Variation in the Biochemical Response to L-Thyroxine Therapy
and Relationship with Peripheral Thyroid Hormone Conversion

Efficiency

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Abstract

Objective: Several influences modulate biochemical responses to weight-adjusted levothyroxine (L-T4) replacement dose. We conducted a secondary analysis of the relationship of L-T4 dose to TSH and FT3, using a prospective observational study examining the interacting equilibria between thyroid parameters.

Methods: We studied 353 patients on steady-state L-T4 replacement for autoimmune thyroiditis or after surgery for malignant or benign thyroid disease. Peripheral deiodinase activity was calculated as a measure of T4-T3 conversion efficiency.

Results: In euthyroid subjects, median L-T4 dose was 1.3 µg/kg/d (IQR 0.94,1.60). Dose was independently associated with gender, age, aetiology and deiodinase activity (all p<0.001). Comparable FT3 levels required higher L-T4 doses in the carcinoma group (n=143), even after adjusting for different TSH levels. Euthyroid athyreotic thyroid carcinoma patients (n=50) received 1.57 µg/kg/d L-T4 (IQR 1.40,1.69), compared to 1.19 µg/kg/d, (0.85,1.47) in autoimmune thyroiditis (p<0.01, n=75,) and 1.08 µg/kg/d, (0.82,1.44) in patients operated for benign disease (p< 0.01, n=80). Stratifying patients by deiodinase activity categories of <23, 23-29 and >29 nmol/s revealed an increasing FT3-FT4 dissociation; the poorest converters showed the lowest FT3 levels in spite of highest dose and circulating FT4 (p<0.001). An L-T4-related FT3-TSH disjoint was also apparent; some patients with fully suppressed TSH failed to raise FT3 above the median level.

Conclusions: These findings imply a) thyroid hormone conversion efficiency is an important modulator of the biochemical response to L-T4, b) FT3 measurement may be an additional treatment target, and c) L-T4 dose escalation may have limited success to raise FT3 appropriately in some cases.
Introduction

Thyroid disorders are among the most prevalent diseases in the western world, affecting as many as one out of seven adults (1). They are frequently associated with overt thyroid dysfunction, particularly various degrees of hypothyroidism that require thyroid hormone replacement (2,3). This is mainly done by administration of synthetic levothyroxine (L-T4), which is a well established, convenient, safe and inexpensive treatment modality (4,5).

However, this does not accurately reflect the natural direct secretion pattern of both thyroid hormones, triiodothyronine (T3) and thyroxine (T4), by the thyroid gland (6,7). Unlike other drugs, dosing of L-T4 is not fixed, but has to be titrated according to individual needs. Dose adequacy is mainly defined by reference to suitable biochemical standards, particularly TSH (8). This parameter has evolved into the main treatment target to be monitored and kept within an assumed euthyroid range (9). A number of studies have attempted to predict T4 requirement and various regimes for a starting dose have been proposed based on an average of 1.6 µg/kg BW or by more refined weight- or BMI-related algorithms (10-16).

While TSH measurement has dominated procedural management of thyroid replacement by its apparent ease and good standardisation a disturbingly high proportion of patients remains unsatisfied with the treatment they receive (17,18). This has prompted some authors including our group to question the validity of relying on the TSH level as the sole measure of dose adequacy in L-T4 treated patients (19-21). We have shown that the homeostatic equilibria between TSH and peripheral thyroid hormones are modulated by various influences such as age, body mass and the treatment modality itself (22). As a controlling element the effective TSH level derived in a healthy normal population cannot necessarily be inferred to be equally optimal for a given patient on L-T4 medication, because the constitutive equilibria between TSH and thyroid hormones, especially FT3 differ in health and disease (22).
In the present analysis, we examined the relationship of L-T4 dose with clinical categories and biochemical outcomes such as TSH, FT4 and FT3 levels. We sought to define the interaction between TSH and the FT3 target and also to analyse the influences of modulators such as gender, age, disease category or the efficiency of T3 conversion from T4.

