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T4+T3 combination therapy: is there a true effect?

Wilmar M Wiersinga

Department of Endocrinology and Metabolism, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Correspondence should be addressed to W M Wiersinga
Email
w.m.wiersinga@amc.uva.nl

Abstract

About 5%–10% of hypothyroid patients on T4 replacement therapy have persistent symptoms, despite normal TSH levels. It was hoped that T4+T3 combination therapy might provide better outcomes, but that was not observed according to a meta-analysis of 11 randomized clinical trials comparing T4 monotherapy with T4+T3 combination therapy. However, the issue is still subject of much research because normal thyroid function tests in serum may not necessarily indicate an euthyroid state in all peripheral tissues. This review evaluates recent developments in the field of T4+T3 combination therapy. T4 monotherapy is associated with higher serum FT4 levels than in healthy subjects, and subnormal serum FT3 and FT3/FT4 ratios are observed in about 15% and 30% respectively. T4+T3 combination therapy may mimic more closely thyroid function tests of healthy subjects, but it has not been demonstrated that relatively low serum FT3 or FT3/FT4 ratios are linked to persistent symptoms. One study reports polymorphism Thr92Ala in *DIO2* is related to lower serum FT3 levels after thyroidectomy, and that the D2-Ala mutant reduces T4 to T3 conversion in cell cultures. Peripheral tissue function tests such as serum cholesterol reflect thyroid hormone action in target tissues. Using such biochemical markers, patients who had a normal serum TSH during postoperative T4 monotherapy, were mildly hypothyroid, whereas those with a TSH 0.03–≤0.3 mU/L were closest to euthyroidism. Peripheral tissue function tests suggest euthyroidism more often in patients randomized to T4+T3 rather than that to T4. Preference for T4+T3 combination over T4 monotherapy was dose-dependently related to the presence of two polymorphisms in *MCT10* and *DIO2* in one small study. It is not known if persistent symptoms during T4 monotherapy disappear by switching to T4+T3 combination therapy. The number of patients on T4+T3 therapy has multiplied in the last decade, likely induced by indiscriminate statements on the internet. Patients are sometimes not just asking but rather demanding this treatment modality. It creates tensions between patients and physicians. Only continued research will answer the question whether or not T4+T3 combination therapy has true benefits in some patients.

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Invited Author's profile
Wilmar M Wiersinga MD PhD, is an Emeritus-Professor of Endocrinology at the Academic Medical Centre, University of Amsterdam, The Netherlands. His research interest is in basic and clinical thyroidology, with focus on thyroid hormone metabolism and receptors, amiodarone, thyroid autoimmunity and Graves' orbitopathy. He founded EUGOGO, and was the member of the Executive Committee of the European Federation of Endocrine Societies and president of the European Thyroid Association.

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Introduction

In 1995 and 1996 Gabriela Morreale de Escobar and her group published two landmark studies demonstrating that only the combined T4+T3 treatment ensured euthyroidism in all tissues of thyroidectomized rats (1, 2).

In 2006, 10 years later, a meta-analysis was published of 11 randomized clinical trials comparing T4+T3 combination therapy vs T4 monotherapy in hypothyroid patients (3). The combination was not better than T4 alone, and the authors stated that 'it is doubtful whether further trials evaluating combination therapy are needed because the chances that the accumulated evidence will change are low'.

In 2016, another 10 years later, the issue of T4+T3 combination therapy is still hot topic of debate, and remains highly controversial.

The experimental animal studies from Morreale de Escobar had an enormous impact because they challenged current wisdom that T4 monotherapy was the perfect treatment of hypothyroidism. It explains why within 10 years after their publication as much as 11 randomized clinical trials were performed on this issue. But it is remarkable that despite the essentially negative results of these trials as evident from the meta-analysis in 2006, the issue of T4+T3 combination therapy is still the subject of much research 10 years later, meanwhile stirring up emotions between patients and doctors. Two factors have greatly contributed to the present confusing state of affairs. First, it became evident that not all hypothyroid patients are satisfied with the outcome of their replacement therapy with T4. Three large community-based studies, carried out at about the same time as the randomized trials, suggested persistent complaints in 5%–10% of T4-treated patients, also in those with a normal serum TSH (4, 5, 6). Secondly, evidence has been accumulating that there exists tissue-specific regulation of thyroid hormone contents in target tissues via differential expression of thyroid hormone transporters and iodothyronine deiodinases (7, 8). For example, T3 content in the brain is predominantly derived from local T4 deiodination into T3 catalyzed by type 2 deiodinase (D2), and not from serum T3. Serum thyroid hormones may thus not always accurately reflect the hormonal status of target tissues. If one assumes that T4 monotherapy may not necessarily fully restore T3 content of target tissues (especially of the brain), it is biologically plausible to suppose that persistent complaints will benefit from T4+T3 combination therapy. Many dissatisfied patients are referring to this hypothetical possibility when they are asking their physicians to switch from T4 to T4+T3.

