

RESEARCH ARTICLE

Reverse T₃ in patients with hypothyroidism on different thyroid hormone replacement

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Abstract

Background

Reverse T₃ (rT₃) is a biologically inactive form of T₃ (triiodothyronine), a thyroid hormone, that is created by peripheral 5 deiodination of T₄ (thyroxine) by type 1 and type 3 deiodinase enzymes (D1 and D3 respectively) and may block T₃ binding to the thyroid hormone receptor. Approximately 15% of patients on L-T₄ replacement therapy with a normalized thyroid-stimulating hormone (TSH) report experience continued fatigue and other hypothyroid symptoms; therefore, efforts are needed to understand why this occurs and how it can be corrected. Decades ago, endocrinologists realized that in patients with severe illnesses, rT₃ is typically high and T₃ is typically low; this was termed “euthyroid sick syndrome”. More recently, functional medicine and other doctors, have argued that high rT₃ is detrimental and can block T₃ from binding to the thyroid hormone receptor. Due to the lack of peer-reviewed publications on this topic, functional medicine doctors continue to rely heavily on rT₃ levels to treat patients that may have no other laboratory findings of hypothyroidism and often prescribe L-T₃-only preparations to patients in an effort to lower rT₃.

Methods

The initial rT₃ measurements done by liquid chromatography/tandem mass spectrometry (LC/MS-MS) were retrospectively analyzed from the initial blood tests in 976 consecutive patients, with symptoms of fatigue and treated for hypothyroidism, in a private Endocrinology practice. TSH, free T₃ and free T₄ were measured by electrochemiluminescence immunoassay (ECLIA). The upper limit of normal rT₃ (24.1 ng/dL) was used as a cut-off for results above the normal range.

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Results

The number of patients with rT_3 levels above normal range varied significantly with the type of thyroid hormone replacement prescribed. The highest rate of an elevated rT_3 was 20.9% (29/139) in patients taking T_4 alone. Nine% (31/345) of patients not taking thyroid hormone replacement had elevated rT_3 . Patients on all types of L- T_4 treatment had higher rT_3 levels than those not on L- T_4 treatment ($p < 0.00001$) and they also had a higher percentage of rT_3 levels above the cutoff of 24.1 ng/dL ($p < 0.00001$). Linear regression analysis showed rT_3 levels correlated with free T_4 and free T_3 levels and inversely with log TSH levels.

Conclusions

This study found elevated rT_3 levels in patients with symptoms of fatigue on various thyroid hormone replacements with the highest levels of rT_3 in those taking L- T_4 replacement alone and the lowest levels of rT_3 in those on preparations that contained L- T_3 alone.

1. Introduction

Under physiological conditions, T_4 (thyroxine) is primarily monodeiodinated to T_3 (3,3',5-triiodo-L-thyronine) or reverse T_3 (rT_3 ; 3,3',5'-triiodo-L-thyronine), depending on the energy or T_3 needs of the body [1]. T_3 is considered the active hormone because its affinity for thyroid hormone receptors is 15 times higher than T_4 , while rT_3 inhibits the effects of T_3 and T_4 without binding to nuclear thyroid hormone receptors [2–5]. The clinical significance of rT_3 has been debated since the 1970s, when the newly adopted “thyroid function test” allowed endocrinologists to realize that severe illness causes a reduction in T_3 and an increase in rT_3 [6]. Endocrinologists termed this “euthyroid sick syndrome” and noted that it was common in many types of chronic diseases, especially in patients hospitalized in intensive care units. Whether this is an adaptive response (to conserve energy) or a pathological response (where illness leads to reduced T_3 production below that what is needed, thus warranting thyroid hormone treatment) is still the subject of intense debate. Overall, it is viewed that these patients should not be treated with thyroid medication [7–9].

