

Combination Treatment with T₄ and T₃: Toward Personalized Replacement Therapy in Hypothyroidism?

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Context: Levothyroxine therapy is the traditional lifelong replacement therapy for hypothyroid patients. Over the last several years, new evidence has led clinicians to evaluate the option of combined T₃ and T₄ treatment to improve the quality of life, cognition, and peripheral parameters of thyroid hormone action in hypothyroidism. The aim of this review is to assess the physiological basis and the results of current studies on this topic.

Evidence Acquisition: We searched Medline for reports published with the following search terms: hypothyroidism, levothyroxine, triiodothyronine, thyroid, guidelines, treatment, deiodinases, clinical symptoms, quality of life, cognition, mood, depression, body weight, heart rate, cholesterol, bone markers, SHBG, and patient preference for combined therapy. The search was restricted to reports published in English since 1970, but some reports published before 1970 were also incorporated. We supplemented the search with records from personal files and references of relevant articles and textbooks. Parameters analyzed included the rationale for combination treatment, the type of patients to be selected, the optimal T₄/T₃ ratio, and the potential benefits of this therapy on symptoms of hypothyroidism, quality of life, mood, cognition, and peripheral parameters of thyroid hormone action.

Evidence Synthesis: The outcome of our analysis suggests that it may be time to consider a personalized regimen of thyroid hormone replacement therapy in hypothyroid patients.

Conclusions: Further prospective randomized controlled studies are needed to clarify this important issue. Innovative formulations of the thyroid hormones will be required to mimic a more perfect thyroid hormone replacement therapy than is currently available. (*J Clin Endocrinol Metab* 97: 2256–2271, 2012)

Hypothyroidism is one of the most common endocrine disorders (1). It occurs in 6–17% of the general population, with an increased prevalence in women and the elderly (1, 2). The severity of the clinical manifestations and complications associated with hypothyroidism depends upon the degree and duration of untreated thyroid failure (2, 3). Replacement therapy with thyroid hormone is indicated once the diagnosis of hypothyroidism is confirmed.

The first preparation employed to treat hypothyroidism was an extract of sheep thyroid, first given by George

Murray in 1891 as im injections and in the following year by mouth (4). It was not until 1914 that Edward Kendall isolated and crystallized the active substance that he named “thyroxin.” Kendall’s attempts to synthesize the compound were unsuccessful, and it was C. R. Harrington who chemically identified the hormone in 1927 and renamed it “thyroxine.” Because synthesized thyroxine (T₄) was expensive to prescribe due to its production costs, most patients with hypothyroidism were treated with a desiccated thyroid preparation until about 1960 (5). This extract contains a combination of T₄ and 3,5,3’-triiodo-

thyronine (T_3) in a ratio 2- to 3-fold higher than that found in human thyroid. Another drawback of therapy with Harrington's T_4 was the fact that it is an acid and as such is poorly absorbed after oral ingestion. The development of the sodium salt of L-thyroxine ($L-T_4$) in the 1950s provided the compound that has to this day been the mainstay of the therapy of hypothyroidism. Finally, there was virtually simultaneous publication in 1952 of the discovery in plasma of the second thyroid hormone, T_3 , by Gross and Pitt-Rivers in the United Kingdom and by Roche, Lissitsky, and Michel in France (5). They determined that T_3 was much more active than T_4 but was present in a lower amount in the thyroid gland. Almost 20 yr later in 1970, Braverman, Sterling, and Ingbar (6) demonstrated that circulating T_3 is largely derived from T_4 deiodination in extrathyroidal tissues by detecting T_3 in the serum of athyretic patients receiving T_4 .

Although the normal thyroid gland secretes both T_4 and T_3 , currently only levothyroxine ($L-T_4$) is recommended as the lifelong replacement therapy of choice for all hypothyroid patients with persistent disease, whether for overt hypothyroidism or subclinical hypothyroidism with serum TSH levels greater than 10 mIU/liter (7–10). Thus, guidelines from all professional societies, including the American Thyroid Association, the American Association of Clinical Endocrinologists, and The Endocrine Society recommend $L-T_4$ monotherapy as the treatment of choice for all hypothyroid patients (7–10).

With appropriate individual dosage adjustment, treatment with $L-T_4$ is generally considered safe and well tolerated, and its use should be associated with relatively constant serum levels of T_4 , given good patient compliance. This is so because available formulations of synthetic $L-T_4$ have a half-life of 6 d and provide stable, relatively constant blood levels of T_4 after ingestion of an oral once-daily dose.

Notwithstanding the fact that $L-T_4$ represents one of the most commonly administered drugs in the world and its proven record of both safety and efficacy, uncertainties still obtain in regard to whether its use as a single drug treatment in hypothyroid patients represents optimal therapy (11). Arguments that $L-T_4$ monotherapy does not mimic normal thyroïdal secretion of both T_4 and T_3 are countered by clear evidence that physiological amounts of T_3 are generated by the monodeiodination of T_4 in patients receiving replacement doses of $L-T_4$ (12, 13). However, some hypothyroid patients given monotherapy with $L-T_4$ complain of symptoms suggestive of thyroid hormone insufficiency despite normal range TSH levels, raising some doubt as to whether *in vivo* generation of T_3 from T_4 is equivalent to thyroïdal secretion of T_3 . In humans, about 80% of circulating T_3 arises from the peripheral

tissue by 5'-deiodination of T_4 , and only about 20% is directly secreted by the thyroid gland (13). T_3 is the most active thyroid hormone because its affinity for the nuclear receptor is 10- to 20-fold that of T_4 . After administration of a dose of T_3 , the hormone reaches a peak level in 2–4 h and has a half-life of only 1 d, in contrast to the long half-life of T_4 . As a consequence, replacement therapy with T_3 is problematic in regard to the ability of a daily dose of T_3 to provide stable levels of the hormone throughout a 24-h period. As a result, at least three daily doses of T_3 are usually required to obtain or approach physiological and stable circulating T_3 levels (14). Given its short half-life and the potential for wide fluctuations in serum levels, replacement therapy with T_3 has not been recommended as long-term replacement therapy for hypothyroid patients. Moreover, the greater degree of T_3 nuclear binding than T_4 results in augmented metabolic activity with clear potential for adverse events, especially when administered in an inappropriate or nonphysiological manner.

In an attempt to better approximate physiological thyroïdal secretion of T_4 and T_3 , several studies have evaluated the potential role and efficacy of combination treatment with T_4 and T_3 . Based on these studies, some meta-analyses and editorials on T_4/T_3 therapy concluded that combined therapy in hypothyroid patients showed little if any beneficial effect. As a consequence, interest in this topic declined in the last few years, although many clinicians continue to be interested in the potential use and safety of combined treatment for some hypothyroid patients.