The current review focuses on recent developments in the field of T4+T3 combination therapy. Are there true effects of T4+T3 combination therapy, and if so, are they related to the remaining complaints of patients?

T4+T3 therapy: Is there a true effect on serum thyroid hormones?

T4+T3 combination therapy undoubtedly affects serum thyroid hormone concentrations, the extent of which depends on the administered doses of T4 and T3. A representative example is presented in Table 1. Hypothyroid patients on stable T4 (baseline values) were randomized to receive either their usual T4 dose or the combination of T4 (usual dose minus 50 µg)+20 µg T3 for 12 weeks (9). The combination results in lower T4 and higher T3 concentrations in serum compared to T4 monotherapy. Which values mimic closest thyroid function tests of healthy controls? Not those obtained during T4 monotherapy. In the 1980s it was already observed that in hypothyroid patients on T4, the serum T4 required to reach a normal serum TSH, is higher than that in controls (10). This was recently confirmed in a large survey of athyreotic patients with normal TSH during T4 treatment: it showed – relative to a healthy population—a shift to the right in the distribution curve of FT4 values; FT4 levels above the upper normal limit occurred in 7.2% of the population (11). The distribution curve of FT3 was shifted to the left, with FT3 values below the lower normal limit in 15.2%. The distribution curve of serum FT3/FT4 ratios was strongly shifted to the left with abnormally low ratios in 29.6%.

Table 1 Serum TSH, T4 and T3 before and after randomization to T4 monotherapy or T4+T3 combination therapy (9).

	Baseline under T4	T4 monotherapy	T4+T3 combination	*P* value T4 vs T4+T3
TSH (mU/L)	1.10 (0.5–2.2)	0.99 (0.6–1.9)	0.76 (0.2–1.8)	0.07
T4 (nmol/L)	124±29	123±30	77±32	<0.001
T3 (nmol/L)	1.6±0.4	1.7±0.6	2.4±1.0	<0.001

Values as median ($P_{2.5}$–$P_{97.5}$) or mean±s.d.

Extrathyroidal T3 production is apparently not always adequate during T4 monotherapy to compensate for absent thyroidal T3 secretion. Indeed, T3 production by remnant thyroid tissue has a substantial effect on the maintenance of T3 levels after thyroidectomy (12). But does it matter that serum FT4 levels are relatively high and FT3 levels are relatively low during T4 monotherapy? High T4 levels inhibit D2 activity, which in D2-expressing tissues such as the brain may result in lower T3 content. D2 inactivation is by ubiquination, and tissue-specific differences in D2 ubiquitination account for the low serum T3/T4 ratio of T4 treatment after thyroidectomy in experimental animals (13). T4 administration decreases whole-body D2-dependent conversion of T4 into T3, but D2 activity in the hypothalamus is only minimally affected by T4. Thus, serum TSH may be normalized by slightly higher FT4 levels whereas the same FT4 levels may inhibit local generation of T3 from T4, resulting in slightly lower tissue and serum T3.

T4+T3 combination therapy may result in serum FT3, FT4 and FT3/FT4 ratios which more closely resemble values in healthy subjects. This was indeed observed in five randomized clinical trials, which had measured FT3 and FT4 (Table 2) (14, 15). Nevertheless, despite almost normal FT3/FT4 ratios in these five trials, the outcome of combination therapy was not superior over T4 monotherapy. A recent Danish study also raised doubts whether serum T3 levels are related to persistent symptoms (16). T4+T3 combination therapy was given to 37 patients; after 12 months 65% were classified as responders and 35% as non-responders. Neither baseline serum T3 nor changes in serum T3 during the treatment predicted the response. Likewise, serum thyroid hormones were not related to quality of life or fatigue in 143 thyroid cancer patients using T4 after total thyroidectomy and 131I therapy (17).

