Presented at the AACE Annual Meeting & Congress, May 23-27, 2012, Philadelphia, PA

Review Article

DOES COMBINATION T_4 AND T_3 THERAPY MAKE SENSE?

Michael T. McDermott, MD

ABSTRACT

Objective: To evaluate the existing evidence regarding the combined use of levothyroxine and liothyronine to treat hypothyroidism.

Methods: Eleven published randomized controlled trials evaluating the efficacy and safety of combined levothyroxine and liothyronine therapy for hypothyroidism were reviewed and summarized. Related basic and clinical research findings were also incorporated for perspective.

Results: An initial randomized controlled trial reported symptomatic improvement in hypothyroid patients taking combined levothyroxine and liothyronine therapy compared with those taking levothyroxine therapy alone. Subsequently, multiple relatively small randomized controlled trials failed to demonstrate any subjective or objective benefit from combined levothyroxine and liothyronine therapy. A polymorphism (Thr92Ala) in the gene encoding the deiodinase 2 (D2) enzyme that converts thyroxine to triiodothyronine in the brain was later identified in about 16% of hypothyroid persons. This polymorphism may impair brain deiodinase activity in the presence of low brain thyroxine levels. One randomized controlled trial found that patients with the D2 Thr92Ala polymorphism had more baseline symptoms than those with the wild type D2 and experienced significantly greater symptomatic improvement in response to combined levothyroxine and liothyronine therapy.

Conclusions: Most hypothyroid patients experience rapid symptomatic relief after institution of levothyroxine replacement therapy, but persistent symptoms remain in some despite what appears to be adequate levothyroxine therapy with normalization of the serum thyrotropin level. A thorough investigation is warranted in these patients to detect and treat other responsible lifestyle issues, medical conditions, and endocrine conditions. A subset of hypothyroid patients has a polymorphism in the gene encoding the D2 enzyme that may prevent full resolution of symptoms with levothyroxine therapy alone; these patients may benefit from combination levothyroxine and liothyronine therapy. **(Endocr Pract. 2012;18:750-757)**

Abbreviations:
T_2 = diiodothyronine; **T_3** = triiodothyronine; **T_4** = thyroxine; **TSH** = thyrotropin

INTRODUCTION

Hypothyroidism is a disorder in which the thyroid gland produces inadequate amounts of thyroid hormones to meet the needs of peripheral tissues. Primary hypothyroidism, when thyroid failure is due to disease of the thyroid gland itself, accounts for more than 99% of all cases (1). In adults, this most commonly results from chronic lymphocytic thyroiditis (Hashimoto thyroiditis); radioiodine thyroid ablation; thyroidectomy; high-dose head and neck radiation therapy; and medications such as lithium, α-interferon, and amiodarone. Overt hypothyroidism is considered to be present when the serum thyrotropin (TSH) level is elevated and the serum total thyroxine (T_4) or free T_4 level is below the population reference range. Subclinical hypothyroidism is mild thyroid failure

Submitted for publication March 13, 2012
Accepted for publication March 29, 2012
From the Endocrinology and Diabetes Practice, University of Colorado School of Medicine, Aurora, Colorado.
Address correspondence to Dr. Michael T. McDermott, Endocrinology and Diabetes Practice, University of Colorado Hospital, 1635 Aurora Ct, F-732, Aurora, CO 80045. E-mail: Michael.mcdermott@ucdenver.edu.
Published as a Rapid Electronic Article in Press at http://www.endocrinepractice.org on May 1, 2012. DOI:10.4158/EP12076.RA
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manifested by slightly or moderately increased serum TSH levels associated with total T_4 and free T_4 values that are within the reference range. The incidence of hypothyroidism is estimated to be 4 to 5 per 1000 population per year for women and 0.6-0.9 per 1000 population per year for men (2,3). The prevalence of overt hypothyroidism is approximately 1% to 2% in women and 0.1% in men (3-6); subclinical hypothyroidism has been reported in 4% to 10% in various populations (3-11) and in up to 18% in elderly cohorts (7-11). Progression from subclinical to overt hypothyroidism occurs in 5% to 18% of persons per year (2,10-13).