In this review, we discuss the physiological mechanisms and rationale for the potential role of combined T_3 and T_4 therapy in hypothyroid patients. We first examine the complex feedback interaction between central hypothalamic control and the production and release of thyroid hormones to the periphery. Moreover, we discuss the intricacies underlying thyroid hormone metabolism by explaining the importance of deiodinases for tissue euthyroidism and the clinical consequences of some deiodinase polymorphisms. Subsequently, we will reassess the results of the available studies and review articles on combined treatment, examining the design of each study, the category of patients selected for this treatment, the T_4/T_3 ratio, the duration of this therapy, the levels of free thyroid hormone and TSH during the two regimens of replacement therapy (monotherapy *vs.* combined therapy), and the effects at the tissue level. This evaluation may help identify patients who could benefit from combined therapy, the sensitivity of some tissue parameters, and the potential physiological reasons why specific organs could be more sensitive to T_3 than to T_4 . We believe that the complexities

inherent in our analyses should reopen the controversy on the potential merits of combined therapy. Our analysis may allow clinicians to consider alternative explanations for the lack of beneficial effects in past investigations and hopefully spur more research on this issue.

The Hypothalamic-Pituitary-Thyroid (HPT) Axis

TSH secretion is the result of a complex feedback interaction between central hypothalamic control and the production of peripheral thyroid hormones. Secretion of TSH by the pituitary gland is stimulated by hypothalamic TRH. TSH release is under negative feedback regulation by thyroid hormone directly at the pituitary and indirectly at the hypothalamus on TRH. This negative feedback loop maintains levels of the circulating thyroid hormones and TSH in a physiological inverse relationship that defines the HPT axis set point (15). The difficulty in identifying a precise normal serum TSH level in an individual as a marker of euthyroidism is due to the variability of the individual HPT axis set point. There are interindividual differences in the HPT axis set point, whereas the intraindividual variability falls within a narrow range. This has been demonstrated in a study of monthly sampling over 1 yr in healthy euthyroid subjects (16). Each individual is characterized by a fixed relationship between their serum free T_4 (FT_4) and TSH concentrations; this point can be considered the individual's HPT axis "set point." The position of this individual set point determines the changes in thyroid hormone levels, also within the conventional reference range, that can be considered abnormal for an individual. Although it is not clear what determines this individual set point, studies of monozygotic and dizygotic twins suggest that it is genetically determined (3). Environmental factors, such as iodine intake, age, and systemic illness, may influence the thyroid function set point.

One aspect of therapy with thyroid hormone that renders the achievement of optimal replacement treatment of hypothyroid patients somewhat more difficult is reflected by the continuing debate over what constitutes the "normal" or reference range of TSH and the desired target serum TSH with therapy (1–3). The basis for this controversy relates in part to individual differences in TSH regulation by the HPT axis as well as to the influence of age, race, and perhaps gender on the achievement of a desirable TSH value (16, 17).

Thyroid Hormone Metabolism

Although T_4 is the main hormone produced by the thyroid gland, T_3 can be shown to be the more active hormone in

many organs. T_4 is synthesized and secreted exclusively by the thyroid gland, whereas the majority of circulating T_3 derives largely from T_4 by metabolism governed by deiodinases in extrathyroidal peripheral tissues. Thyroid hormone signaling in individual tissues can even change when serum hormone concentrations remain normal and stable, due to local activation or inactivation of the deiodinases. The biological activity of thyroid hormone in regard to T_3 availability is regulated by three deiodinase isoforms termed deiodinase type 1 (D1), type 2 (D2), and type 3 (D3) (12, 13). Because the organism autoregulates T_3 conversion from T_4 under certain conditions, it is of interest that deiodinase activity may change during aging and critical illness.

D1 may activate or inactivate T_4 because it can catalyze either 5' or 5 deiodination. D1 is expressed mainly in the thyroid gland, liver, and kidney, where it converts T_4 to T_3 and thus contributes significantly to the pool of circulating T_3 . D3 inactivates T_3 , maintaining T_3 homeostasis by decreasing local T_3 concentrations and thereby protecting tissues from thyroid hormone excess (13). The most important pathway for T_4 metabolism is its monodeiodination to active T_3 . D2 catalyzes 5' deiodination and converts T_4 to T_3 . D2 activity is present in the brain, pituitary gland, skeletal muscle, brown adipose tissue, thyroid gland, osteoblasts, and aortic smooth muscle cells; moreover, D2 mRNA has been detected in the human heart (12, 13).

Serum T_4 is effective as a regulator of TSH secretion, although T_4 acts at hypothalamic and pituitary levels after enzymatic local conversion into T_3 . Therefore, D2 is essential for the regulation of the HPT axis, and it enables the pituitary to respond to changes in the circulating T_4 level. The set point for TSH secretion depends on both serum T_3 and intracellular pituitary T_3 generated by D2. Therefore, this may explain why intracellular TSH in thyrotrophs rises during mild hypothyroidism. On the other hand, the increased sensitivity of the pituitary/hypothalamic feedback mechanism to serum T_4 may explain why replacement doses of L- T_4 can be associated with normal TSH levels, whereas T_3 levels are low and T_4 levels are high (18–21). Despite the normalization of TSH levels, the low serum T_3 levels in this circumstance may imply nonphysiological hormone replacement due to reduced availability of the active form of thyroid hormone at the tissue level.

In fact, D2 activity is important for tissue-specific T_3 production. The major role of D2 is to control the intracellular T_3 concentration to protect tissues from the detrimental effects of hypothyroidism (12, 13). The efficiency of conversion of T_4 to T_3 by D2 increases as the serum T_4 decreases; consequently, in the presence of a low level of T_4 or in case of a hypothyroid state, D2 expression and

activity are increased and can generate a significant quantity of plasma T_3 (3). On the contrary, D2 expression and activity are reduced in thyrotoxicosis and in the presence of increased T_4 levels (3). The importance of thyrotroph D2 in TSH regulation and the local activation or inactivation of thyroid hormone induced by deiodinases at the tissue level represents a mechanism that is essential to understanding why TSH “normalization” during L- T_4 replacement therapy might not accurately reflect euthyroidism in all tissues and organs.

Of importance in this context, polymorphisms in genes involved in thyroid hormone metabolism may affect thyroid hormone bioactivity. Deiodinases are tissue-specifically regulated, and this may have consequences for the peripheral effects of thyroid hormone and for set points of endocrine feedback regulation (22–24). A common Thr92Ala polymorphism has been identified in D2, and thyroid and skeletal muscle tissue extracts from Ala/Ala individuals display reduced D2 activities (22–24). These interactions help to clarify the complexity of peripheral and central thyroid hormone production and control and reflect the current body of knowledge that relates to understanding hormone replacement therapy with T_4 or T_3 .

Why Treat with Combination Treatment with T_4 and T_3 ?

The goal of replacement therapy in hypothyroid patients is to restore biochemical euthyroidism indicated by serum TSH concentrations and thyroid hormone levels within their respective reference ranges, together with restoration of clinical euthyroidism marked by the disappearance of all symptoms and signs of thyroid hormone deficiency (3, 11).

Thyroid hormone has profound effects on the central nervous system, cardiovascular system, lipid profile, bone metabolism and structure, energy expenditure, and body weight. Consequently, hypothyroid patients may complain of cognitive deficit, mood alteration, cardiac dysfunction, dyslipidemia, osteoporosis, fractures, and weight gain (1). Similar, albeit milder, effects are seen in patients with subclinical hypothyroidism to a variable degree, depending upon the age of the patients and the duration and/or severity of thyroid hormone deficiency (2, 3).