As for the clinical significance of rT_3 in thyroidal illness, the data is sparse. In 1977, Burman et al. developed one of the first rT_3 assays and demonstrated that its levels varied significantly based on a person's thyroid status (normal, hyperthyroid, and hypothyroid), but also based on the dosage of levothyroxine that patients received [10]. In particular, they showed that patients that were hypothyroid and receiving 0.05 mg per day of levothyroxine (suboptimal dosage) had below normal rT_3 levels, while patients receiving 0.4 mg per day (supraoptimal dosage) had above normal rT_3 levels, suggesting that knowledge of rT_3 levels could be useful in the management of hypothyroidism. However, commercial rT_3 assays were not available and the measurement of rT_3 was confined to research settings. In 1995, Burmeister et al.

published her evaluation of 246 patients whose rT_3 levels were measured while being treated in a university teaching hospital. She showed rT_3 levels varied tremendously and judged its measurement to be unreliable in distinguishing between hypothyroid sick patients and the euthyroid sick patients [11]. Even though this work looked at the variance of rT_3 levels in nonthyroidal illness, many in the field felt that this unreliability extended to thyroid illness, and it is currently viewed that the measurement of rT_3 is of little clinical use [12,13].

The authors believe this conclusion should be reevaluated for several reasons. Firstly, rT_3 measurements have recently become more accurate with the wide-spread use of mass-spectrometry in commercial laboratories [2] and are available at both Quest Diagnostics and Labcorp. Since rT_3 inhibits the action of the biological hormone T_3 at the T_3 receptor, knowledge of rT_3 levels is required to completely understand the effects of thyroid hormone administration [5,14]. Importantly, thyroid medication is the second most prescribed drug in the U.S. [15] and yet as many as 40–50% of patients with these medications do not take them as prescribed [16]. Furthermore, many patients turn to alternative doctors, including functional medicine doctors, for the management of thyroid illness. These doctors often measure rT_3 and use it to guide patient treatment. These providers have argued that high rT_3 is detrimental and can block T_3 from binding to the thyroid hormone receptor. With little peer-reviewed publications [17], these functional medicine doctors rely heavily on rT_3 levels to treat patients that may have no other laboratory findings of hypothyroidism and often prescribe them L- T_3 -only preparations to try to lower the rT_3 . Studies looking at rT_3 with valid assays are needed to determine the role of this hormone. Functional medicine doctors have proposed risk factors for elevated rT_3 levels including stress, depression, pain, inflammation, dieting and iron deficiency [17].

In this paper, we retrospectively analyzed initial rT_3 measurements from 976 consecutive patients seen by TCF from 2010 to 2021 in a private Endocrinology practice. Six hundred thirty-one patients were on varying types of thyroid hormone replacement and 345 patients were not on any thyroid hormone replacement.

2. Methods

2.1 Study population and methodology

The rT_3 measurements were retrospectively analyzed from initial blood tests along with other thyroid function tests from 976 consecutive patients seen by TCF from 2010 to 2021 in a private Endocrinology practice. Three hundred forty-five patients were not on thyroid hormones, 226 were on desiccated thyroid extract (DTE) (Armour thyroid, NP thyroid, Nature-throid and WP thyroid were the most common brands) and not synthetic thyroid hormones, 15 were on desiccated thyroid and L- T_3 , 138 were on desiccated thyroid and L- T_4 , 7 were on desiccated thyroid, L- T_3 and L- T_4 , 23 were on L- T_3 alone, 139 were on L- T_4 alone, and 83 were on L- T_3 and L- T_4 .