Clinical features of hypothyroidism result mainly from deficient thyroid hormone action at the tissue level. Thyroid hormone receptors are present in most of the organs and tissues of the body and, therefore, thyroid hormone deficiency produces a diverse array of multisystem clinical manifestations (5,14-18). The symptoms and signs of overt primary hypothyroidism that are most commonly reported are shown in Box 1. Noteworthy is that many of these manifestations are nonspecific and may also be present in other medical disorders. Elderly persons with hypothyroidism appear to experience fewer classic symptoms and signs; prominent features in this age group include fatigue and weakness (19).

Treatment of hypothyroidism involves thyroid hormone replacement in quantities sufficient to relieve symptoms and return serum TSH levels into the normal range. Levothyroxine is the most commonly used form of thyroid hormone replacement; this is based on the premise that the thyroid gland makes predominantly T_4 and a small amount of triiodothyronine (T_3), while most of the body's T_3 comes from conversion of T_4 into T_3 by deiodinase enzymes in the liver and various other organs throughout the body (20-22). Most hypothyroid patients have satisfactory resolution of symptoms with adequate levothyroxine therapy.

Box 1
Common Symptoms and Signs of Hypothyroidism

Symptoms	
Fatigue	Constipation
Sleepiness	Hoarseness
Depression	Impaired hearing
Memory loss	Arthralgias
Weight gain	Muscle cramps
Cold intolerance	Menstrual disturbances
Signs	
Bradycardia	Dry skin
Hypertension	Sallow complexion
Coarse hair	Non-pitting edema
Facial puffiness	Delayed reflex relaxation

TREATED HYPOTHYROID PATIENTS MAY HAVE PERSISTENT SYMPTOMS

Published literature and the experience of many clinicians indicate that some hypothyroid patients have persistent symptoms despite what appears to be adequate levothyroxine therapy (23-27). Saravanan et al conducted a community-based questionnaire study of 397 hypothyroid patients with normal serum TSH levels on levothyroxine therapy and 397 matched control participants. They reported that treated hypothyroid patients had significantly more general health symptoms and thyroid-related symptoms than did control participants (23). Wekking et al evaluated 141 euthyroid patients with treated hypothyroidism and reported poor performance on neurocognitive testing and lower well-being scores in these participants compared with standard reference values (24). Samuels et al compared 34 treated hypothyroid patients with 20 euthyroid control participants and found that euthyroid levothyroxine-treated patients had diminished general health status, psychological function, working memory, and motor learning (25). In a baseline study for a large clinical trial to be discussed later in this article, Saravanan et al found that treated hypothyroid patients' psychological well-being might be related to variations of serum TSH and free T_4 levels even within the reference range (26).

Patients with persistent symptoms despite apparently adequate levothyroxine replacement therapy should be evaluated for other causative disorders with a complete history and physical examination and a laboratory evaluation for other endocrine and nonendocrine conditions (Box 2). It is well known, for example, that Hashimoto thyroiditis is often associated with other autoimmune diseases (28) that may also cause symptoms. Furthermore, recent

Box 2
Recommended Evaluation for Patients Who Have Persistent Symptoms Despite Normalization of Serum Thyrotropin Concentrations While on Levothyroxine Therapy

Complete history and physical examination
General laboratory evaluation
Comprehensive metabolic panel
Complete blood cell count
Erythrocyte sedimentation rate
Celiac disease testing
Sleep apnea screening or testing
Endocrine laboratory evaluation
25-Hydroxyvitamin D
Thyroid antibodies
Serum cortisol
Consider a cosyntropin stimulation test

evidence indicates that some chronic symptoms, such as fatigue, irritability, nervousness, and lower quality of life, may be due to Hashimoto thyroiditis independent of thyroid hormone levels (29). Appropriate tests may include, but are not limited to, a complete blood cell count; a comprehensive metabolic panel; and measurement of erythrocyte sedimentation rate, serum 25-hydroxyvitamin D, serum cortisol (basal or stimulated), and testosterone (in men). Testing for sleep apnea and celiac disease may also be considered.

General health measures (Box 3), such as a proper diet, regular exercise, adequate sleep, and stress reduction, should be encouraged when no responsible cause for their symptoms is identified. The possibility of depression may also need to be addressed. If optimal levothyroxine therapy has already been established, with a TSH level in the goal range, and no other conditions are apparent, the practitioner may choose to, or the patient may request to, discuss the use of combination therapy with levothyroxine plus liothyronine. Background evidence to support this practice came from the elegant studies of Escobar-Morreale et al, who demonstrated that in thyroidectomized rats, neither levothyroxine nor liothyronine alone could normalize tissue thyroid hormone levels (30), but that complete normalization of tissue levels of both T_3 and T_4 could only be achieved with combined levothyroxine and liothyronine therapy (31). Well-designed randomized controlled trials in humans followed soon thereafter.