In healthy subjects, 20% of serum T3 is derived from thyroidal T3 secretion and 80% originates from the extrathyroidal conversion of T4 into T3 catalyzed by type 1 and type 2 deiodinases (D1 and D2). Polymorphisms in the thyroid hormone pathway genes are associated with serum TSH and iodothyronine concentrations in healthy subjects (18). For example, the C-allele of a particular SNP in *DIO1* (rs2235544) is associated with increased D1 activity, resulting in slightly higher FT3 and lower FT4. In addition, in T4-treated hypothyroid patients, the FT3/FT4 ratio is higher in subjects who are homozygote for this SNP as compared to wildtype (0.19 vs 0.17), but it is not related to persistent symptoms (19). D2 accounts for about 70% of circulating serum T3 in humans. Common genetic variants in *DIO2* have not been linked to serum iodothyronines. The most studied variant is rs225014 (Thr92Ala), which also had no effects on serum TSH, FT4 or T3 (20, 21) but interestingly has been associated with diabetes, psychological well-being, hypertension and the risk of osteoarthritis (22). A recent large study reports the presence of *DIO2* Thr92Ala in 10.7% of the general population and in 11.3% of T4 users (23). In neither group was the polymorphism associated with differences in serum TSH, FT3, FT4, FT3/FT4 ratio, quality of life or cognitive functioning. The only study so far relating *DIO2* Thr92Ala to reduced D2 activity and lower serum T3 is a very recent one, in which serum FT3 and FT4 were measured before surgery and after thyroidectomy when patients were treated with T4 (with similar TSH levels as before surgery) (24). The mean postsurgical FT3 was significantly lower in patients carrying the mutated allele than that in wild-type patients, in whom postsurgical FT3 levels were similar to presurgical levels (Table 3). The same paper reports that the D2-Ala mutant was less efficient than D2-WT in converting T4 into T3 in muscle cells *in vivo*.

It can be concluded that T4+T3 combination therapy may mimic more closely FT3, FT4 and FT3/FT4 ratio of healthy subjects than T4 monotherapy, but there is currently no evidence that relatively low serum FT3 or FT3/FT4 ratios are linked to persistent symptoms.

Table 2 Serum FT3/FT4 concentration ratios in euthyroid controls and T4-treated hypothyroid patients (11), and in hypothyroid patients randomized to receive either T4 or T4+T3 (14, 15).

	Serum FT3 (pmol/L)	**Serum FT4** (pmol/L)	**FT3/FT4 ratio**
Euthyroid controls (11)	4.47	13.8	0.32 (IQR 0.27–0.37)
Hypothyroid on T4 (11)	3.70	15.4	0.24 (IQR 0.20–0.28)
Randomized to T4 monotherapy (14, 15)	4.40	20.2	0.24 (range 0.18–0.25)
Randomized to T4+T3 combination(14, 15)	4.70	14.7	0.30 (range 0.25–0.45)

Values as median; IQR, interquartile range.

Table 3 *DIO2* polymorphism Thr92Ala reduces D2 activity and serum T3 in hypothyroid patients on T4 (24).

Deiodinase-2 Thr92Ala	Presurgical serum FT3	Postsurgical serum FT3	*P* value
Wild types Thr/Thr *n*=37	4.92±0.54 pmol/L Median 4.92	4.76±0.55 pmol/L Median 4.76	0.097
Heterozygotes Thr/Ala *n*=52	5.22±0.80 pmol/L Median 5.07	4.61±0.43 pmol/L Median 4.45	<0.0001
Homozygotes Ala/Ala *n*=13	5.22±0.57 pmol/L Median 5.22	4.45±0.52 pmol/L Median 4.45	0.01

T4+T3 therapy: Is there a true effect on thyroid hormone dependent actions?

Tests to evaluate thyroid hormone action in target tissues are well known. For example, before the advent of sensitive assays for TSH and T4, serum cholesterol was a useful aid in the diagnosis of thyroid function: the finding of a low or high cholesterol suggested hyperthyroidism or hypothyroidism respectively. Such peripheral tissue function tests have been used to evaluate whether T4+T3 therapy and T4 monotherapy differ in their effects on target tissues.

In one study, in which patients were randomized already when primary hypothyroidism was diagnosed, T4+T3 combination therapy not only resulted in more favorable changes in serum cholesterol but also in higher activation of bone resorption compared to T4 monotherapy; TSH was similar in both groups (25). Two other RCTs observed likewise a slightly better profile in some tests during treatment with T4+T3 therapy or desiccated thyroid extract (Armour) compared to T4 monotherapy despite similar TSH values; the differences between groups in SHBG, PINP, NT-proBNp, cholesterol were however small and not always significant (26, 27). The pharmacodynamic equivalence of L-T4 and L-T3 was found to be 3:1 in a randomized double-blind cross-over study in thyroidectomized patients (28). Thus, therapeutic substitution of 30 μg L-T4 by 10 μg L-T3 can be done without changes in TSH. Interestingly, in this study serum LDL cholesterol was significantly lower and SHBG was higher when patients were on L-T3 (40±11 μg) rather than on L-T4 (115±38 μg) whereas serum TSH was similar (1.48±0.78 vs 1.21±0.62 mU/L respectively); group differences in calorie intake, macronutrient preference and hunger were absent (29). Thus, there exists some, but weak, evidence that T4+T3 therapy is associated with peripheral tissue function tests indicating more often an euthyroid state in target tissues than that with T4 monotherapy.