All patients had fatigue as one of their main symptoms and none had a severe chronic disease in which they would be considered “sick euthyroid.” All patients had rT_3 , free T_3 , free T_4 , anti-thyroid peroxidase (anti-TPO), and TSH measured, usually in the morning after their visit at either Quest Diagnostics or Labcorp. rT_3 at both laboratories were done by liquid chromatography/tandem mass spectrometry (LC/MS-MS). JW and ME. performed chart review and were not able to identify free T_3 , free T_4 , anti-TPO, and TSH in several patients during their chart review. The normal range for rT_3 at Labcorp was 9.1 to 24.1 ng/dL and Quest Diagnostics was 8.0 to 25.0 ng/dL. The cut-off for results above the range used the value of 24.1 ng/dL and these values were determined in euthyroid patients. TSH, free T_3 and free T_4 were measured by electrochemiluminescence immunoassay (ECLIA) with a range of 0.45–4.5 mIU/mL, 2.0 to 4.4 pg/mL and 0.82–1.77 ng/dL, respectively at Labcorp and 0.45–4.5 mIU/mL, 2.3–4.2 pg/mL and 0.8–1.8 ng/dL at Quest. Anti-TPO was done by chemiluminescence at Esoterix Laboratories (subsidiary of Labcorp) and Quest with a range of < 9.0 IU/mL at both laboratories.

2.2 Statistical analyses

Sub-analyses of the pairwise comparisons of the thyroid treatment groups, and significance of anti-TPO status within these groups were performed using Dunn’s test. The Wilcoxon rank-sum test was used to compare rT_3 levels between all

groups on L-T₄ treatment and all groups not on L-T₄ treatment. The chi-square test for homogeneity was used to compare the % of patients with rT₃ above range between all groups on L-T₄ treatment and all groups not on L-T₄ treatment. Pearson correlations between rT₃, free T₃, free T₄ and log TSH (to compensate for severe non-normality) levels were calculated and the significance of these (from zero) were determined by the appropriate t-test. The patients with circulating anti-TPO antibodies who had elevated rT₃ levels were compared to patients without these antibodies or who did not have them tested were compared by the Fisher's exact test.

2.3 IRB approval

The Charles R. Drew University of Medicine and Science (CDU) Institutional Review Board (IRB) approved this retrospective study under Exemption Category # 4 (45CFR46.104, category 4iii). The most recent approval date was January 3, 2024. The data was accessed for research purposes on January 18, 2022, and accessed again on January 1, 2024. The authors had access to information that could identify individual participants during or after data collection, however the CDU IRB approved the use of PHI as involving no more than minimal risk and did not require a waiver of consent.

2.4 Patient and public involvement

Patients and the public were not involved in the design or the interpretation of the study although patients in this study have informed the investigators about the importance of measuring rT₃.

3. Results

[Table 1](#) shows the Mean, SD, and N of rT₃, free T₃, free T₄ and TSH in the study population. 810 patients were female and 166 were male. Overall, 107 (11.0) patients had an elevated rT₃ value. The proportion of patients with above normal rT₃ values was found to be significantly affected by treatment ([Fig 1](#)) with the highest rate of elevated rT₃ in 20.9% (29/139) of patients taking T₄ alone. Nine percent (31/345) of patients not taking thyroid hormone replacement had elevated rT₃ values. In contrast, only 3.5% (8/226) of patients taking desiccated thyroid hormone had above normal rT₃ values, compared to 12% (10/83) of patients taking a T₃-T₄ combination and 17.4% (24/138) of patients taking desiccated thyroid-T₄ combination. The proportion of patients taking desiccated thyroid hormone replacement with above normal rT₃ levels was found to be significantly less than all other groups except for patients taking a desiccated-T₃ combination ([Fig 1](#)). [Table 2](#) shows the P-values of pairwise comparisons of the groups using Dunn's test.

[Table 3](#) shows that patients on all types of L-T₄ treatment had higher mean rT₃ levels than those not on L-T₄ treatment ($p < 0.0001$) and a higher percentage of rT₃ levels above the cutoff of 24.1 ng/dL ($p < 0.0001$). Linear regression analysis ([Table 4](#)) showed rT₃ levels strongly correlated with free T₄ and free T₃ levels and inversely with log TSH levels.