COMBINED LEVOTHYROXINE AND LIOTHYRONINE THERAPY: RANDOMIZED CONTROLLED TRIALS

Bunevicius et al (32,33) published a randomized controlled crossover trial in which 33 hypothyroid patients (31 women, 2 men; 17 with thyroid cancer, 16 with Hashimoto thyroiditis) were given either their usual levothyroxine dosage or their usual levothyroxine dosage minus 50 mcg plus liothyronine, 12.5 mcg daily, for 5 weeks and then crossed over to the other treatment scheme for 5 more weeks. Serum TSH levels were not significantly different during the 2 treatment intervals, but free T_4 levels were lower and free T_3 levels were higher during the combined levothyroxine and liothyronine period; sex hormone–binding globulin levels were also higher with combined treatment. Patients reported significant improvement in mood (11 of 17 measures), cognitive performance (3 of 8 measures), and physical symptoms (3 of 7 measures) during the time they were receiving combined levothyroxine and liothyronine therapy. Furthermore, patients indicated a significant preference for the combined treatment period. As a result, combination levothyroxine and liothyronine therapy gained cautious acceptance as a reasonable option for thyroid hormone replacement therapy.

Following this, multiple studies (Table 1) were conducted to confirm these findings using combination levothyroxine and liothyronine in various amounts and ratios in different populations of hypothyroid patients (34-43). All of these studies failed to demonstrate significant objective or subjective benefit of combination levothyroxine and liothyronine therapy, although in 2 reports (38,39), patients did express a significant preference for the levothyroxine and liothyronine treatment period. A subsequent review paper (44) and 2 meta-analyses (45,46) concluded that there was no benefit of combination levothyroxine and liothyronine therapy compared with levothyroxine therapy alone. More recently, a randomized, double-blind crossover trial by Celi et al compared levothyroxine alone with liothyronine alone (not combined levothyroxine and liothyronine therapy) in 14 hypothyroid patients and found that despite similar TSH values, the provision of exogenous liothyronine produced weight loss and beneficial lipid effects without any harmful effects on cardiovascular function (47).

Box 3
Recommended Management Options for Patients Who Have Persistent Symptoms Despite Normalization of Serum Thyrotropin Levels With Levothyroxine Therapy

Well-balanced diet: adequate amounts of fruits, vegetables and high value protein
Regular exercise: 30 to 45 minutes daily, 6 days/week; combination of aerobic and resistance work
Good sleep habits: go to bed at the same time 5 to 6 nights each week; sleep 7 to 8 hours per night
Stress reduction: relaxation, biofeedback, entertainment, meditation, yoga, counseling
Depression management: biofeedback, counseling, medications
Medical illness management: appropriately treat existing medical illness, comanage with primary care physician
Optimize levothyroxine therapy: maintain serum thyrotropin in 0.5-2.0 mIU/L range
Change to another levothyroxine brand: be knowledgeable about medication fillers and colors
Consider combination levothyroxine and liothyronine therapy

Table 1
Randomized Controlled Trials of Combination Levothyroxine and Liothyronine Therapy in Hypothyroid Patients

Study	No. of patients	Study duration	Objective benefit	Subjective benefit	Patient preference for the combined levothyroxine and liothyronine period[a]
Bunevicius (32,33)	35	5 weeks	No	Yes	Yes
Walsh (34)	110	10 weeks	No	No	No
Sawka (35)	40	15 weeks	No	No	NA
Clyde (36)	46	4 months	No	No	NA
Siegmund (37)	26	12 weeks	No	No	NA
Saravanan (38)	697	3 months	No	No	NA
Apellhof (39)	141	15 weeks	No	No	Yes
Escobar-Morreale (40)	28	8 weeks	No	No	Yes
Rodriguez (41)	30	16 weeks	No	No	NA
Regalbuto (42)	20	6 months	No	No	No
Slawik (43)	29	5 weeks	No	No	NA

Abbreviation: NA, not applicable.
[a] Patient preference for the combined levothyroxine and liothyronine treatment. NA indicates the patients were not asked about their preference.