We do not fully understand why some hypothyroid patients given replacement therapy with L- T_4 appear to achieve a satisfactory functional level when biochemical euthyroidism is restored, whereas others continue to complain of persistent symptoms of thyroid hormone deficiency such as mood changes, decreased psychomo-

tor performance, cognitive disturbances, weight gain, fatigue, lethargy, and depression. Physicians do not expect these symptoms to continue with adequate replacement L- T_4 dosage reflected by normal TSH levels and normal thyroid hormones and become frustrated with the management of these patients and their ongoing complaints.

If one accepts the validity of persistent symptoms and cardiovascular risk factors in L- T_4 -replaced patients despite TSH normalization, then it is necessary to hypothesize that standard therapy with L- T_4 alone is not sufficient to restore optimal quality of life and tissue euthyroidism, at least not in all patients. When hypothyroid patients are given L- T_4 alone, it is assumed that the peripheral conversion of T_4 to T_3 provides the exact amount of T_3 needed by each particular tissue or organ. However, on the basis of polymorphisms and variable tissue distribution of the deiodinase enzymes, it is theoretically possible that some tissues could be underexposed to T_3 despite apparently normal circulating levels of TSH (25).

In experimental studies carried out by Escobar-Morreale *et al.* (26), T_4 monotherapy did not normalize tissue concentrations of T_4 and T_3 in rats made hypothyroid by thyroidectomy or radioiodine therapy. Moreover, the dose of T_4 needed to normalize circulating T_3 and TSH levels resulted in supraphysiological concentrations of plasma T_4 (26). Interpretation of the significance of these findings requires accounting for the differences between rats and humans in their respective molar T_4/T_3 ratio in thyroid hormone secretion (14:1 in adult men, and approximately 6:1 in adult male rats). Moreover, levels of circulating thyroid hormones are higher in rats than in humans related to very low levels of T_4 binding globulin, the greater dominance of hormone binding, and transport by transthyretin (26). Furthermore, deiodinase activity is tissue and species specific (13, 26).

These differences between humans and rats notwithstanding, the clinical evidence could support a role for combination T_4/T_3 treatment in humans. In fact, just as in experimental studies, about 25–32% of hypothyroid patients on L- T_4 therapy require serum T_4 levels at the upper limit of the normal range or even higher to normalize T_3 levels and both serum TSH and its normal response to TRH (27, 28).

Evaluating the Effects of Combined T_4/T_3 Therapy (Table 1)

Mood, cognition, and quality of life

Hypothyroidism may induce affective and cognitive dysfunction (mood, attention, concentration, memory

TABLE 1. Summary of studies evaluating the effects of combined T4 plus T3 vs. T4 alone as replacement therapy in hypothyroid patients

Author Year Reference	Study Design Randomization	Number of patients Sex Age	Cause and Degree of Hypothyroidism	T3(µg)Treatment	Duration of treatment (weeks)	Parameters : Symptoms Peripheral parameters Preference	Benefit	Thyroid hormones and TSH during L3+LT4 vs LT4	Adverse effects
Smith et al 1970 Ref 44	Double Blind Crossover	87 Sex NR 11-71 years	Autoimmune Hypothyroidism Thyroid surgery RAI Degree of hypothyroidism NR	T4 4 80 + T3 20 T4/T3 doses variable	Two periods of eight weeks	Quality of life Preference	** T3+T4>T4 in 16 T3>T4=T4 in 42 T4>T3+T4 in 29	↑Serum PBI →T3 uptake ↑FT4 index	Hyperthyroid symptoms
Bunevicius et al 1999 Ref 36	Double-blind cross-over	33 31 W 2M 46±13	17 Surgery for thyroid cancer 16 Autoimmune Hypothyroidism Degree of hypothyroidism NR	T4 4 50 + T3 12.5 T4/T3 doses variable	Two periods of five weeks	Psychological state Cognition Depression Mood SHBG Heart rate Cholesterol Triglyceride SBP DBP Preference	↑ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ T3+T4>T4 in 20 T3+T4=T4 in 11 T4>T3+T4 in 2	FT4 ↓ TT4 ↓ TT3 ↑ TSH ↓Low - Undetectable	NO
Bunevicius et al 2002 Ref 61	Randomized double-blind cross-over	26 25-75 yrs	11 Autoimmune Hypothyroidism 15 Thyroidectomised for cancer Degree of hypothyroidism NR	T4 4 50 + T3 12.5 T4/T3 doses variable	Two periods of five weeks	Mood Cognition Depression	↑ ↓ Improvement only in athyretic thyroid cancer patients	TSH low -undetectable	NR
Bunevicius et al 2003 Ref 58	Randomized double-blind cross-over	10 19-58 yrs	Surgery for GD Degree of hypothyroidism NR	T4 4 50 + T3 10 T4/T3 doses variable	Two periods of five weeks	Mood Cognition Symptoms of hypothyroidism SHBG Body composition Weight Lean mass Fat mass Water mass Echocardiography: HR LVEF(%) Early to late diastolic velocity ratio Early Diastolic velocity of mitral annulus motion (cm/sec)	** ↑ ↓ ** ** ** ** ** ** ** ** ** ** **	FT4 ↓ TT3 ↑ TSH ↓Low - Undetectable	NR
Sawka et al 2003 Ref 37	Randomizes double-blind placebo controlled Not crossover	40 90% F 25-75 yrs	100% Autoimmune Hypothyroidism All with depressive symptoms (General Health Questionnaire above 5) Degree of hypothyroidism NR	T4 4 50 + T3 12.5 twice daily T4/T3 doses variable	15 weeks	Mood Quality of life Depression	** ** **	TSH ** FT4 ↓ FT3 ↑	NR
Walsh et al 2003 Ref 39	Randomized double-blind cross-over	101 92% W 47 ±12 yrs	85 % Autoimmune Hypothyroidism 11%Surgery 4% RAI Degree of hypothyroidism NR	T4 4 50 + T3 10 T4/T3 doses variable	Two periods of 10 weeks 4-weeks washout period	Quality of life Cognitive function Symptoms of hypothyroidism SHBG Cholesterol Osteocalcin Ur DPD/creatinine ratio Alkaline phosphatase Weight HR SBP DBP Preference	** ** ** ** ↓ ↑ ↓ ** ** ** ** T3+T4>T4in 36/101 T4>T3+T4 in 46/101 T3+T4=T4 in 18/101	TSH ↑ FT4 ↓ FT3 **	NR
Clyde et al 2003 Ref 40	Randomized double-blind placebo controlled No cross-over	44 86% W 24-65 yrs	Surgery Cancer 67%Autoimmune Hypothyroidism Degree of hypothyroidism NR	T4 4 50 + T3 7.5 twice daily T4/T3 doses variable	16 weeks	Symptoms of hypothyroidism Neuropsychological state Cognition SHBG Weight SBP DBP HR Total cholesterol HDL LDL Triglycerides	** ** ** ** ** ** ** ** ** ** ** ** **	TSH ** FT4 ↓ FT3 ↑	NR
Saravanan et al 2005 Ref 41	Randomized Double blind placebo controlled No cross-over	697 84% W 18-75 yrs	Primary hypothyroidism No cancer Degree of hypothyroidism NR	T4 4 50 + T3 10 T4/T3 doses variable	52 weeks	Psychiatric score Well being Depression Mood Cognition SHBG Weight Fat mass SBP DBP HR Total cholesterol HDL LDL Triglycerides Alkaline phosphatase	** ** ** ** ** ** ** ** ** ** ** ** **	TSH ↑ FT4 ↓ FT3 **	Hyperthyroid symptoms in 11 pts Hypothyroid symptoms in 30 pts
Rodriguez et al 2005 Ref 45	Randomized Double blind No cross-over	26 83%F 18 or older	77%Autoimmune Hypothyroidism 10% Surgery 13%RAI Degree of hypothyroidism NR	T4 4 50 + T3 10 T4/T3 doses variable	13 weeks	Depression Fatigue Symptoms of hypothyroidism Working memory Weight HR Blood pressure	** ** ** ** ** ** **	TSH ↑ FT4 ↓ TT4 ↑ TT3 ↑	Hyperthyroid symptoms
Siegmond et al 2004 Ref 47	Randomized double-blind,two-period (each 12 weeks) cross-over design	23 20 W, 3M 23-69 years	2 Autoimmune Hypothyroidism 21 Surgery and RAI Degree of	T4/T3 = 14:1	Two periods of 12 weeks	Psychological tests Mood Cognition SHBG Cholesterol	** ** ** ** **	TSH suppressed FT4 ↓ FT3 ↑	Hyperthyroid symptoms Atrial arrhythmias