Animal studies support the notion that T4+T3 therapy is more effective than T4 monotherapy in restoring the euthyroid state in target tissues, despite similar serum TSH levels between the two treatment modalities. T4+T3 therapy but not T4 monotherapy in thyroidectomized rats restored serum cholesterol and mitochondrial content and α-glycerolphosphate dehydrogenase activity in liver and skeletal muscle (13). T4+T3 therapy also normalized the expression of all studied T3-responsive genes in the brain, whereas T4 monotherapy restored gene expression partially (13). Further studies in humans underline again that a normal serum TSH not necessarily indicates adequate thyroid hormone replacement (30). Participants in the NHANES study using T4 who had a normal serum TSH, were compared to controls matched for age, sex, race and TSH (31). Serum FT3/FT4 ratios in T4-users were approximately 15%–20% lower than that in controls. Serum TSH below the mean of 1.75 mU/L in T4-users was associated with a higher FT4 (but similar FT3) than that in T4-users with TSH 1.75–5.40 mU/L; yet they exhibited lower serum LDL cholesterol. Lastly, a study from Japan evaluated peripheral tissue function tests in patients before total thyroidectomy and at one year

Table 4 Biochemical markers in athyreotic patients on T4 monotherapy (32).

	Postop. TSH before Tx → after Tx		
	TSH≤0.03 *n*=58	0.03<TSH≤0.3 *n*=46	0.3<TSH≤5.0 *n*=29
TSH (mU/L)	1.48 → 0.01 ↓	1.56 → 0.07 ↓	1.59 → 1.51 NS
FT4 (ng/dL)	1.07 → 1.56 ↑	1.09 → 1.45 ↑	1.12 → 1.38 ↑
FT3 (pg/mL)	2.79 → 3.17 ↑	2.92 → 2.96 NS	2.92 → 2.76 ↓
Thyroid function	Hyperthyroid	Subclinical hyperthyroid	Euthyroid
LDL-C (mg/dL)	114 → 111 NS	104 → 104 NS	108 → 114 ↑
SHBG (nmol/L)	69 → 82 ↑	66 → 66 NS	67 → 72 NS
TRACP (mU/dL)	377 → 371 NS	361 → 328 NS	362 → 319 ↓
BAP (μg/dL)	13 → 15 ↑	13 → 13 NS	15 → 14 NS
Peripheral tissues	Mildly hyperthyroid	Closest to euthyroid	Mildly hypothyroid

BAP, bone alkaline phosphatase; LDL-C, LDL cholesterol; NS, no significant change; SHBG, sex hormone binding globulin; TRACP, tartrate-resistant acid phosphatase; Tx, total thyroidectomy; ↓, significant fall; ↑, significant rise.

postoperatively under T4 therapy (32). In patients with postoperatively strongly suppressed TSH (≤0.03 mU/L), SHBG and BAP had increased; in patients with mildly suppressed TSH (0.03–≤0.3 mU/L), FT3 and metabolic markers remained equivalent to their preoperative levels; in patients with postoperatively normal TSH (0.3–≤5.0 mU/L), LDL cholesterol had increased and TRACP decreased (Table 4). Patients with mildly suppressed TSH levels during postoperative T4 replacement appear closest to euthyroidism according to peripheral tissue function tests, whereas those with normal TSH were mildly hypothyroid and those with strongly suppressed TSH were mildly hyperthyroid (32). A normal TSH during T4 therapy is thus no guarantee for a euthyroid state in all target tissues.

T4+T3 therapy: Is there a true effect on the clinical condition?

Primary outcomes in the RCTs comparing T4+T3 combination therapy and T4 monotherapy were mostly questionnaires on quality of life, fatigue, mood, anxiety and depression, and cognitive function tests. Outcomes of T4+T3 were not better than that of T4 in a meta-analysis (3). In 7 RCTs patients were asked about preference if any for a particular treatment modality. Preference for T4+T3 therapy was expressed by 48% of patients, for T4 monotherapy by 27%, and 25% had no preference (Table 5). Remarkably, only in 1 of these 7 RCTs the combination therapy was not preferred by most patients (14) (Table 6). One wonders about the determinants of patients' preference. Changes in body weight at the end of the intervention are reported in 3 of these 7 RCTs, and patients randomized to receive T4+T3 lose weight whereas T4-treated patients do not (Table 7). A recent study, however, does not find a relationship between preference for T4+T3 therapy and changes in body weight (34).