DEIODINASE FUNCTION AND POLYMORPHISMS

T_3 is known to be the main metabolically active thyroid hormone that binds to thyroid hormone receptors and produces thyroid hormone effects at the tissue level. The thyroid gland, as mentioned earlier, produces predominantly T_4 and only small amounts of T_3. Pilo et al demonstrated that the human thyroid daily produces approximately 101 mcg of T_4 and 6 mcg of T_3, while 20 mcg of circulating T_3 is made from peripheral conversion of T_4 to T_3 by the deiodinase enzymes (20). Deiodinases are selenocysteine enzymes that remove iodine molecules from thyroid hormones (21,22). There are 3 known deiodinase subtypes: deiodinase 1 (D1), deiodinase 2 (D2) and deiodinase 3 (D3) (Table 2 and Fig. 1). D1 converts T_4 to T_3 in the liver and kidneys, accounting for most of circulating T_3, and converts reverse T_3 to diiodothyronine (T_2); D1 has a higher affinity for reverse T_3 than for T_4. D2 converts T_4 to T_3 in the brain and pituitary gland, accounting for most cellular T_3 in these tissues; D2 has a higher affinity for T_4 than for reverse T_3. D3 converts T_4 to reverse T_3 and T_3 to T_2 (21,22). It is estimated that approximately 80% of brain T_3 is the product of local conversion of T_4 to T_3 by brain D2, whereas only about 20% of brain T_3 comes from the circulation (21,22). Therefore, in humans, it appears that the thyroid gland functions mainly to produce a sufficient supply of the circulating prohormone T_4 and that deiodinases serve to provide appropriate intracellular T_3 concentrations by regulating local T_4 to T_3 conversion in a highly tissue-specific manner (21,22).

The 2 largest combination levothyroxine and liothyronine therapy studies (38,39,48,49) reported subsequent subgroup analyses investigating whether polymorphisms in deiodinase enzymes might result in individual differences in baseline symptoms and in patients' responsiveness to combined levothyroxine and liothyronine. Appelhof et al (48) examined two D2 polymorphisms. Patients who were homozygous for the Thr92Ala polymorphism in D2, which consists of a threonine to alanine substitution at amino acid 92, had significantly worse baseline neurocognitive scores. However, they were unable to demonstrate a significant difference in the response to combination levothyroxine and liothyronine therapy in this relatively small subset. Panicker et al (49) did a similar analysis in the much larger population of the WATTS study (Weston Area T4/T3 Study) (38). They found that 16% of the study population was homozygous for the Thr92Ala polymorphism in D2 and that this subset had worse scores on a general health questionnaire and showed significant improvement with combination levothyroxine and liothyronine therapy compared with those who had the wild type D2

Table 2
Deiodinase Enzymes: Selenocysteine Enzymes That Deiodinate Thyroid Hormones

Characteristics	Deiodinase 1 (D1)	Deiodinase 2 (D2)	Deiodinase 3 (D3)
Substrate	Reverse T_3>>T_4	T_4>>reverse T_3	$T_4 + T_3$
Tissue	Liver, kidney	Brain, pituitary, fat	Placenta, brain
Function	Clear reverse T_3, increase serum T_3	Increase cellular T_3, increase serum T_3	Protect fetus, decrease cellular T_3, clear $T_4 + T_3$

enzyme. They postulated that this relatively common D2 gene variation may be causally related to poorer psychological well-being and a better response to combination levothyroxine and liothyronine therapy. To explain why previous studies had failed to find a benefit of combination therapy, they reasoned that those studies, which had only 20 to 141 participants, would have had just 3 to 12 participants with the Thr92Ala D2 polymorphism (16%) and were therefore inadequately powered to detect a significant treatment effect in such a small subset of patients. In contrast, the WATTS study of 697 patients (38), 552 of whom underwent genotyping (49), had sufficient power to detect this treatment effect.

The mechanism by which the Thr92Ala D2 polymorphism might affect thyroid hormone economy is not completely clear. Thr92Ala was shown to have normal in vitro deiodinase activity in one study (50), but was reported to have reduced activity and to be associated with insulin resistance in a cohort of individuals with type 2 diabetes (51). The Thr92Ala polymorphism appears to have no effect on basal circulating thyroid hormone levels (52); however, an attenuated serum T_3 rise in response to a