The presence of anti-TPO antibodies was assessed in 712 of these patients with 212 patients having anti-TPO antibodies above the range and 500 patients not having elevated levels. For the patients not on thyroid hormone replacement, 41 of 345 patients had anti-TPO antibodies and 304 patients did not have antibodies or were not assessed. For the patients on thyroid hormone replacement, 170 of 631 patients had anti-TPO antibodies and 461 patients did not have antibodies or were not assessed. For most thyroid treatment regimens, the proportion of patients with above normal rT₃ levels did not vary significantly with TPO antibody status, except for patients taking desiccated thyroid hormone replacement. For this

Table 1. Mean, SD, N of rT₃ (ng/dL), Free T₃ (pg/mL), Free T₄ (ng/dL) and TSH (μIU/mL).

	rT ₃	FreeT ₃	FreeT ₄	TSH
Mean	16.4	3.2	1.2	2.3
SD	6.6	1.0	0.3	4.3
N	976	452	455	513

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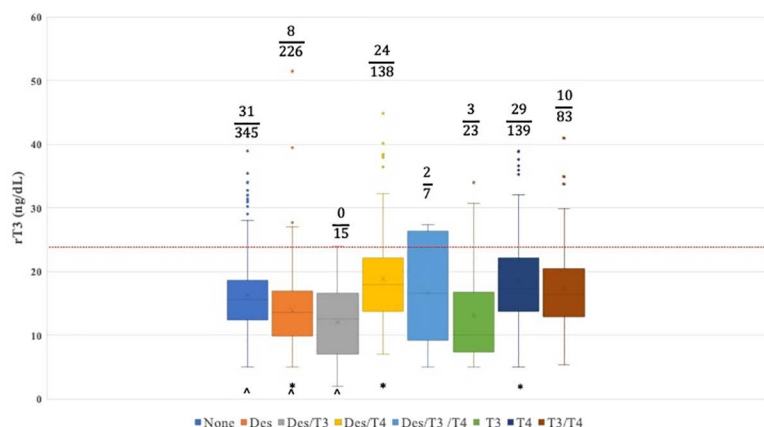


Fig 1. Box and whisker plot of patient rT_3 based on the type of thyroid hormone replacement. None= Not taking any thyroid hormone replacement; Des= Desiccated thyroid hormone replacement; Des/ T_3 = Desiccated thyroid- T_3 combination; Des/ T_4 = Desiccated thyroid- T_4 combination; Des/ T_3/T_4 = Desiccated thyroid- T_3 - T_4 combination; T_3/T_4 = T_3 - T_4 combination. * $P < 0.05$ compared to none. ^ $P < 0.05$ compared to T_4 .

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Table 2. P-values of pairwise comparisons of the groups using Dunn's test.

	None	Des	Des/ T_3	Des/ T_4	Des/ T_3/T_4	T_3	T_4	T_3/T_4
None	—	0.01	0.22	0.01	0.08	0.52	3×10^{-4}	0.39
Des	0.01	—	0.46	6×10^{-6}	1×10^{-3}	0.03	1×10^{-7}	5×10^{-3}
Des/T_3	0.22	0.46	—	0.08	0.03	0.14	0.05	0.16
Des/T_4	0.01	6×10^{-6}	0.08	—	0.45	0.61	0.46	0.29
Des/T_3/T_4	0.08	1×10^{-3}	0.03	0.45	—	0.33	0.63	0.22
T_3	0.52	0.03	0.14	0.61	0.33	—	0.38	0.90
T_4	3×10^{-4}	1×10^{-7}	0.05	0.46	0.63	0.38	—	0.09
T_3/T_4	0.39	5×10^{-3}	0.16	0.29	0.22	0.90	0.09	—

None= Not taking any thyroid hormone replacement; Des= Desiccated thyroid hormone replacement; Des/ T_3 = Desiccated thyroid- T_3 combination; Des/ T_4 = Desiccated thyroid- T_4 combination; Des/ T_3/T_4 = Desiccated thyroid- T_3 - T_4 combination; T_3/T_4 = T_3 - T_4 combination.

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Table 3. Effect of L- T_4 treatment on rT_3 levels.