(Continued)

TABLE 1. Continued

			hypothyroidism NR			HDL cholesterol LDL cholesterol Triglyceride SHBG HR SBP DBP	** ** ** ** ** **		
Escobar-Morreale et al. 2005 Ref 46	Randomized double-blind controlled cross-over	28 W 18-70 yrs	23 Autoimmune Hypothyroidism 5 RAI Overt Hypo	T4/T3 = 15 : 1 10:1	Two periods of 8 weeks	Hypothyroid Symptoms Quality of life Mood Cognition SHBG Total Cholesterol LDL Cholesterol Urinary deoxyypyridinolines Echocardiographic parameters HR Hypothyroid Symptoms Urinary deoxyypyridinolines Preference	75µT4+5µT3 ** ** ** ** ↓ ↑ ↑ ** ** ↓ 87.5µT4+7.5µT3 ↓ ↑ T3+ T4> T4 69% T3+ T4=T4 23% T4>T3+T4 8%	75µT4+5µT3 TSH ↑ FT3 ** FT4 ↓ 87.5µT4+7.5µT3 TSH↓ FT3† FT4 ↓	NO
Appelhof et al. 2005 Ref 38	Randomized parallel design No cross-over	130 80% w 18-70 yrs	100% Autoimmune Hypothyroidism Degree of hypothyroidism NR	T4/T3= 10:1 5:1	15	Quality of life Mood Cognition SHBG Cholesterol Triglyceride Osteocalcin Alkaline phosphatase Weight HR SBP DBP Preference	** ** ** ↑ ↓ ↓ ↑ ↑ ↑ ↑ ** ** T3+T4>T4 in 41% 10:1 52% 10:1	TSH↓low-undetectable FT3† FT4 ↓	NR
Regalbuto et al. 2007 Ref 43	Randomized study No cross-over	20 17F 3 M 18-58 yrs	100% Patients with differentiated thyroid cancer after total thyroidectomy Degree of hypothyroidism NR	3:1	24 weeks	Quality of life Symptoms of hypothyroidism Psychological symptoms SHBG Cholesterol Triglyceride Osteocalcin AST,ALT Alkaline phosphatase Urine hydroxyprolyne Echocardiographic parameters : PEPc AVc Vmax MAAc SBP DBP Preference	** ** ** ↑ ↓ ↓ ↑ ↑ ↑ ↑ ↑ ↓ ↑ ↑ ** ** T3+ T4>T4 in 6 pts T3+ T4=T4 =in 8 T4>T3+T4 in 6	TSH+low-undetectable FT3† FT4 ↓	NO
Nygaard et al. 2010 Ref 48	Double-blind randomized cross-over	59 55 W 4 M 46.5±13.1 yrs	100% Autoimmune overt Hypothyroidism	T4 + 50 + T3 20 T4/T3 doses variable	Two periods of 12 weeks	Quality of life Depression Psychiatric symptoms Body weight Preference	↑ ↑ ↑ ↓ T3+T4>T4 in 49% T3+ T4=T4 =in 38% T4>T3+T4 in 15%	TSH ** FT3 ↑ FT4 ↓	Hyperthyroid symptoms
Fadjevov et al. 2007 Ref 42	Randomized parallel No cross-over	36 pre-menopausal women	Hypothyroidism (cause and degree NR)	T4 +25 + T3 12.5 T4/T3 doses variable	24 weeks	Quality of life Symptoms of hypothyroidism Psychological symptoms Cholesterol LDL cholesterol Triglyceride HR (Holter ECG) Osteocalcin Urine hydroxyprolyne Densitometry Preference	** ** ** ↓ ↓ ** ** ↑ ↑ ** T3+ T4>T4 in 27% T3+ T4=T4in 50% T4>T3+T4 in 8%	TSH ** FT3 NR FT4 NR	NO

NR, Not reported; HR, heart rate; c, corrected for heart rate; RAI, radioiodine; PEP, preejection period; AV, late transmitral flow velocity; V_{max} aortic peak flow velocity; MAAc, mean aortic acceleration; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; PBI, protein-bound iodine; TT3, total T3; TT4, total T4; GD, Graves' disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ECG, electrocardiogram; SHBG, sex hormone-binding globulin; Ur DPD, urinary deoxyypyridinoline.

function, language, executive function, and motor function) (29, 30). The most commonly affected domains are working memory and executive function. Moreover, alterations in mood, characterized by increased rates of depressive and anxiety symptoms, have also been reported

(29, 30). T₃ nuclear receptors are dominant in brain tissue, with a high concentration in the amygdala and hippocampus (essential regions for mood) (30–32). This may explain why minor changes in local T₃ production may lead to changes in behavior.

Small interventional studies using magnetic resonance spectroscopy and fluorodeoxyglucose positron emission tomography have provided a possible neuroanatomical basis for these defects in adults with overt and subclinical hypothyroidism, demonstrating reduced cerebral blood flow as well as altered oxygen and glucose metabolism, with associated frontal lobe dysfunction (31, 32). Moreover, the lower regional glucose metabolism in specific brain areas of untreated overt and subclinical hypothyroid patients may be seen to improve after L-T₄ treatment (32).

However, some studies have reported that successful treatment of hypothyroidism is associated with only a partial recovery or improvement of neurocognitive function and psychological well-being (29, 33), suggesting that replacement treatment with L-T₄ might not be fully adequate for optimal brain function. In one large community-based survey, 26% of the patients with normal thyroid function levels on L-T₄ monotherapy scored significantly worse than did euthyroid controls on measures of well-being [General Health Questionnaire (GHQ), 32.3 *vs.* 25.6%] and on hypothyroid symptoms (47 *vs.* 35%) (33). A 6.7% absolute increase in psychiatric morbidity was found in patients with TSH in the normal range while receiving replacement therapy with L-T₄ compared with a matched control group (33).

Although the physiological basis for these differences in patients' responses to replacement therapy is unclear, we should strive to achieve a regimen of therapy providing both biochemical and clinical euthyroidism that will be associated with a premonitory and normal quality of life.