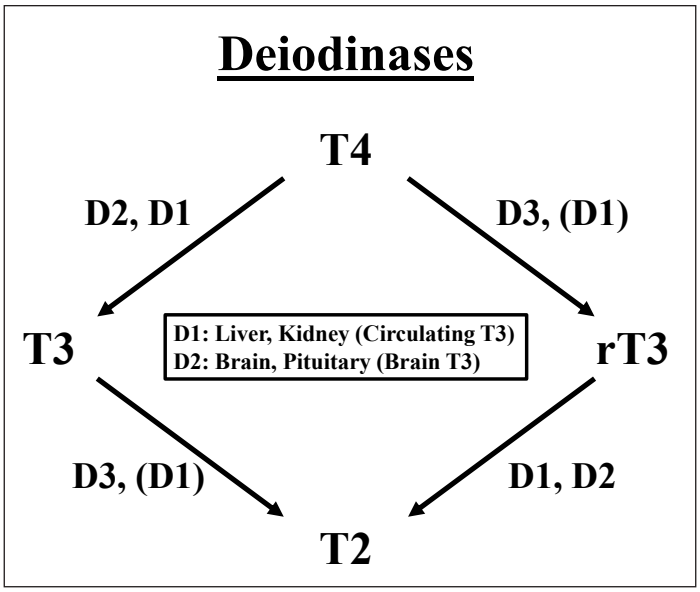

Fig. 1. Deiodinase Function. Deiodinase 1 (D1) converts thyroxine (T4) to triiodothyronine (T3) (liver, kidney) and converts reverse T3 (rT3) to diiodothyronine (T2), with a higher affinity for rT3. Most circulating T3 comes from this process. Deiodinase 2 (D2) converts T4 to T3 (brain, pituitary, fat) and converts rT3 to T2, with a higher affinity for T4. Most cellular T3 in the brain and pituitary comes from this process. Deiodinase 3 (D3) converts T4 to rT3 and converts T3 to T2.

thyrotropin-releasing hormone infusion has been reported in patients with Thr92Ala (53). Patients with thyroid cancer and the Thr92Ala polymorphism were found to require higher levothyroxine dosages in one study (54), but not in another (55).

To explain the clinical benefit from combination levothyroxine and liothyronine therapy observed in their Thr92Ala subgroup, the WATTS investigators postulated that the Thr92Ala enzyme may deiodinate local brain T_4 less effectively under hypothyroid conditions (49). When the supply of T_4 is low, the brain protects itself against deficient tissue T_3 levels by increasing D2 activity through substrate (T_4)-induced D2 ubiquitination (56-58); they suggested, therefore, that the Thr92Ala polymorphism may be associated with decreased D2 ubiquitination at low T_4 levels and thereby with reduced local tissue T_4 to T_3 conversion in the presence of a low T_4 supply, leading to increased dependence on circulating T_3 levels to maintain optimal brain T_3 levels in hypothyroid patients (49).

CLINICAL USE OF COMBINATION LEVOTHYROXINE AND LIOTHYRONINE THERAPY

The evidence indicates, therefore, that combination levothyroxine and liothyronine therapy is not necessary or appropriate for all patients with hypothyroidism. However, there may be a subset, perhaps as many as 16% of hypothyroid patients, who have a D2 polymorphism (Thr92Ala) that has suboptimal function in the brain in the presence of low T_4 levels, resulting in a need for higher circulating T_3 levels to maintain tissue T_3 levels. These patients, according to one study (49), may derive symptomatic benefit from combined levothyroxine and liothyronine therapy. Clinical genetic testing to determine in advance who may and who may not benefit from this therapy (pharmacogenetics) is not currently available. It may therefore be appropriate for the willing provider to consider a trial of combination levothyroxine and liothyronine therapy in hypothyroid patients who have persistent symptoms despite normalization of the serum TSH level with levothyroxine therapy.

The physiological ratio of T_4 to T_3 production in the human body is approximately 14:1 (20). It would seem prudent, therefore, when using combination therapy, to administer exogenous levothyroxine and liothyronine in a ratio of approximately 10:1 to 14:1 to attempt to maintain the normal physiological T_4 to T_3 production ratio. Liothyronine has a much shorter half-life than levothyroxine and therefore is often given in 2 divided doses approximately 8 to 12 hours apart. This may not be necessary if a sustained-release preparation of liothyronine eventually becomes available (59). The author recommends that patients on combination levothyroxine and liothyronine have their TSH levels measured in the morning before taking either levothyroxine or liothyronine because of the rise in serum T_3 that occurs in the first few hours after liothyronine is ingested. Serum TSH levels in these patients, as with those on standard levothyroxine therapy, should be maintained within the reference range because thyroid hormone excess, whether mild or overt, is associated with a significantly increased risk of osteoporosis (60-62), atrial fibrillation (63,64), and cardiovascular and all-cause mortality (65) in the elderly population.