Subjects and methods

Study design and objective

An open prospective observational study (ClinicalTrials.gov NCT01969552) was conducted at the Department of Nuclear Medicine at Klinikum Luedenscheid, Germany between July 2013 and February 2014, and approved by the Ethics Committee of the University of Muenster, Germany. Participants gave written informed consent.

The present secondary analysis is restricted to the subgroup of patients on steady L-T4 treatment, examining dose requirements of L-T4 including conditioning modulators, thyroid hormone conversion efficiency and relationships with biochemical outcomes such as TSH, FT4 and FT3 levels. The primary study outcome, the analysis of the interacting equilibria and interrelations between thyroid parameters under various conditioning influences such as gender, age, body mass, L-T4 treatment has been reported (22).

Patients

The original study involved 1912 adult patients who were consecutively seen, free of severe comorbidity and provided written informed consent. For this subgroup analysis, 353 patients on thyroid hormone replacement meeting the following criteria were included, seen as outpatients, presenting in a controlled functional state (FT4 ≥ 10 pmol/l and TSH ≤ 4 mU/l), and having reached steady state on a constant L-T4 medication. Although infrequently seen in an ambulatory setting, patients with severe non-thyroidal illness or potentially interfering comorbidities were ineligible to participate in the study. This
exclusion extended to other conditions and use of comedications that may interfere with
the resorption or measurement of thyroid hormones or interfere with pituitary TSH.

Patients with T3/T4 combination therapy (n=9), anti-thyroid drug use (n=99),
hypothalamic/pituitary diseases (n=5) or pregnancy (n=3) were excluded before analysis.

Diagnostic procedures included a detailed history, physical examination, standardised
questionnaire documenting gender, age, height, weight, smoking habits (75% answered),
prior surgery or radioiodine treatment, thyroid medication (brand, dosage, duration, time of
intake), other drugs, laboratory tests (FT3, FT4, TSH, and, if autoimmune thyroiditis was
suspected or to be excluded, TPO-Ab or TSH-R Ab) and thyroid imaging.

**Laboratory methods**

TSH, FT3 and FT4 were measured with an automated direct chemoluminescence method
(Advia Centaur XP, Siemens Healthcare Diagnostics, Erlangen, Germany). TSH is
traceable to the 3rd International Standard for TSH (WHO, IRP 81/565). A TSH range from
0.006 to 160 mU/l was linear, and CVs of inter-assay imprecision ranged from 0.9% to
2.4%. Reference intervals were laboratory-established and pre-evaluated for the local
population, using 10 - 23 pmol/l for FT4, 3.1 - 6.8 pmol/l for FT3, and 0.4 - 4.0 mU/l for
TSH (23).

Thyroid peroxidase antibodies (TPO-Ab) were determined by a competitive
chemoluminescence method (ADVIA Centaur XP, Siemens Healthcare Diagnostics,
Erlangen, Germany, reference range < 60 U/mL) and TSH-receptor antibodies (TSH-R Ab)
by competitive ELISA (Euroimmun AG, Lübeck, Germany, reference range <2 U/L).

**FT3-FT4 ratio and calculated deiodinase activity**
As measures of conversion efficiency, we calculated 1) the FT3-FT4 ratio by simple division of both parameters in pmol/l, and 2) the sum activity of peripheral deiodinases (SPINA-GD, termed “deiodinase activity” thereafter, nmol/s) from equilibrium levels of FT4, FT3 and estimated constant parameters for plasma protein binding, distribution and elimination with 

\[
\hat{G}_D = \frac{\beta_{31}(K_{M1} + [FT_4])(1 + K_{30}[TBG])[FT_3]}{\alpha_{31}[FT_4]} \text{ nmol/s},
\]

as previously described (20,21,24). Although the two measures are closely related in the linear part of the substrate relationship defined by Michaelis-Menten kinetics, only the more complex formula \( (G_D) \) accounts for the saturation kinetics of the enzyme.