A fair number of studies have investigated the relationship between outcome of thyroid hormone replacement therapy and polymorphisms in deiodinases

Table 5 Preference of patients for T4 monotherapy or T4+T3 combination therapy in seven randomized clinical trials (14).

No. of patients	Preference T4	Preference none	Preference T4+T3
Cross-over study design			
298 (100%)	74 (25%)	81 (27%)	143 (48%)
Parallel study design			
140 (100%)	14/48 (29%)		43/92 (47%)

Table 6 The putative relationship between preference T4 monotherapy or T4+T3 combination therapy and body weight (9, 27, 33).

Reference	Randomization	Weight change	TSH (mU/L)	T3 (nmol/L)
(33)	T4	+0.1 kg	0.64	1.73
	T4+T3 (ratio 10:1)	−0.5 kg	0.35	1.86
	T4+T3 (ratio 5:1)	−1.7 kg	0.07	2.24
(9)	T4	+0.2 kg	0.99	1.7
	T4+T3 (ratio 4:1)	−1.5 kg	0.75	2.4
(27)	T4	+0.5 kg	1.30	–
	T4+T3 (ratio 4:1)	−0.5 kg	1.67	–

and thyroid hormone transporters. SNPs in *DIO1* are not associated with psychological well-being or response to T4+T3 therapy, also not in case of SNP rs2235544 (the only SNP that affects serum FT4 and FT3) (19). SNPs in *DIO2* and *DIO3* are not associated with changes in serum TSH, FT4 and FT3, but may affect tissue T3 content by catalyzing local T4 to T3 conversion and degradation of T4 and T3 respectively. SNP rs225014 in *DIO2* (Thr92Ala) has been associated with decreased psychological well-being in T4-treated patients and with improved response to T4+T3 therapy; the effect, however, is limited (21). The absence of such an association in another study might be due to a smaller sample size (20). A recent large population-based cohort study did not find an association between Thr92Ala and outcomes of T4 therapy such as quality of life and cognitive functioning (23). SNPs in the brain-specific thyroid hormone transporter OATP1C1 (also known as SLCO1C1) are associated with fatigue and depression in T4-treated patients, but not with neurocognitive test results or a preference for combination therapy (35). The latest development in this area is an elegant study from Denmark, in which the combination of polymorphisms in *DIO2* (rs225014) and *MCT10* (rs17606253) enhanced patients' preference for T4+T3 combination therapy (Fig. 1) (34). Preferences were 42, 63 and 100% in patients with wild-type nucleotides of both SNPs, with 1 of the 2 possible polymorphisms, and with both polymorphisms present respectively; the dose-response pattern is statistically significant. Odds ratios for harboring these SNPs in case of preference for the combination T4+T3 therapy over standard T4 therapy are: 6.40 (1.06–49.7), $P=0.018$ for *MCT10* rs17606253, and 2.80 (0.66–12.3), $P=0.11$ for *DIO2* rs225014. The limitation of this study is the small sample size ($n=45$), but the results make sense from a biological point of view as T3 content of brain cells may depend more on local *MCT10* and *DIO2* activity than that on serum T4 and T3. The study awaits confirmation by other investigators. It has, however, not been studied

Table 7 Danish internet-based questionnaire study on T4+T3 combination therapy (40).

Respondents	*n*=293: 94%: female, 63%: 41–60 year, 60%: tertiary education
TSH at diagnosis	26%: <4 mU/L, 18%: 4–10 mU/L, 29%: >10 mU/L, 26%: unknown
Symptoms before starting T4+T3	91%: tired, 87%: lack of energy, 83%: cognitive problems, 76%: musculoskeletal symptoms, 75%: weight problems, 49%: pain, 42%: constipation, 39%: depression
Prescriptions	43%: L-T3, 50%: desiccated thyroid, 7%: other; 44%: general practitioner, 41%: specialist, 4%: internet, 11%: no answer
Dose adjustments	44%: physician (blood samples), 17%: physician (symptoms), 28%: myself (symptoms), 11%: no answer
Duration T4+T3	56%: 3–6 months, 16%: 6–12 months, 14%: 1–3 year, 10%: >3 year
Most recent TSH	14%: <0.01 mU/L, 54%: 0.01–1.0 mU/L, 22%: 1.0–4.0 mU/L, 5%: >4.0 mU/L
Response to T4+T3	19%: miraculous, 43%: much better, 22%: better, 6%: no difference, 2%: worse, 8%: no answer

if persistent complaints in hypothyroid patients on stable T4 monotherapy carrying such SNPs, disappear by switching to T4+T3 combination therapy.