In an open-label and nonrandomized study, it was observed that some patients with primary hypothyroidism can improve well-being when the T₄ dosage is titrated until serum TSH is in the lower part of the reference range (34). However, whereas some patients appear to feel better on higher doses of L-T₄ (34), this is not universally the case (35). Moreover, the altered cognitive and psychological performances in L-T₄-treated patients have not been clearly associated with given serum levels of TSH and the thyroid hormones (29). This is illustrated by the double-blind, randomized clinical trial with a crossover design performed by Walsh *et al.* (35) on 56 subjects with primary hypothyroidism taking L-T₄ (100 μg/d). A regimen of three doses (low, middle, and high) was employed by administering 25-μg increments of L-T₄ to achieve a TSH in the upper, middle, or lower part of the reference range (35). After noting any changes in general health status or cognition, these workers concluded that changes in T₄ dosage did not produce significant changes in hypothyroid symptoms, well-being, or quality of life despite the associated and expected changes in serum TSH. Sixteen of 50 patients (32%) who completed all three treatments pre-

ferred a low dose, 13 (26%) preferred a middle dose, 10 (20%) preferred a high dose, and 11 (22%) had no preference ($P = 0.75$) (35). These data do not support the suggestion that the target TSH for treatment of primary hypothyroidism should be in the lower part of the reference range to reduce symptoms and optimize quality of life.

In a study by Bunevicius *et al.* (36), partial substitution of L-T₄ with T₃ was associated with improved mood and neuropsychological function in thyroidectomized patients with hypothyroidism and depression compared with treatment with T₄ alone. However, although T₄ levels were lower during combined T₃ and T₄ treatment in this 5-wk crossover study, TSH levels were at the lower normal range during both combined treatment and L-T₄ treatment (36). As a consequence, it is not clear whether the observed results were related to the cause of hypothyroidism, the patient selection of subjects with depression, or the degree of TSH suppression (36). Concerns with the validity of the latter observations appeared justified when these data were not confirmed in subsequent studies (25, 37).

The responses by study subjects to questionnaires on bodily pain, quality of life, mood, symptoms of hypothyroidism, depression, anxiety, and fatigue have not indicated improvement in the majority of studies that examined combination treatment with different doses of T₃ plus T₄ (37–47). One large, community-based, randomized controlled study by Saravanan *et al.* (41) reported a slight improvement in these symptoms after 3 months of combination treatment, which was not confirmed subsequently after 1 yr. However, the same authors emphasized the limits of their study: *i.e.* the large placebo effect with an improvement in psychiatric cases in the control group, and the significant fall in T₄/T₃ ratio observed over a 9-month period (41).

As mentioned above, suboptimal dosing regimens of the combination treatment resulted in subclinical hypo- or hyperthyroidism in the majority of these studies (Table 1). TSH levels were similar at the end of both treatments in only two studies, although they showed higher free T₃ (FT₃) levels and lower FT₄ levels during combined therapy (37, 48). Indeed, only one randomized double-blind crossover study has reported significant improvement of quality of life and depression and anxiety scales during combination therapy (48). It is far from clear whether traditional subjective procedures to assess symptoms and quality of life are reliable markers for evaluation of the peripheral effects of T₃, and whether these parameters are sufficiently sensitive to detect small changes that might be clinically relevant. There are no randomized controlled studies that have evaluated the potential improvement in

cerebral blood flow, oxygen, and glucose metabolism by morphological imaging techniques (such as magnetic resonance imaging or fluorodeoxyglucose positron emission tomography) to support the potential role of combined T_4/T_3 treatment *vs.* $L-T_4$ therapy.

Patient preference for combined T_4/T_3 therapy *vs.* $L-T_4$ treatment alone

Patient preference for combination treatment has been assessed in some studies (36, 38, 39, 42–44, 46, 48) (Table 1). In four studies, the combined T_4/T_3 therapy was preferred, despite the lack of other demonstrable clinical benefit (36, 38, 46, 48). Interestingly, TSH was suppressed in some studies in which combination treatment was favored, suggesting that patients preferred being slightly overtreated (36, 38). In the double-blind randomized controlled study by Appelhof *et al.* (38), the percentage of patients preferring combination $L-T_4$ /levotriiodothyronine ($L-T_3$) therapy *vs.* $L-T_4$ monotherapy was 41% in the arm receiving a T_4/T_3 ratio of 10:1 and 52% in the arm receiving a 5:1 ratio, compared with a stated preference for $L-T_4$ monotherapy in 29%. The stated preferences were expressed despite no changes in mood, fatigue, well-being, and neurocognitive functions (38). In the randomized double-blind crossover trial by Escobar-Morreale *et al.* (46), 69% of patients preferred combination treatment, 8% preferred standard treatment with T_4 alone, and 23% had no preference. In the double-blind randomized crossover study by Nygaard *et al.* (48), 49% of patients preferred combination treatment, 15% preferred monotherapy with $L-T_4$, and 36% had no preference (48). In this latter study, patients preferring the combination therapy had higher depression scores at baseline than patients without a preference.

Such expressions of patient preference for a given therapeutic regimen clearly are highly subjective. Responses might be influenced by the method of patient recruitment; notably, patients were enrolled in the majority of these studies irrespective of their satisfaction with their prior $L-T_4$ monotherapy, whereas patients were invited to participate in other trials. Symptomatic patients might be more motivated to change their traditional treatment, representing a selected group of subjects that could demonstrate a significant placebo effect on a new drug regimen. The Hawthorne effect cannot be excluded in some studies, with patients describing feeling better simply because they are participating in a trial.

Cardiovascular function and lipid profile

Untreated subclinical and overtly hypothyroid patients have an increased risk of atherosclerosis, coronary heart disease, and heart failure (49–51). Ideally, optimal re-

placement therapy in hypothyroid patients should improve their prognosis and reduce their cardiovascular risk. However, some cardiovascular risk factors [such as lipid parameters, endothelial function, body mass index (BMI), and diastolic hypertension] may not be completely normalized after replacement therapy (29, 52–55). This was observed in a population-based cohort study on primary hypothyroid patients who remained at an increased risk of morbidity associated with circulatory diseases and ischemic heart disease despite treatment with $L-T_4$ (56).

On the other hand, some patients with primary hypothyroidism may improve their lipid profile and body weight if the T_4 dosage is titrated until serum TSH is in the lower part of the reference range (52, 54, 57).

Combination treatment with T_3 and T_4 could theoretically reduce cardiovascular risk in patients with underlying cardiovascular risk factors. However, very few published trials of patients on combined T_3 and T_4 treatment *vs.* $L-T_4$ monotherapy have evaluated lipid profiles and cardiovascular parameters during randomized controlled trials (Table 1).

The available data indicate that no significant differences have been seen in total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides (36, 40, 41, 46, 47) during combined treatment with T_3 and T_4 . A slight improvement in lipid profile was noted only when associated with TSH suppression during combined treatment (38, 42, 43).

Few studies compared the effects of combined therapy *vs.* $L-T_4$ monotherapy on cardiovascular parameters (42, 43, 58), and only two of these studies performed a complete Doppler echocardiographic evaluation (43, 58). A definitive conclusion cannot be reached, however, because these studies did not normalize TSH and thyroid hormone levels during combined therapy, and their results were not compared with a control group of matched euthyroid subjects.

