



MANAGING HYPOTHYROIDISM: A REVIEW OF THYROID HORMONES

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Hypothyroidism is a heterogeneous disorder defined by biochemical markers and clinical symptoms caused by deficient secretion of thyroid hormones from the thyroid glands. The most common hormone deficiency with a pathological cause is hypothyroidism.¹ In the United States, hypothyroidism is prevalent in 4.6% of the total population and an estimated 10.4 million Americans have thyroid disease, goiter, or are currently taking thyroid medications.² Abnormally high serum thyrotropin, or thyroid-stimulating hormone (TSH) concentrations are found in 7.5% of women and 2.8% of men.³ Women are 10 times more likely to have hypothyroidism than men.^{2,3} Additionally, hypothyroidism incidence increases with age especially after the age of 45.^{3,4} More cases of hypothyroidism are seen in Caucasians (5.1%) and Hispanics (4.1%) than in African Americans (1.7%).² Furthermore, the majority of people being treated for hypothyroidism are not well controlled. The Colorado Health Fair Survey reported 60% of patients receiving treatment with thyroid medications did not have TSH levels within the therapeutic range (0.39-4.6 mIU/L).⁵ This article will discuss the etiology, clinical manifestations, and general approaches to treatment of hypothyroidism and review the current treatment options that are available.

ETIOLOGY

Primary hypothyroidism is defined as a thyroid hormone deficiency resulting from thyroid gland fail-

ure. Causes of primary hypothyroidism include iatrogenic hypothyroidism, autoimmune, iodine deficiency, enzyme defects, thyroid hypoplasia, and goitrogens.¹ Iatrogenic hypothyroidism is a type of primary hypothyroidism that occurs after an individual has been exposed to an excessive amount of radiation, such as radioiodine or external radiation, as well as post-operatively. In populations with sufficient iodine consumption, the most common cause of primary hypothyroidism is chronic autoimmune thyroiditis or Hashimoto's disease.^{1,6,7} Chronic autoimmune thyroiditis is thought to result from defective suppressor T-lymphocytes that are unable to stop mutations of helper T lymphocyte clones that target thyroid membrane antigens which stimulates thyroid antibody production.⁷ Women with thyroid autoantibodies are 8 times more likely to develop overt/clinical hypothyroidism than women without thyroid autoantibodies.³ Furthermore, women with thyroid autoantibodies and elevated isolated thyrotropin are 38 times more likely to progress to overt/clinical hypothyroidism with a 4% annual risk.³

Secondary hypothyroidism, also referred to as central hypothyroidism, is caused by hypothalamic or pituitary failure resulting in a thyroid hormone deficiency.¹ Secondary hypothyroidism is less common than primary hypothyroidism.² Hypothalamic diseases that can lead to secondary hypothyroidism include

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Table 1 | Medications causing hypothyroidism.⁸

Medications	Mechanism of Induction
Propylthiouracil (PTU), methimazole	Inhibition of T ₄ /T ₃ Synthesis
Lithium, iodide, amiodarone, aminoglutethimide	Inhibition of T ₄ /T ₃ Secretion
Interferon, interleukin-2, amiodarone, sunitinib	Thyroiditis
Iodide, amiodarone	Jod-Basedow Hyperthyroidism
Glucocorticoids, dopamine agonists, somatostatin analogs, rexinoids, carbamazepine/oxcarbamazepine, metformin	TSH Suppression
Metyrapone	TSH Elevation
Furosemide, phenytoin, probenecid, heparin, NSAIDs	Displacement from thyroxine binding globulin (laboratory artifact)

NSAIDs = non-steroidal anti-inflammatory drugs; T₃= triiodothyrene; T₄= thyroxine; TSH = thyroid-stimulating hormone

tumors, trauma, or infiltrative disorders. Similarly, hypopituitary-induced secondary hypothyroidism can result from tumors, surgery or irradiation of the pituitary gland, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies, bexarotene treatment, or in rare cases isolated TSH deficiency or inactivity.^{1,2,8}

Drug-induced hypothyroidism can occur as an adverse reaction during the treatment of hyperthyroidism with antithyroid drugs or with medications being used for conditions not directly related to the thyroid. Medications known to cause drug-induced hypothyroidism and the mechanism of action by which they affect thyroid function are listed in **Table 1**.⁸ Amiodarone and lithium are two of the most frequently identified medications that cause drug-induced hypothyroidism. The incidence of drug-induced hypothyroidism is estimated to be between 4.3-5% for amiodarone-treated patients and 4-34% for those treated with lithium.⁹⁻¹² Bocchetta and colleagues determined that lithium-treated patients with resultant antithyroid antibodies had a relative risk of 8.4 of developing hypothyroidism compared with patients without detectable antithyroid antibodies.¹⁰ The incidence of drug-induced hypothyroidism is unknown for many medications, since many have been identified in case reports only.