MCT10 is expressed in many organs including the brain, and is at least as active as *MCT8* in terms of influx and efflux of thyroid hormones with a preference for T3 over T4 (34, 36). Basic studies have shown more light on polymorphism Thr92Ala in *DIO2*. Patients with type 2 diabetes who were homozygous for D2-92Ala, had decreased D2 activity in muscle samples compared to D2-Thr92 carriers; however, decreased D2 activity was not observed in transfected D2-92Ala cells (22, 37). In contrast, a more recent study showed that DR-92Ala has a longer half-life in transfected human embryonic kidney cells (22, 38). Expression profiles of T3-responsive genes in the cerebral cortex of 19 D2–92Ala carriers were not affected but those of non-T3 responsive genes were, suggesting that the effects of the 92Ala variant on cognitive endpoints might not be mediated via changes in thyroid hormone levels (22, 38). The most recent study showed no differences in protein stability between genotypes, but intracellular T4 to T3 conversion was lower in D2-92Ala than that in D2-Thr92 transfected myoblasts (24). Taken together, these basic studies suggest cell-specific effects of Thr92Ala , and the 92Ala variant itself being responsible for the observed effects (22).

In conclusion, there is limited evidence that polymorphisms in thyroid hormone transporters and deiodinases (especially the combination of SNPs in MCT10 and DIO2) is associated with a preference for T4+T3 combination therapy.

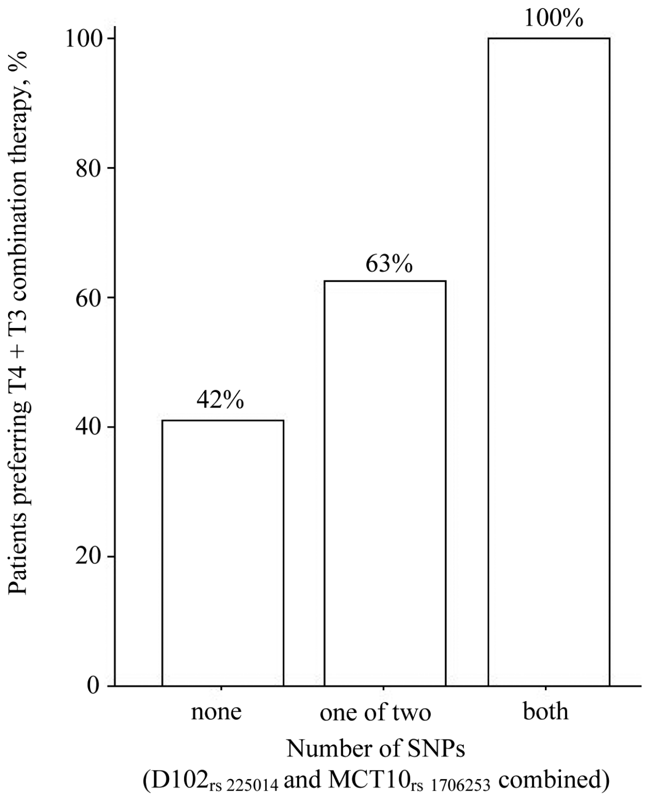

Figure 1
Preference of hypothyroid patients for T4+T3 combination therapy over T4 monotherapy as a function of the presence of polymorphisms in *DIO2* (rs225014) and *MCT10* (rs1706253). Trend tests indicate a significant dose-response relationship (reproduced with permission from Carle *et al*. Reference 34).

T4+T3 therapy: Is there a true effect on clinical practice?