	All groups on L- T_4 treatment	All groups not on L- T_4 treatment	p-value
rT_3 (Mean \pm SD)	18.4 \pm 7.1	15.2 \pm 6.0	<0.00001*
% with $rT_3 > 24.1$	65/367 (17.7%)	42/609 (6.9%)	$p = 1.63 \times 10^{-7\wedge}$

*Wilcoxon rank-sum test, ^chi-square test for homogeneity

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Table 4. Correlations between rT_3 levels and other hormones.

	Free T_3	Free T_4	Log TSH
Pearson correlation	0.184	0.624	-0.298
p	0.0001	<0.0001	<0.0001

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group, 0% (0/67) of the patients with circulating anti-TPO antibodies had elevated rT_3 levels, while 7% (6/88) of patients without these antibodies or who did not have them tested had elevated rT_3 levels ($p=0.037$). For those taking thyroid hormone preparations besides DTE, 20 of 103 had anti-TPO antibodies and 49 of 270 did not have antibodies or were not assessed ($p=NS$).

4. Discussion

The initial rT_3 measurements were retrospectively analyzed from 976 consecutive patients before management by TCF. Patients with hypothyroidism generally sought out TCF due to dissatisfaction with their current management, including persistent fatigue despite being on what their previous provider considered adequate treatment. We did not track what type of providers treated these patients but posit that it included primary care providers, other Endocrinologists, functional medicine doctors, mid-level health care providers (i.e., physician assistants, nurse practitioners, etc.), and holistic doctors. The high prevalence of patients treated with thyroid preparations other than $L-T_4$ reflects the heterogeneity of providers as well as the dissatisfaction with conventional treatment among this group of patients. We found that the proportion of patients with above normal rT_3 values varied significantly depending on the type of thyroid medication they were taking. This proportion was higher in patients taking preparations containing $L-T_4$ but was lower in patients taking desiccated thyroid or $L-T_3$ preparations. Groups that took preparations containing desiccated thyroid and/or $L-T_3$ with $L-T_4$ had a larger proportion of patients with above normal rT_3 values than groups that took the same preparations without $L-T_4$. The group taking $L-T_4$ alone had the highest percentage of elevated rT_3 values at 20.9%. Our results are consistent with previous findings that in short-term settings, $L-T_4$ can raise rT_3 levels [18] and $L-T_3$ can lower rT_3 levels [19], although these effects need to be verified prospectively in larger, newer studies.

Although the majority of patients do have a satisfactory response on $L-T_4$ therapy, up to 15% of properly treated hypothyroid patients fail to achieve a sense of well-being on levothyroxine and continue to have hypothyroid symptoms despite normalized thyrotropin levels. The causes of patients' lack of well-being have been discussed including by the American Thyroid Association Task Force on Thyroid Hormone Replacement [20] and include decreased serum T_3/T_4 ratio and alterations in the inherited *D/O2* polymorphism [20,21]. Combination therapy with $L-T_4$ plus $L-T_3$ has been found to be helpful in some, but not all studies [22]. One review proposed that some patients likely have a compounding condition that increases the likelihood of developing symptoms [21]. Could this be elevated rT_3 levels?

It is estimated that about 10–29% of patients with hypothyroidism use DTE as their primary thyroid hormone replacement medication in the US [23–25] despite concerns about the potential risk of thyrotoxicosis associated with DTE use [26,27]. Tolesa et al. surveyed the content of online posts from three popular hypothyroidism forums from patients currently taking DTE and found the most frequently described benefits associated with DTE use were an improvement in symptoms (56%) and a change in overall well-being (34%) [25].