Although no significant differences in heart rate or systolic and diastolic function were observed between the two regimens of monotherapy *vs.* combined therapy (36, 38, 39–43, 45–47, 58), the presence of atrial arrhythmias has been reported in two studies in which patients were overtreated during combination treatment (44, 47). Future large prospective randomized controlled trials will be necessary to establish the potential beneficial effects of combination treatment to improve cardiovascular risk factors and morbidity in patients with thyroid hormone deficiency and to establish the optimal T_4/T_3 ratio that could avoid the potential adverse effects of T_3 on heart rate and rhythm.

Body weight, body composition, and energy expenditure

It is well known that slight variations in thyroid hormone levels during L-T₄ therapy may affect body weight, body composition, and energy expenditure (57). Patients experiencing weight gain while hypothyroid often complain of persistence of the increase in body weight even after treatment and full normalization of serum TSH levels (29, 52, 53). Thus, hypothyroid-treated patients may have a higher BMI with an increased fat mass and decreased lean body mass than control subjects (29, 53, 57). Although many factors may influence BMI, small changes in TSH levels, induced by variations in L-T₄ dosage to obtain TSH suppression, may improve resting energy expenditure and fat mass in hypothyroid patients maintaining a higher body weight despite adequate substitution therapy (57). However, increasing evidence suggests that TSH suppressive doses of L-T₄ can be associated with adverse effects on both bone metabolism and the heart (2, 3). As a consequence, current guidelines and recommendations suggest titration of L-T₄ dosages to TSH levels in the reference range and not lower.

Some studies have assessed changes in body weight during combination therapy with T₄/T₃ compared with monotherapy with L-T₄ (38–41, 45, 48, 58) (Table 1). In two double-blind randomized studies, there was a mean body weight change with a decrease of 1.7 kg seen with combination treatment compared with monotherapy with L-T₄ (38, 48). In these two studies, the stated patient preference for, and greater satisfaction with, combination therapy was linked to their significant reduction in body weight and improvement in BMI (38, 48). In one of these two studies (38), a decrease in body weight, but not a decrease in serum TSH, correlated with increased satisfaction with the study medication.

Sex hormone-binding globulin (SHBG)

Some studies comparing physiological effects of combination T₄/T₃ treatment to L-T₄ monotherapy have evaluated various parameters indicative of thyroid effects in the liver, in which tissue concentration of T₃ depends almost entirely on the circulating T₃ concentration. For example, the fact that increases in serum SHBG are seen in hyperthyroidism led some investigators to determine whether alterations in SHBG during combination treatment *vs.* L-T₄ monotherapy (36, 38–41, 43, 46, 47, 58, 59) might indicate relative thyroid hormone overdosage (Table 1). Few of these studies reported an increase in serum SHBG after T₃ treatment, although TSH was suppressed and FT₃ values were higher compared with L-T₄ monotherapy in the majority of these studies (36, 38, 43).

Markers of bone turnover

Hypothyroidism in adults results in reduced bone turnover with impaired osteoclastic bone resorption and osteoblastic bone formation (60). T₃ enhances expression and synthesis of osteocalcin and alkaline phosphatase. In the skeleton, D2 activity plays a crucial role in maintaining optimal bone mineralization (60). Conflicting results have been reported on the potential role of TSH receptors in bone (60). Few studies have evaluated the effects of combination therapy on markers of bone turnover (38, 39, 41–43, 46) (Table 1). In those reports, increases in serum markers of bone turnover were observed when treatment was associated with TSH suppression during treatment (38, 39, 43).

Initiation of thyroid hormone replacement therapy for hypothyroidism is associated with an increased bone turnover, especially in the first years after the diagnosis and especially in the age group above 50 yr (62), with a strong dose-response relation (63); the available studies did not give any data on the duration of hypothyroidism and on the length of previous treatment with T₄.

How Should Combination Treatment with T₃ and T₄ Be Employed? (Table 1)

In some reports, a fixed dose of L-T₄ (usually 50 μg) was substituted with a fixed amount of L-T₃ (ranging from 7.5 to 20 μg), leading to a very variable ratio of T₄/T₃, without reaching the optimal ratio (36, 37, 39, 40–42, 44, 45, 48, 58, 61). Any possible clinical improvement that might have been attributed to the combined T₃ and T₄ treatment could have been obscured in these studies by a relative undertreatment or overtreatment during L-T₄ therapy, essentially constituting states of subclinical hypo- or hyperthyroidism. In other trials of combination therapy, a specific T₄/T₃ ratio was employed, which was 3:1 (43), 5:1 (38), 10:1 (38, 46), 14:1 (47), and 15:1 (46). However, in similar fashion to the previous reports, euthyroidism was not reached in the majority of these studies because the investigators induced overtreatment in most cases as documented by TSH suppression, high FT₃ levels, peripheral parameters of thyroid hormone action (SHBG, heart rate, markers of bone metabolism) in the thyrotoxic range, all associated with the appearance of hyperthyroid signs and symptoms (atrial arrhythmias, weight loss, and increased bone turnover).

The majority of studies evaluating combined T₃ and T₄ treatment used one or two daily doses of T₃. This may have induced spikes in serum T₃ after each dose with a progressive decline of T₃ levels related to its rapid turnover and short half-life with loss of any potential beneficial

effects in the tissues (64). The question of potential benefit of combined therapy will not be adequately addressed until large trials are performed that employ the correct T_4/T_3 ratio in formulations resulting in steady-state concentrations of both hormones, consistent with the fact that the thyroid gland secretes T_4 and T_3 in a ratio of about 14:1.

Who Could Benefit from Combination Therapy?

Conceivably, four different groups of hypothyroid patients could benefit from combination treatment with T_4 and T_3 : 1) patients with hypothyroidism due to an underlying autoimmune condition (38, 64, 65); 2) thyroidectomized patients or patients submitted to radioiodine activities resulting in a lack of sufficient endogenous thyroid function and absence of residual thyroidal T_3 production (36); 3) patients with certain D2 polymorphisms (the enzyme responsible for T_3 tissue availability) who tend to have a preference for combination T_4/T_3 replacement therapy (66, 67); and 4) depressed hypothyroid patients who might benefit from the antidepressant effect of liothyronine (68).

Combination treatment in patients with autoimmune thyroid disease

Patients with autoimmune hypothyroidism may have a progressive thyroid failure with the potential development of mild, subclinical, or overt hypothyroidism (1–3). However, in these patients, residual T_3 production from the thyroid gland is thought to be maintained to a variable degree due to the healthy follicular elements within the thyroid gland. This may explain why lower doses of L- T_4 are necessary to replace patients with autoimmune hypothyroidism compared with athyreotic patients (3).

However, according to the experience of some expert clinicians (64, 65), patients with autoimmune hypothyroidism frequently remain symptomatic despite L- T_4 monotherapy. These patients may complain of mood dysfunction and impaired quality of life because of the underlying autoimmune diathesis, which may reflect a chronic and progressive disease, or because of the potential association with other comorbidities. Neurocognitive function and psychological well-being were not completely restored in an uncontrolled study on 141 patients with primary autoimmune hypothyroidism despite adequate long-term L- T_4 replacement therapy (69). These results led several investigators to evaluate the effects of combination treatment with T_3 and T_4 in hypothyroid patients with autoimmune disease (37–39, 48). Although no differences were observed in cognitive function, mood,

psychological symptoms, quality of life, or thyroid disease-related symptoms in the majority of these studies, it is important to note that TSH was not completely normalized in some of these trials, suggesting that biochemical euthyroidism was not achieved in two of these trials (38, 39). It remains unsettled whether or not combined treatment with T_3 and T_4 may be beneficial in patients with an autoimmune basis for their hypothyroidism.