The issue of T4+T3 combination therapy has an enormous impact on daily clinical practice, both in quantitative and in qualitative terms. There has been a steady increase in the use of T4+T3 combination therapy. In the period 2005–2011, the number of T4+T3 users in the Netherlands increased by 67% (39). To explain this huge rise, it was speculated that many subjects with vague nonspecific complaints searched the internet and consulted websites such as those of the Dutch 'Hypo but not Happy' group which recommends combination

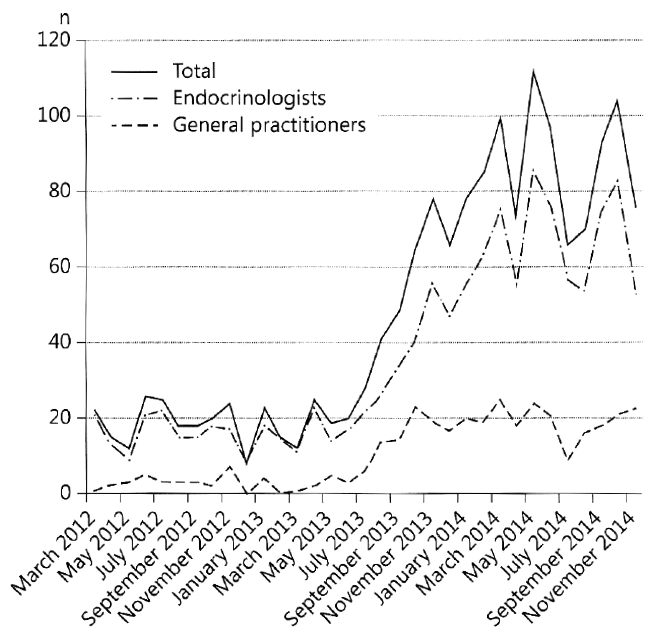

Figure 2
Number of applications for reimbursement of T4+T3 therapy in Denmark (reproduced with permission from Michaelsson *et al*. Reference 40).

therapy. Remarkably, in Denmark, sales of T3 increased 6 fold and of desiccated thyroid almost 2 fold between the first and the last quarter of 2013 (40). The number of applications for reimbursement of T4+T3 therapy rose rather abruptly 3.8 fold in July 2013–June 2014 compared to July 2012–June 2013 (Fig. 2), most likely due to increased focus in the media (40). Patients not any longer take for granted the explanation given by physicians why they are reluctant to prescribe combination therapy. The point is well illustrated by the book 'Stop the thyroid madness. A patient revolution against decades of inferior thyroid treatment' (41). The editor is Janie A. Bowthorpe, a thyroid patient activist, author, editor, website owner, blogger and speaker. She stepped into her activism when her life made a huge turnaround after 20 years of a T4-only, Synthroid nightmare. Janie's blog on April 2, 2017 said: Stupidity Award of the Year: the UK's NHS states that T3 has 'little or no clinical value' (42). Patients nowadays may demand combination therapy, often in an aggressive manner. Physicians in turn may feel threatened, and have to defend what they consider as good practice (43). It looks like the T4+T3 issue has become a real 'hype' (defined as something that, in particular thanks to media attention, functions as fashionable or sensational within certain circles). The uproar on the combination therapy is present in the USA, Canada, Australia and many but not all European countries. It would be interesting to evaluate why in some countries, like Greece, T4+T3 therapy has not become an issue.

In the meantime, the Danish study is providing much information on what is going on in real life (Table 7) (40). Available data suggest that the combination therapy is taken in particular by middle-aged well-educated women with many different symptoms (69% had ≥6 symptoms). The medication is prescribed mostly by general practitioners, and dose adjustments are done by about a quarter of the patients themselves. TSH during T4+T3 therapy is rather often suppressed, and 84% of respondents describe a positive effect and 81% want to continue the combination therapy (40). Selection and other bias may have influenced the results of this Danish study, but could it be 'there is something rotten in the state of Denmark, in particular with regard to T4 monotherapy.'

The huge quantity of patients on thyroid hormone replacement therapy is relevant for the pharmaceutical industry, and they became interested in the combination therapy although so far this has not resulted in the development of a slow-release T3-preparation. But it has led to the introduction of low-strength T3-tablets of 5 µg, which are very helpful in dosing the T3-component of the combination therapy. An adverse effect of its heightened interest is the sudden price increase in the UK for a 20 µg generic T3 tablet from £0.16 to £9.22, leading to lack of T3 availability on the basis of cost (44, 45). This incident stands not alone. The past few years have seen a series of dramatic price hikes on essential off-patent medications (46). These actions, though arguably unethical, have so far not been found to be illegal (46). But legislation has passed the State of Maryland (USA) by the end of May 2017 prohibiting price gouging on essential off-patent or generic drugs. Firms may be prosecuted that engage in price increases in noncompetitive off-patent-drug markets that are dramatic enough to 'shock the conscience' of any reasonable consumer (46). Hopefully, the price of generic T3 will remain low.

