous sulfate. Iodine-containing drugs such as amiodarone can reduce the production of thyroid hormones with iodine overload and instantly block the synthesis of thyroid hormone (i.e., Wolff-Chaikoff effect). Approximately 15% of subjects managed with amiodarone progress to hypothyroidism. Likewise, lithium results in hypothyroidism by persuading the release and synthesis of thyroid hormones. Tyrosine kinase inhibitors are used to treat cancer. Clinical reports from the US Drug and Food Administration's

Adverse Event Reporting System show that subjects receiving sunitinib develop hypothyroidism much regularly than subjects managed with sorafenib[31]. Certain medications can correspondingly cause primary hypothyroidism, counting thalidomide, interferon alpha, antiepileptic drugs, certain monoclonal antibodies and second-line drugs for treating multi-drug resistant TB.

Hypothyroidism is communal after therapy with radioiodine and after neck irradiation or surgery to treat cancer. In the long term, approximately 81% of Graves patients treated with radioiodine may progress hypothyroidism, even at minimum doses[30-31]. Hypothyroidism has been described in 56% of subjects treated for toxic nodular goiter and in approximately 9% of subjects treated for single toxic nodules.

RESULTS

Hypothyroidism is a communal thyroid hormone deficit disorder. It affects ten percent of the general population and it is estimated that 5% go undiagnosed. It is treated with levothyroxine. The physician using levothyroxine should be aware of the use of levothyroxine and its relations with medications, dietary and food supplements. Studies have shown that taking L-T4 at bedtime or in the morning is just as operative. The endorsed L-T4 administration with assumed food be contingent on its composition. The medicines muse be taken 60 minutes prior to meal; The soft gelatin and oral liquid capsules may be taken with food, if this may improve patient compliance.

There is limited evidence of interactions between L-T4 and soy products, enteral nutrition, coffee, calcium, iron supplements, fiber derived from non-randomized studies, uncontrolled clinical trials and cohort studies, all of which led to a reduction in L-T4 levels and T4 absorption.

Similarly, there are reports of varying efficacy of L-T4 consumed with juice, milk, aluminum-containing preparations, papaya and chromium supplements, but the clinical significance of these relations requires more investigation.

CONCLUSION

Switching from tablets to new formulations can solve the L-T4 malabsorption problem caused by coffee, calcium and iron. Leaving a gap between food intake and L-T4 can also reduce the danger of interactions, particularly with calcium, iron and coffee supplements.

This appraisal helps doctors and pharmacists better understand the interactions amid food and L-T4. We hope that this will also contribute to increasing patients' alertness of the correct use of L-T4. Though, more in-depth and dependable research is needed.

To shed further light on the complex but important issue of how L-T4 interacts with food and dietary supplements.

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