CLINICAL MANIFESTATIONS

The most common signs and symptoms of hypothyroidism are fatigue, dry skin, cold intolerance, hair loss, slowed mental processing, constipation, weight gain, hoarseness, and bradycardia.^{1,6} Clinical presentation is dependent on the progression, duration, and severity of the condition, as well as the patient's psychological status.⁶ Less frequent signs of hypothyroidism include coagulopathy, depression, psychosis, hypothermia, pleural and pericardial effusions, CHF, and

coma.¹ Hypothyroidism is classified as being overt (clinical) or subclinical (mild) based upon severity and laboratory parameters. Overt hypothyroidism is characterized by increased levels of serum TSH and decreased levels of free T₄ (FT₄) and free T₃ (FT₃) in a symptomatic patient.⁶ A mild increase in serum TSH and normal levels of FT₄ and FT₃ are seen in subclinical hypothyroidism with the patient presenting as either symptomatic or asymptomatic.²

PHARMACOLOGIC TREATMENT OPTIONS

Two sets of guidelines have been published outlining the general management of hypothyroidism. The American Thyroid Association published their most recent set of practice guidelines in 1995 and the American Association of Clinical Endocrinologists (AACE) published their most recent set of thyroid guidelines in 2002.^{6,13} The AACE Thyroid Guidelines provides specific criteria to aid clinicians in assessing each patient's condition in order to determine the most appropriate course of therapy. More specific information has been published regarding treatment in pregnant women and the elderly since these special populations require additional considerations.³⁰⁻³² The ultimate goal of treatment is to restore the patient's thyroid function biochemically to its euthyroid state.^{6,13} In addition, another goal of therapy is to reverse the physiological changes that resulted from the deficiency.^{1,2} Both the American Thyroid Association and AACE treatment guidelines identify thyroid hormone replacement as the gold standard of treatment for hypothyroidism.^{6,13}

Thyroid preparations are currently available in the United States and FDA-approved for the treatment of hypothyroidism (**Table 2**). Formulations of thyroid hormones are described as being either synthetic (i.e. levothyroxine, liothyronine, liotrix) or natural from animal origin (i.e. Thyroid USP).^{1,6} Of the available

Table 2 | Currently available thyroid hormone preparations.¹⁴⁻¹⁹

Generic Name	Brand Names	Contents	Relative Dose	Pharmacokinetics
levothyroxine	Synthroid® Levothroid® Levoxyl®	Synthetic T ₄	50-60 mcg	<ul style="list-style-type: none"> • Absorption = 40-80% • t ½ = 6-7 days (euthyroid) • Bioavailability = 93-98%
liothyronine	Cytomel®	Synthetic T ₃	15-37.5 mcg	<ul style="list-style-type: none"> • Absorption = 95% in 4hrs • t ½ = 2-3 days (euthyroid) • Bioavailability = Variable
liotrix	Thyrolar®	Synthetic T ₄ :T ₃ in 4:1 ratio	50-60 mcg T ₄ 12.5-15 mcg T ₃	<ul style="list-style-type: none"> • Absorption = 48-79% ; 41% gelatin vs 74% albumin • t ½ = 6-7 days (T₄) & 2-3 days (T₃) • Bioavailability = Variable
Thyroid USP	Armour Thyroid®	Desiccated beef or pork thyroid gland	1 grain (equivalent to 60 mcg T ₄)	<ul style="list-style-type: none"> • Absorption = 48-79% ; 41% gelatin vs 74% albumin • t ½ = 6-7 days (T₄) & 2-3 days (T₃) • Bioavailability = Variable

T₃ = triiodothyronine; T₄ = thyroxine; mcg = micrograms; t ½ = half-life

agents, the preferred pharmacologic treatment is synthetic levothyroxine (L-thyroxine/T₄).^{6,13}

T₄ Monotherapy: Levothyroxine

Levothyroxine (LT₄) is a synthetic and pure T₄ thyroid hormone that is classified as pro-hormone.¹⁴⁻¹⁶ Approximately 80% of LT₄ is converted in vivo to the biologically active form, T₃.²⁰ Following LT₄ administration, increased concentrations of both T₄ and T₃ inhibit thyrotropin-releasing hormone (TRH) secretion from the hypothalamus and TSH secretion from the anterior pituitary.²⁰ Consequently, serum TSH levels are returned to the normal therapeutic range.²¹ Levothyroxine is preferred over other thyroid preparations because the amount of T₄ is standardized and its pharmacokinetics are more predictable than other formulations. Furthermore, levothyroxine has a longer half-life allowing for once daily dosing and it is well tolerated.