A 2013 crossover study by Hoang and colleagues compared levothyroxine to a DTE preparation (Armour Thyroid) [28]. They used 70 patients that were enrolled in a military healthcare system, were on a stable dose of levothyroxine, and had a normal TSH before the study started. During the study, patients lost an average of three pounds during once-a-day Armour Thyroid therapy, and at the conclusion of the study, they found that 49% (34/70) preferred Armour Thyroid, 19% (13/70) preferred levothyroxine, and 33% (23/70) had no preference. Importantly, patients had thyroid function tests performed at the beginning of the study and they compared the patients' initial rT_3 levels to ultimate preference for thyroid medication. The baseline (on $L-T_4$) rT_3 level was 32.3 ± 12.9 ng/dL that stayed elevated at 31.4 ± 12.1 ng/dL after receiving $L-T_4$ but decreased to 21.1 ± 10.9 ng/dL ($p < 0.001$) following DTE treatment. rT_3 was measured by RIA at Radim in Pomezia, Italy with the range not given. This prospective cross-over study supports that DTE lowers rT_3 levels and is preferred by the majority of patients, although causality between rT_3 levels and patient preference for DTE was not established and needs to be examined in larger studies.

This study was confirmed by Shakir and colleagues [29] who randomized patients to $L-T_4$, $L-T_4 + L-T_3$, or DTE for 22 weeks. They found quality of life outcomes were similar among hypothyroid patients taking DTE vs $L-T_4 + L-T_3$ or

L-T₄. However, those patients that were most symptomatic on L-T₄ preferred and responded positively to therapy with L-T₄+L-T₃ or DTE. In support of our data, rT₃ levels were highest in L-T₄ treatment, lowest in DTE-treated patients and in the middle for those on L-T₄+L-T₃ ($p < 0.001$). They did not find any difference between the rT₃ levels in autoimmune and non-autoimmune patients and did not analyze if the rT₃ levels correlated with symptoms.

The strengths of our study include a large number of subjects taking different types of thyroid preparations, similar to what many patients are taking in real world settings. Another strength is the measurement of rT₃ levels with an accurate mass-spectrometry methodology. The limitations of the study include a potential bias of subjects more inclined to taking L-T₄+L-T₃ and DTE preparations than would be seen in a typical Endocrinology clinic. However, our findings of the highest rT₃ levels in those on L-T₄ alone would favor higher rT₃ levels in a typical Endocrinology clinic in which most patients are on L-T₄ alone. Other limitations include the retrospective nature of the study, lack of objective measurements of fatigue and quality of life (QOL), and the lack of a causal relationship between rT₃ levels and fatigue and QOL symptoms, a limitation that should be addressed in future studies.

5. Conclusions and future studies

In conclusion, our study found elevated rT₃ levels in patients with symptoms of fatigue on various thyroid hormone replacements with the highest levels seen in patients on L-T₄ replacement alone and the lowest levels seen in those on preparations that contain L-T₃, including DTE. It would be premature to conclude that elevated rT₃ levels are the cause of the symptoms in approximately 15% of patients on L-T₄ replacement, and further studies are needed to understand the relationship better. Nine percent of patients not taking thyroid hormone replacement in our study had elevated rT₃ values.

Further studies are needed to understand the implications of elevated rT₃ values in patients both on and off thyroid hormone replacement and whether its measurement will be useful in clinical practice to guide thyroid hormone replacement. Randomized control studies are needed to determine if treatment with DTE or L-T₃ in patients with elevated rT₃ values will both lower elevated rT₃ values and improve measurements of fatigue and QOL. Additional further studies are needed to determine what factors raise rT₃ values and if correcting them improves hypothyroid symptoms. Overall, our study will open new avenues of thyroid disease research that could lead to improvement in clinical outcomes in patients with hypothyroidism.

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Raw data used for the findings is available in the following public repository:

<https://www.ebi.ac.uk/biostudies/studies/S-BSST1973>

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Investigation: Theodore Friedman.

Methodology: Theodore Friedman, Martin L. Lee.

Supervision: Theodore Friedman.

Writing – original draft: Theodore Friedman, Julian B. Wilson.

Writing – review & editing: Theodore Friedman, Julian B. Wilson, Thanh D. Hoang, Martin L. Lee, Ma'ayan Epstein.

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