Combination treatment in thyroidectomized patients

A recent study suggests that approximately 10% of patients who are hypothyroid after thyroidectomy might potentially benefit from T_3 supplementation (20). In thyroidectomized subjects, the 20% of T_3 secretion normally secreted by the thyroid gland theoretically should be compensated for by an increase in peripheral deiodination of T_4 . However, the requisite increase in deiodinase activity needed to produce a physiological amount of circulating T_3 has not been demonstrated during replacement therapy with L- T_4 in humans. Furthermore, our understanding of possible homeostatic changes in thyroid hormone economy and deiodinase activity has been confounded by recent observations of alterations during long-term TSH-suppressive therapy in thyroidectomized patients with differentiated thyroid cancer (DTC) (70). Recently, an altered set point of the HPT axis was reported in DTC patients homozygous for the D2-rs12885300 polymorphism, resulting in a weaker negative feedback of FT_4 on TSH (71).

Some studies have reported that hypothyroid thyroidectomized patients on L- T_4 replacement therapy need higher serum T_4 levels to obtain similar serum TSH levels and lower serum T_3 concentrations compared with euthyroid controls (72, 73). Moreover, normal serum FT_3 and significantly higher serum FT_4 levels have been observed after total thyroidectomy in a prospective study in patients receiving L- T_4 treatment compared with their prethyroidectomy levels, especially in those with suppressed TSH (21). These results could suggest that higher serum T_4 levels are necessary in thyroidectomized patients to obtain normal serum T_3 concentrations and thereby compensate for the absence of the 20% fraction of circulating T_3 normally directly secreted by the thyroid (74). It must be emphasized that recent studies have documented the adverse effect of high FT_4 levels in patients receiving L- T_4 therapy (75).

Combination treatment in hypothyroid patients with depression

There is a possible link between depression and impaired thyroid function (76, 77). About 15% of patients with

depression display hypothyroid states including subclinical hypothyroidism (76); moreover, autoimmune thyroiditis is more frequent in depressed patients than in healthy euthyroid individuals (20 *vs.* 5%) (77). On the other hand, there are conflicting results on the relationship between the presence of positive thyroperoxidase antibodies and depression (77–81). A recent population-based study found no association between antithyroid antibodies and depression or anxiety (79). Among studies that have investigated the effects of combined T₃ and T₄ treatment in depressed hypothyroid patients (36, 37), only one reported a beneficial effect of this treatment in depressed patients with an improvement in mood and cognition (36).

Several meta-analyses have described beneficial therapeutic effects of T₃ in combination with tricyclic antidepressants compared with placebo in euthyroid patients with resistant depression (82, 83). In one recent study, the addition of T₃ has been able to enhance the antidepressant effect of sertraline in euthyroid patients without significant adverse effects (84). Double-blind placebo-controlled studies are needed to investigate the potential beneficial effects of combined T₃ and T₄ treatment in hypothyroid patients with persistent depression despite TSH normalization during L-T₄ therapy.

Combination treatment in patients with deiodinase polymorphisms

Individuals with a polymorphism in D2 may have important clinical implications that could explain why normal serum levels of T₃ may not be sufficient to normalize symptoms and improve the quality of life in some hypothyroid patients receiving L-T₄ replacement therapy alone. The D2 Thr92Ala polymorphism (D2-Thr92Ala) has been associated with insulin resistance, obesity, and hypertension (85, 86). On the other hand, the Thr92Ala 12 polymorphism has also been associated with a variation in the HPT axis (22, 23), altered bone turnover (60), cognition, and response to thyroid hormone replacement therapy (67, 87–89).

In a study from Italy, the presence of the D2-Thr92Ala polymorphism was able to predict the need for a higher T₄ intake in 191 consecutive cancer patients, previously treated by near total thyroidectomy and radioiodine ablation (89). Although this observation is highly intriguing, the same polymorphism was not associated with a requirement for higher T₄ doses to normalize serum TSH levels in patients with autoimmune hypothyroidism (88). Related studies have investigated whether the polymorphism in the D2 gene (D2-Thr92Ala) is associated with well-being and neurocognitive dysfunction in hypothyroid patients receiving replacement therapy and with a preference for combination treatment of T₄/T₃ (67, 87).

Appelhof *et al.* (87) reported that two polymorphisms in the D2 gene (the D2-ORFa-Gly3Asp and D2-Thr92Ala polymorphisms) were not determinant of differences in well-being, neurocognitive functioning, or appreciation of T₄/T₃ combination therapy in 141 patients with primary autoimmune hypothyroidism. A subsequent study of 552 patients on L-T₄ replacement therapy from the Weston Area T₄/T₃ (WATTS) suggested that there may be a small number of patients with a D2 polymorphism that could benefit from combination therapy (67). The more rare CC genotype of the rs225014 polymorphism in the deiodinase 2 gene was present in 16% of this study population (67). Although this polymorphism had no impact on circulating thyroid hormone levels, it was associated with impaired baseline psychological well-being and a worse baseline GHQ score in patients on L-T₄ (67). These patients showed a greater degree of improvement on T₄/T₃ therapy compared with being on T₄ monotherapy (2.3 GHQ points at 3 months, and 1.4 points at 12 months) (67). Interestingly, the results of this study suggest that circulating T₃ levels may not directly reflect intracellular T₃ levels because this polymorphism had no impact on circulating thyroid hormone levels (67). These data suggest that the evaluation of changes in persistent specific symptoms of hypothyroidism may be useful for the selection of patients that could benefit from combined T₃ and T₄ treatment. Prospective trials will be necessary to further evaluate the neuropsychiatric response to combined T₄/T₃ treatment *vs.* monotherapy with L-T₄ in patients with the Thr92Ala polymorphism.

Meta-Analyses on Combined T₄/T₃ Therapy

Three meta-analyses have appeared that have evaluated the effects of combination treatment with T₃ and T₄ *vs.* T₄ alone (90–92). Grozinsky-Glasberg *et al.* (90) analyzed 11 randomized controlled trials with a total of 1216 patients and concluded that T₄/T₃ combination therapy provided no advantage when compared with standard L-T₄ monotherapy in any of the following parameters: bodily pain, depression, anxiety, fatigue, quality of life, body weight, total serum cholesterol and triglycerides, and serum low-density lipoprotein and high-density lipoprotein, and also demonstrated no difference in adverse events.

A second meta-analysis by Ma *et al.* (91) including a total of 1243 patients suggested that T₄/T₃ combination therapy was beneficial for the psychological and physical well-being of patients previously on L-T₄ monotherapy. Their analysis did not find a statistically significant difference in the other variables. A meta-analysis by Joffe *et al.* (92) of nine controlled studies examining the effects of

combination T₃ and T₄ therapy *vs.* L-T₄ alone on psychiatric symptoms found no significant differences. It is important to note that only a few studies included in the three meta-analyses were randomized placebo-controlled studies (37, 40, 41). Many of the studies were randomized parallel-design studies (38, 42, 43) or crossover studies (36, 39, 44, 46–48, 58, 61).