One may ask how the professional societies responded to these emerging controversies over T4+T3 combination therapy. All guidelines do agree that T4 monotherapy remains the standard treatment of hypothyroidism (47). Only the European Thyroid Association has specific guidelines on the use of T4+T3 (14). To qualify for an experimental trial of 3 months combination therapy, patients should have persistent complaints despite normalized TSH values on L-T4 and despite psychological support to deal with the chronic nature of their disease, and co-existent autoimmune

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diseases should have been excluded. It is recommended that 1/20th of the daily T4 dose in µg would be the daily T3 dose in µg, and that the remaining T4 dose would be the usual T4 dose minus 3× the T3 dose (13). Thus, for a patient using 100 µg T4 on monotherapy, the dosages in the combination therapy would be 85 µg T4+5 µg T3 (that is a T4:T3 dose ratio of 17:1 by weight, close to the T4:T3 thyroidal secretion ratio of 16:1 by weight) (48). The replacement of 15 µg T4 by 5 µg T3 is in a ratio of 3:1, precisely the pharmacodynamic equivalence dose ratio between both hormones (28); in doing so, one may expect no or little changes in TSH when switching from monotherapy to combination therapy. The 2012 ETA guidelines were offered to enhance the safety of combination therapy and to counter its indiscriminate use (14). A recent 17-year observational population-based study from Scotland reports on the safety of long-term liothyronine use (49). Compared to T4-users, T3-users had no additional risk of atrial fibrillation, cardiovascular diseases, fractures or death; they had only an increased risk of new prescriptions for antipsychotic medication (hazard ratio: 2.26, CI: 1.64–3.11), proportional to the number of T3 prescriptions. The ATA 2014 guidelines state 'For patients with primary hypothyroidism who feel unwell on levothyroxine therapy alone, there is currently insufficient evidence to support the routine use of a trial of a combination of T4 and T3 therapy outside a formal clinical trial or $n=1$ trial' (50). As compared to the ETA, the ATA thus takes a conservative stand with regard to combination therapy. The ATA did a very large survey in early 2017 on hypothyroidism treatment among patients, which would be very helpful in gaining more insight on patient' perspectives (51). A statement from the British Thyroid Association in 2016 reads 'If a decision is made to embark on a trial of L-T4/L-T3 combination therapy in patients who have unambiguously not benefited from L-T4, then this should be reached following an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data. Such patients should be supervised by accredited endocrinologists with documentation of agreement after fully informed and understood discussion of the risks and potential adverse consequences' (52, 53). Recent Italian guidelines support the ETA and ATA guidelines. In addition, they mention Combined therapy may be indicated in thyroidectomized adult patients with persistent symptoms of hypothyroidism and postoperative serum T3 levels and FT3/FT4 ratio lower than their preoperative values during L-T4 monotherapy. The L-T4+L-T3 dose during combined therapy should be between 13:1 and 20:1 by weight. To avoid potential adverse events the starting dose should be about 17:1 (54).

In conclusion, T4+T3 combination therapy had and still has an enormous impact on clinical practice, both quantitatively and qualitatively. The number of T4+T3 users has multiplied in the last decade. Patients may demand combination therapy in an aggressive manner, and physicians may feel threatened, resulting in a strained patient-doctor relationship. Pharmaceutical interest led to the welcome introduction of low-strength T3-tablets of 5 µg, but also to an unethical price hike of 20 µg T3 tablets in the UK. All guidelines agree T4 monotherapy remains the standard treatment, but only the ETA provides detailed guidelines on indications, dosage and control of combination therapy.

T4+T3 therapy: Epicrisis

Due to progress in basic and clinical research, we now have a better but by no means full understanding why T4 monotherapy may not work in all patients and why T4+T3 combination therapy may work in some patients. It is biologically plausible that particular polymorphisms in thyroid hormone transporters and deiodinases are causally related to persistent complaints during T4 monotherapy, but proof that T4+T3 combination therapy will alleviate such complaints is lacking. The present uncertainty can only be solved by further research. The danger is that the present hype about the combination therapy, causing tensions between patients and physicians, will jeopardize efforts to identify which patients may benefit or will not benefit from T4+T3 therapy. Thyroid patient associations could be instrumental in keeping communication between patients and their physicians optimal. For instance, a study supported by the British Thyroid Foundation reports 'It was also felt by most patients that focusing only on having a normal thyroid hormone reading rather than symptoms and concerns is not a good way to measure patient well-being, and it often meant that discussion with their GP about improving their levothyroxine treatment did not happen' (55). In contrast, patients should acknowledge that 'Many clinicians may not agree that a trial of L-T4/L-T3 combination therapy is warranted in these circumstances and their clinical judgment must be recognized as being valid given the current understanding of the science and evidence of the treatments' (52, 53).

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