CONCLUSION

Hypothyroid patients on levothyroxine therapy may have persistent symptoms despite having normal serum TSH levels. Because the symptoms of hypothyroidism are nonspecific, a thorough evaluation for lifestyle situations and other illnesses should be diligently undertaken. Combination levothyroxine and liothyronine therapy is not necessary or appropriate for all, or even most, hypothyroid patients, since multiple randomized controlled trials have not shown a benefit. However, in those with persistent symptoms on apparently adequate levothyroxine therapy, combination levothyroxine and liothyronine therapy may be considered. This approach is supported by evidence that up to 16% of hypothyroid patients have a D2 polymorphism (Thr92Ala) that may result in reduced T_4 to T_3 conversion in the brain when the T_4 supply is low. If this therapy is used, a physiological ratio of levothyroxine to liothyronine of about 10:1 to 14:1, the normal human production ratio, should be administered and the serum TSH level should be maintained within the reference range to prevent potentially adverse effects of thyroid hormone excess on the skeleton and the heart.

DISCLOSURE

The author has no multiplicity of interest to disclose.

REFERENCES

1. **McDermott MT, Ridgway EC.** Hypothyroidism. In: Cooper DS, ed. *Medical Management of Thyroid Disease*. 2nd ed. New York, NY: Informa Healthcare, 2008: 145-202.
2. **Vanderpump MP, Tunbridge WM, French JM, et al.** The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. *Clin Endocrinol (Oxf)*. 1995;43:55-68.
3. **Flynn RW, MacDonald TM, Morris AD, Jung RT, Leese GP.** The thyroid epidemiology, audit, and research study: thyroid dysfunction in the general population. *J Clin Endocrinol Metab*. 2004;89:3879-3884.
4. **Tunbridge WM, Evered DC, Hall R, et al.** The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf)*. 1977;7:481-493.
5. **Canaris GJ, Manowitz NR, Mayor G, Ridgway EC.** The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160:526-534.