The bioequivalence of the available levothyroxine preparations remains controversial. The ACCE Thyroid Guidelines recommend that once a patient is started on a certain brand of levothyroxine or a specific manufacturer of a generic, they should continue taking the same one throughout the course of treatment.⁶ However, in June 2007, FDA rejected a citizen's petition questioning the bioequivalence of levothyroxine and subsequently approved the first generic.²¹ The American Thyroid Association issued their own statement that strongly disagreed with the FDA's and warned consumers about the serious and potentially life-threatening risks of switching between different formulations.²²

T₃ & T₄/T₃ Combination Therapy

Three prescription-only T₃-containing products are available in the United States: liothyronine (Cytomel®), liotrix (Thyrolar®), and desiccated thyroid (Thyroid USP®). Liothyronine (Cytomel®) is pure T₃ with a shorter half-life (2-3 days) than levothyroxine (6-7 days).¹⁴⁻¹⁷ Liothyronine is rapidly absorbed in the small intestine, with 94% absorption occurring within 4 hours, which can lead to increased physiological levels of T₃ for the first few hours following administration.¹⁷ Increased T₃ levels lead to an increased risk of cardiovascular patients, especially in patients with underlying coronary artery disease.⁷ Liotrix (Thyrolar®) is also a synthetic thyroid hormone containing a combination of T₄/T₃ in a 4:1 ratio in an attempt to mimic what occurs naturally.^{6,18} Desiccated thyroid (Thyroid USP®) is a natural T₄/T₃ preparation containing desiccated beef or pork thyroid gland that is associated with high antigenicity resulting from animal protein.^{1,19} Both combination thyroid hormone formulations contain a high T₄/T₃ ratio that makes titration to an euthyroid state more difficult.^{18,19}

Several trials have compared levothyroxine with combination liothyronine (**Table 3**). Escobar-Morreale and colleagues compared standard L-thyroxine therapy with combination L-thyroxine and liothyronine therapy in a randomized, double-blind crossover trial.²³ Combination therapy resulted in overreplacement of thyroid hormone, causing a decrease in free T₄ (FT₄) levels by 3.9 pmol/L (95% CI, 2.5-5.3 pmol/L) and an increase in TSH levels by 0.62 mU/L (95% CI, 0.01-1.0 pmol/L).²³ Additionally, patients whose thy-

Table 3 | Clinical trials comparing levothyroxine monotherapy to combination liothyronine.