Moreover, it is also clear that each of these studies had several relevant methodological limitations (Table 1), including:

- 1) Small sample size, which may have induced a reduced power analysis in some studies.
- 2) Lack of homogeneity of the hypothyroid patient population in most of the studies. The cause of hypothyroidism was not clarified in several of the reports, and a heterogeneous group of subjects was enrolled in other studies (grouping together athyreotic patients, patients with autoimmune Hashimoto thyroiditis, and patients with thyroid hormone deficiency induced by radioiodine for previous hyperthyroidism). Moreover, the severity of hypothyroidism was quite variable in some studies, including patients with subclinical hypothyroidism who may have retained some residual secretion of both T₄ and T₃.
- 3) Large variation in the T₄/T₃ ratio administered in many studies.
- 4) Low sensitivity of some of the outcome measures of cognition or mood, which may explain the poor results reported in the literature. The majority of these studies evaluated subjective symptoms or preference to treatment.
- 5) Only a few studies evaluated the effects of combined T₃ and T₄ therapy on objective peripheral parameters of thyroid hormone action. Moreover, some of these studies did not compare tissue parameters with those obtained in a control group of well-matched euthyroid subjects.
- 6) Brief duration of combination therapy, generally restricted to only a few weeks, which may be an insufficient period to evaluate the potential beneficial effects of this treatment on peripheral tissues. A potential carryover effect might be induced by the long half-life of T₄ with persistence of the effects of the L-T₄ for a long time in some tissues such as the brain (65).

In the future, large trials involving a homogeneous group of patients with primary hypothyroidism should be performed to clarify what kind of patients with thyroid hormone deficiency (patients with autoimmune hypothyroidism, thyroidectomized or depressed patients or some

with particular D2 polymorphisms) could benefit from the addition of replacement doses of T₃. Moreover, it will be important to evaluate more significant clinical and tissue parameters during combination therapy (bone, heart, cardiovascular risk factors, more sensitive and specific symptoms) and to treat the patients for a sufficient period to obtain clinical and tissue euthyroidism.

Treatment with T₃ vs. T₄

Currently, clinical use of L-T₃ is quite limited. L-T₃ may be administered after L-T₄ withdrawal for DTC patients in preparation for radioiodine therapy to reduce the duration of hypothyroid symptoms and to improve the quality of life (93). Recent findings by Celi *et al.* (14, 94) have increased interest in examining the role for T₃ replacement therapy in hypothyroid patients. These authors achieved a steady-state pharmacodynamic equivalence by completely substituting L-T₄ with L-T₃, using a three-daily regimen at an approximate ratio of 1:3 (14). Peripheral parameters of thyroid hormone action were evaluated in response to doses of L-T₃ *vs.* L-T₄ that produced equivalent steady-state baseline and TRH-stimulated TSH levels (94). Interestingly, significant weight loss, without changes in body fat mass, and a decrease in total cholesterol, low-density lipoprotein-cholesterol, and apolipoprotein B were observed during L-T₃ therapy compared with L-T₄ treatment (94). Notably, L-T₃ resulted in a significant increase in SHBG levels, suggesting an important peripheral effect on the liver and slight overtreatment (94). On the contrary, no significant differences were observed in fasting glucose or insulin sensitivity as measured by the hyperinsulinemic-euglycemic clamp (94). Moreover, no significant differences were observed in cardiovascular parameters such as heart rate, blood pressure, exercise tolerance, and flow-mediated vasodilation during the two treatment regimens (92). Furthermore, no significant difference was observed in the Short Form-36 and Health-Related Quality of Life questionnaires (94).

At the end of the study, four patients expressed no preference for either treatment, five preferred L-T₄, and five preferred L-T₃ (94). Unfortunately, hypothyroid symptoms were not evaluated in this study. In view of the fact that T₃ has important effects on cardiovascular hemodynamics, it is possible that the small number of patients and the relatively short period of treatment may have precluded observation of T₃-induced significant changes in cardiovascular parameters. Increased FT₃ levels during T₃ therapy were necessary to obtain TSH levels comparable to those observed with L-T₄ treatment. Three daily doses

of LT₃ were able to achieve stable serum levels of TSH and T₃ with an observable beneficial tissue effect.

Thus, based on these intriguing results from Celi *et al.* (14, 94) and on the paucity of other well-conducted trials of combination T₄/T₃ therapy, we suggest the need for a further examination of the role of adjunctive T₃ therapy in selected patients. In our opinion, it is essential to normalize serum FT₃ as well as TSH levels to observe significant effects on some peripheral parameters of thyroid hormone action in hypothyroid patients. However, treatment with T₃ is not recommended in pregnant women, nor is it advisable in patients with a history of arrhythmias or chronic ischemic heart disease.

Moreover, the common difficulties in obtaining a stable euthyroid condition in hypothyroid patients receiving replacement therapy cannot be ignored (2, 3). Only 60% of patients receiving thyroid hormone had normal thyroid function in the Colorado Disease Prevalence Study (95). Given this high prevalence of overtreatment in patients with hypothyroidism, treatment monitoring to assess compliance and to prevent complications is very important. This is particularly true in patients receiving combination treatment to avoid potential adverse effects that could be more significant than those associated with T₄ therapy.

Conclusions

Although earlier meta-analyses failed to find clear benefit in treatment of hypothyroid individuals with combination T₄ and T₃, continued interest in such approaches to replacement therapy is warranted due to methodological deficiencies in the majority of the prior studies. New insights into deiodinase polymorphisms may explain differences in both tissue and relative individual clinical responses to treatment.

Experimental and clinical evidence suggests that a TSH level within the reference range is not a sufficiently optimal marker of adequate thyroid hormone replacement therapy in hypothyroid patients. Prospective double-blind randomized large studies are necessary to clarify the potential beneficial effects of combination treatment with T₃ and T₄ *vs.* L-T₄ monotherapy to improve symptoms and to reverse the biochemical abnormalities of patients with primary hypothyroidism. Further studies will be necessary to assess the tissue distribution of deiodinases and all of the potential factors that could control their activity and correlate with phenotypical patients requiring thyroid hormone replacement therapy. Resolving the question of optimal therapy with L-T₃ is hampered by the lack of an available formulation that will achieve steady-state con-

centrations of T₃. Although the use of three daily doses of T₃ can improve the T₃ serum levels during the day, it is likely to be associated with less than optimal compliance to therapy. A long-acting, slow-release form of T₃ (64) will be required to mimic normal physiological endogenous T₃ production and achieve the equivalent of a true “thyroid transplant” in patients lacking their thyroid gland or normal thyroid function. Such a preparation would effectively treat all associated symptoms and maintain a normal and stable TSH level, a circadian T₃ rhythm, and a consistently physiological ratio of serum FT₄/FT₃ over 24 h. Increasingly accelerated progress to personalized medicine holds the promise to achieve this dream.

Successful resolution of impediments to both practical and physiological dosing of a T₄/T₃ combination agent could allow clinicians to more effectively treat patients with primary hypothyroidism.

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