6. **Hollowell JG, Staehling NW, Flanders WD, et al.** Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489-499.
7. **Bagchi N, Brown TR, Parish RF.** Thyroid dysfunction in adults over age 55 years. A study in an urban US community. *Arch Intern Med*. 1990;150:785-787.
8. **Guel KW, van Sluisveld IL, Grobbee DE, et al.** The importance of thyroid microsomal antibodies in the development of elevated serum TSH in middle-aged women: associations with serum lipids. *Clin Endocrinol (Oxf)*. 1993;39: 275-280.
9. **Sawin CT, Chopra D, Azizi F, Mannix JE, Bacharach P.** The aging thyroid. Increased prevalence of elevated serum thyrotropin levels in the elderly. *JAMA*. 1979;242:247-250.
10. **Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS.** Thyroid failure in the elderly. Microsomal antibodies as discriminant for therapy. *JAMA*. 1987;258:209-213.
11. **Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC.** Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol (Oxf)*. 1991;34:77-83.
12. **Tunbridge WM, Brewis M, French JM, et al.** Natural history of autoimmune thyroiditis. *Br Med J (Clin Res Ed)*. 1981;282:258-262.
13. **Kabadi UM.** 'Subclinical hypothyroidism'. Natural course of the syndrome during a prolonged follow-up study. *Arch Intern Med*. 1993;153:957-961.
14. **Means JH.** Relative frequency of the several symptoms and signs of myxedema. *The Thyroid and its Diseases*. 2nd ed. Philadelphia, PA: JB Lippencott Company, 1948: 232-234.
15. **Billewicz WZ, Chapman RS, Crooks J, et al.** Statistical methods applied to the diagnosis of hypothyroidism. *Q J Med*. 1969;38:255-266.
16. **Oddie TH, Boyd CM, Fisher DA, Hales IR.** Incidence of signs and symptoms in thyroid disease. *Med J Aust*. 1972; 2:981-986.
17. **Zulewski HK, Müller B, Exer P, Miserez AR, Staub JJ.** Estimation of tissue hypothyroidism by a new clinical score: Evaluation of patients with various grades of hypothyroidism and controls. *J Clin Endocrinol Metab*. 1997; 82:771-776.
18. **Canaris GJ, Steiner JF, Ridgway EC.** Do traditional symptoms of hypothyroidism correlate with biochemical disease? *J Gen Intern Med*. 1997;12:544-550.
19. **Doucet J, Trivalle C, Chassagne P, et al.** Does age play a role in clinical presentation of hypothyroidism? *J Am Geriatr Soc*. 1994;42:984-986.
20. **Pilo A, Iervasi G, Vitek F, Ferdeghini M, Cazzuola F, Bianchi R.** Thyroidal and peripheral production of 3,5,3'-triiodothyronine in humans by multicompartmental analysis. *Am J Physiol*. 1990;258:E715-E726.
21. **Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR.** Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev*. 2002;23:38-89.
22. **Gereben B, Zavacki AM, Ribich S, et al.** Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocr Rev*. 2008;29:898-938.
23. **Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM.** Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. *Clin Endocrinol (Oxf)*. 2002;57:577-585.
24. **Wekking EM, Appelhof BC, Fliers E, et al.** Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. *Eur J Endocrinol*. 2005;153:747-753.
25. **Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky J.** Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. *Thyroid*. 2007;17:249-258.
26. **Saravanan P, Visser TJ, Dayan CM.** Psychological well-being correlates with free thyroxine but not free 3,5,3'-triiodothyronine levels in patients on thyroid hormone replacement. *J Clin Endocrinol Metab*. 2006;91:3389-3393.
27. **Walsh JP.** Dissatisfaction with thyroxine therapy – could the patients be right? *Curr Opin Pharmacol*. 2002;2:717-722.
28. **Boelaert K, Newby PR, Simmonds MJ, et al.** Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med*. 2010;123:183. e1-9.
29. **Ott J, Promberger R, Kober F, et al.** Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: a prospective case-control study in women undergoing thyroidectomy for benign goiter. *Thyroid*. 2011;21:161-167.
30. **Escobar-Morreale HF, Obregon MJ, Escobar del Rey F, Morreale de Escobar G.** Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. *J Clin Invest*. 1995;96:2828-2838.
31. **Escobar-Morreale HF, del Rey FE, Obregón MJ, de Escobar GM.** Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. *Endocr J*. 1996;137:2490-2502.
32. **Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr.** Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med*. 1999;340:424-429.
33. **Bunevicius R, Prange AJ.** Mental improvement after replacement therapy with thyroxine plus triiodothyronine: relationship to cause of hypothyroidism. *Int J Neuropsychopharmacol*. 2000;3:167-174.
34. **Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG.** Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. *J Clin Endocrinol Metab*. 2003;88:4543-4550.
35. **Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT.** Does a combination regimen of thyroxine (T4) and 3,5,3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. *J Clin Endocrinol Metab*. 2003;88:4551-4555.
36. **Clyde PW, Harari AE, Getka EJ, Shakir KM.** Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. *JAMA*. 2003;290:2952-2958.
37. **Siegmund W, Spieker K, Weike AI, et al.** Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14:1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. *Clin Endocrinol (Oxf)*. 2004;60:750-757.
38. **Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM.** Partial substitution of thyroxine (T4) with tri-iodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial. *J Clin Endocrinol Metab*. 2005;90:805-812.