Study	Design	Treatment	Results	Conclusions
Escobar-Morreale, et al. ²³ (2005) N=28 Overt primary hypothyroidism	R, DB, CO, 8 wk	L-thyroxine 100 µg/d vs. L-thyroxine 75 µg/d liothyronine 5 µg/d	<ul style="list-style-type: none"> TSH level 0.62 mU/L higher in combination group Free T₄ level 3.9 pmol/L lower in combination group No difference in FT₃, profile of mood states, cognitive performance, QOL scores, or Visual Analogue Mental Scale 	Combination therapy did not offer any clear advantage over levothyroxine monotherapy.
Appelhoff, et al. ²⁴ (2005) N=141 Primary autoimmune hypothyroidism	R, DB, CT, 15 wk	Grp 1: continue LT ₄ Grp 2: LT ₄ /LT ₃ ratio 10:1 Grp 3: LT ₄ /LT ₃ ratio 10:1	<ul style="list-style-type: none"> Median endpoint serum TSH 0.29 mU/L (Grp 2) and 0.57 mU/L lower in combination group Median loss in BW of 0.5 kg and 1.7 kg in combination group vs. 0.1 kg weight gain in monotherapy group Patients preferred combination T₄/T₃ therapy by 29% in Group 1, 45% in Group 2, and 48% in Group 3 (p<0.05) No difference in cognitive speed, attention, or memory 	An increase in satisfaction with T ₄ /T ₃ combination therapy was directly associated with an increase in weight loss, but did not correlate with biochemical parameters or mood, well-being, fatigue, and neurocognitive functions.
Siegmund, et al. ²⁵ (2005) N=23 Hypothyroidism s/p surgery, radioiodine, & 2 with autoimmune thyroiditis	R, DB, CO, 2-period w/o wash-out, 12 wk	Pre-study T ₄ dose 100-175 µg vs. 95% pre-study T ₄ dose with 5% T ₃	<ul style="list-style-type: none"> No difference in TSH levels (mU/L), mood scores, or cognitive performance 	No difference in steady-state hormonal, metabolic, & CV characteristics. No improvement in mood & cognitive performance.
Clyde, et al. ²⁶ (2003) N=46 Primary hypothyroidism @ military treatment center	R, DB, PC, 22 mth,	Pre-study T ₄ dose vs. combo of 50% pre-study T ₄ dose & 7.5 µg T ₃ x 4mth	<ul style="list-style-type: none"> Grooved Peg Board performance decreased in T₄/T₃ combination group No difference in serum TSH levels, mean BDI score, hypothyroid HQRL symptom scores, or neuropsychological tests 	Combination therapy did not offer any advantage over levothyroxine monotherapy.
Sawka, et al. ²⁷ (2003) N=40 Depression+ Hypothyroidism	R, DB, P, 15 wk	Prestudy T ₄ dose + placebo vs. 50% pre-study T ₄ dose and T ₃ 12.5 µg bid	<ul style="list-style-type: none"> Increased FT₃ and FT₄ concentrations only during weeks 2-4 of combination therapy No difference in mean TSH concentration following therapy 	Combination therapy did not offer any advantage over levothyroxine monotherapy.
Walsh, et al. ²⁸ (2003) N=101 completed Primary Hypothyroidism	R, DB, CT, CO	Pre-study T ₄ dose vs. liothyronine 10 µg substituted for 50 µg of pre-study T ₄ dose	<ul style="list-style-type: none"> Nausea and anxiety were worse for T₄/T₃ combination therapy (<0.05) No difference in cognitive function QOL scores, thyroid symptom questionnaire 	Combination therapy was associated with more anxiety, more nausea, and did not help with depressive symptoms.

BW = body weight; **CO** = cross-over; **CT** = controlled trial; **CV** = cardiovascular; **DB**= double-blinded; **Mth** = month; **QOL** = Quality-of-Life; **R** = randomized; **sig** = significant; **sx(s)** = symptom(s); **T₃** = triiodothyrene; **T₄** = thyroxine; **TSH** = thyroid-stimulating hormone; **wk** = week

roid hormones were overreplaced from combination T₄/T₃ therapy, or whose serum TSH levels were lower than 0.2 mU/L, were more likely to be depressed than patients with serum TSH levels within the normal reference range.²⁵ Walsh et al.²⁸ showed that patients taking combination therapy reported more anxiety on the visual analog scales than did those taking LT₄ alone (p=0.035). Since approximately 80% of T₄ is converted to T₃ in vivo, the only pharmacological benefit of adding T₃ is rapid absorption to acutely raise thyroid function to a temporary euthyroid state.

COSTS

Levothyroxine is available under three brand names in the U.S., including Synthroid®, Levothroid®, and Levoxyl®. Two generic formulations are also available which are included on the Wal-Mart \$4 list (30-day supply) and CVS \$9.99 list (90-day supply). Levothyroxine is available in strengths ranging from 25-300 mcg and each strength is associated with a unique color regardless of brand name or manufacturer. A comparison of the average monthly cost for each thyroid hormone preparation demonstrates that levothyroxine therapy is much less expensive than combination therapy with liothyronine (Table 4).

SUMMARY

Hypothyroidism is the most common thyroid disorder and the most common cause worldwide, iodine deficiency, is preventable. While some brands of thyroid hormones have come and gone over the years, levothyroxine continues to be a mainstay in therapy. Due to the controversy surrounding the bioequivalence of levothyroxine, prescribers should generally

Table 4 | Cost comparison of available thyroid hormone preparations.³³

Medication	Average Monthly Cost
Synthroid®	\$21.99 - \$41.99
Levoxyl®	\$16.99 - \$22.99
Levothroid®	\$14.99 - \$20.87
levothyroxine	\$12.99 - \$19.99 ^a
Cytomel®	\$97.96 - \$177.85
liothyronine	\$75.99 - \$139.99
Thyrolar®	\$29.99 - \$39.99
Armour Thyroid®	\$14.99 - \$32.99

^a Available at Wal-Mart for \$4 (30-day supply) and CVS \$9.99 (90-day supply) as of 11/30/10.

attempt to maintain patients on the same formulation levothyroxine that was initiated. Combination T₄/T₃ therapy should be avoided in most patients, until future studies prove this combination to be advantageous in the general population.

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