39. **Appelhof BC, Fliers E, Wekking EM, et al.** Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. *J Clin Endocrinol Metab*. 2005;90:2666-2674.
40. **Escobar-Morreale HF, Botella-Carretero JI, Gómez-Bueno M, Galán JM, Barrios V, Sancho J.** Thyroid hormone replacement in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. *Ann Intern Med*. 2005;142:412-424.
41. **Rodriguez T, Lavis VR, Meininger JC, Kapadia AS, Stafford LF.** Substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: effect on fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone. *Endocr Pract*. 2005;11:223-233.
42. **Regalbuto C, Maiorana R, Alagona C, et al.** Effects of either LT4 monotherapy or LT4/LT3 combined therapy in patients totally thyroidectomized for thyroid cancer. *Thyroid*. 2007;17:323-331.
43. **Slawik M, Klawitter B, Meiser E, et al.** Thyroid hormone replacement for central hypothyroidism: a randomized controlled trial comparing two doses of thyroxine (T4) with a combination of T4 and triiodothyronine. *J Clin Endocrinol Metab*. 2007;92:4115-4122.
44. **Escobar-Morreale HF, Botella-Carretero JI, Escobar del Rey F, Morreale de Escobar G.** Review: Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. *J Clin Endocrinol Metab*. 2005;90:4946-4954.
45. **Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L.** Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab*. 2006;91:2592-2599.
46. **Joffe RT, Brimacombe M, Levitt AJ, Stagnaro-Green A.** Treatment of clinical hypothyroidism with thyroxine and triiodothyronine: a literature review and metaanalysis. *Psychosomatics*. 2007;48:379-384.
47. **Celi FS, Zemskova M, Linderman JD, et al.** Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine. *J Clin Endocrinol Metab*. 2011;96:3466-3474.
48. **Appelhof BC, Peeters RP, Wiersinga WM, et al.** Polymorphisms in type 2 deiodinase are not associated with well-being, neurocognitive functioning, and preference for combined thyroxine/3,5,3'-triiodothyronine therapy. *J Clin Endocrinol Metab*. 2005;90:6296-6299.
49. **Panicker V, Saravanan P, Vaidya B, et al.** Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. *J Clin Endocrinol Metab*. 2009;94:1623-1629.
50. **Peeters RP, van Toor H, Klootwijk W, et al.** Polymorphisms in thyroid hormone pathway genes are associated with plasma TSH and iodothyronine levels in healthy subjects. *J Clin Endocrinol Metab*. 2003;88:2880-2888.
51. **Canani LH, Capp C, Dora JM, et al.** The type 2 deiodinase A/G (Thr92Ala) polymorphism is associated with decreased enzyme velocity and increased insulin resistance in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2005;90:3472-3478.
52. **de Jong FJ, Peeters RP, den Heijer T, et al.** The association of polymorphisms in the type 1 and 2 deiodinase genes with circulating thyroid hormone parameters and atrophy of the medial temporal lobe. *J Clin Endocrinol Metab*. 2007;92:636-640.
53. **Butler PW, Smith SM, Linderman JD, et al.** The Thr92Ala 5' type 2 deiodinase gene polymorphism is associated with a delayed triiodothyronine secretion in response to the thyrotropin-releasing hormone-stimulation test: a pharmacogenomic study. *Thyroid*. 2010; 20:1407-1412.
54. **Torlontano M, Durante C, Torrente I, et al.** Type 2 deiodinase polymorphism (threonine 92 alanine) predicts L-thyroxine dose to achieve target thyrotropin levels in thyroidectomized patients. *J Clin Endocrinol Metab*. 2008;93:910-913.
55. **Heemstra KA, Hoftijzer HC, van der Deure WM, et al.** Thr92Ala polymorphism in the type 2 deiodinase is not associated with T4 dose in athyroid patients or patients with Hashimoto thyroiditis. *Clin Endocrinol (Oxf)*. 2009;71:279-283.
56. **Leonard JL, Kaplan MM, Visser TJ, Silva JE, Larsen PR.** Cerebral cortex responds rapidly to thyroid hormones. *Science*. 1981;214:571-578.
57. **Silva JE, Larsen PR.** Comparison of iodothyronine 5'-deiodinase and other thyroid-hormone-dependent enzyme activities in the cerebral cortex of hypothyroid neonatal rat. Evidence for adaptation to hypothyroidism. *J Clin Invest*. 1982;70:1110-1123.
58. **Gereben B, Goncalves C, Harney JW, Larsen PR, Bianco AC.** Selective proteolysis of human type 2 deiodinase: a novel ubiquitin-proteasomal mediated mechanism for regulation of hormone activation. *Mol Endocrinol*. 2000;141: 1697-1708.
59. **Hennemann G, Docter R, Visser TJ, Postema PT, Krenning EP.** Thyroxine plus low-dose, slow-release triiodothyronine replacement in hypothyroidism: proof of principle. *Thyroid*. 2004;14:271-275.
60. **Schneider DL, Barrett-Connor EL, Morton DJ.** Thyroid hormone use and bone mineral density in elderly women. Effects of estrogen. *JAMA*. 1994;271:1245-1259.
61. **Bauer DC, Ettinger B, Nevitt MC, Stone KL; Study of Osteoporotic Fractures Research Group**. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. *Ann Intern Med*. 2001;134:561-568.
62. **Murphy E, Williams GR.** The thyroid and the skeleton. *Clin Endocrinol (Oxf)*. 2004;61:285-298.
63. **Sawin CT, Geller A, Wolf PA, et al.** Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med*. 1994;331:1249-1252.
64. **Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B.** Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *Am Heart J*. 2001;142:838-842.
65. **Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA.** Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet*. 2001;358:861-865.