In addition to using estimated deiodinase activity as a continuous variable, we divided deiodinase activity in three distinct categories defining poor (<23 nmol/s), intermediate (23 to 29 nmol/s) or good converters (>29 nmol/s). The cut-offs were pre-specified based on observations in L-T4-treated patients vs healthy untreated subjects and in low (< 5 ml) vs higher thyroid volumes (22). They approximate turning points in the relationship between deiodinase activity and FT3 defining a central region with a derivative of about 0 and low or high regions with steeper slopes.

Thyroid ultrasound and scintigraphy

Thyroid volume was sonographically (10 MHz transducer) determined according to the ellipsoid formula. Reference values were <18 ml for females and <25 ml for males. A volume <1 ml was considered athyreotic. Larger nodules were further examined by scintigraphy.

Statistical methods
Descriptive data are reported as median plus interquartile range (IQR). We used Wilcoxon’s rank sum or chi square test in case of categorical variables for comparison of baseline characteristics. Correlations are based on Pearson’s product-moment where suitable or Kendall’s tau. Multiple variables and conditional influences were analysed by a generalized linear model (GLM) and approximated by a linear regression function over restricted intervals. Beta coefficients were derived from a linear model. TSH was used after logarithmic transformation. We tested for collinearity in the models using the variance inflation factor. A GLM with a binomial function (logistic regression) was used to assess success rates of L-T4 dose for reaching a TSH or FT3 target and create dose-related probability plots. Relative proportions were statistically compared by receiver operating characteristic curves and Delong’s test. P values < 0.05 were considered significant for all tests. Statistical analyses were performed using Deducer (version 0.7-7) and the R statistical package (Mac version 3.1.2) (25,26).

Results
The present analysis comprises 353 patients in a stable controlled non-hypothyroid state on thyroid hormone replacement with L-T4. Patient characteristics are shown in Table 1. Of the total study group, 304 patients were euthyroid according to FT4, 342 according to FT3 and 216 according to TSH, based on their respective reference intervals with all displaying clinically satisfactory levels of medication.

Dose requirements associated with biochemical euthyroidism (n= 208) defined by the reference ranges of all three parameters varied widely from 25 to 275 (mean 98, median 100 (IQR 75, 125) µg/d L-T4 or 0.3 to 2.2 (mean 1.2, median 1.3 (IQR 0.94, 1.60) µg/kg BW/d. In univariate linear models, L-T4 dose in the treated euthyroid panel was
significantly associated with gender, age, body mass index, aetiology of disease, T3-T4 ratio, calculated deiodinase activity (all p<0.001), but not with TSH (p=0.94). The influences remained independently predictive in a multivariable model (Table 2).

TSH levels in the euthyroid range were unrelated to any of the above influences except disease category (p=0.003), as might be expected considering the lower TSH target in malignant disease. Deiodinase activity was positively associated with thyroid volume (tau = 0.23, p<0.001, n=208), but inversely correlated with weight adjusted L-T4 dose (r= -0.37, p<0.001, n=208).

In a biochemically defined euthyroid state excluding subclinically hyperthyroid subjects, athyreotic thyroid carcinoma patients, received significantly higher doses of L-T4 (1.57 (IQR1.40, 1.69) µg/kg BW/d, n=50) than patients with autoimmune thyroiditis (1.19 (IQR 0.85, 1.47) µg/kg BW/d, n=76, p<0.001) or benign thyroid disease post surgery (1.08 (IQR 0.82, 1.44) µg/kg BW/d, n=80, p<0.001). Furthermore, after adjusting for differing levels of TSH suppression in a linear model the weight adjusted L-T4 dose was higher in athyreotic carcinoma patients, compared to autoimmune thyroiditis or benign disease (p<0.001, Fig. 1a). Similarly, the dose required to achieve the same FT3 concentration was higher in the carcinoma group (p<0.001, Fig. 1b).

Median thyroid volume was 0 ml (IQR 0, 0 ml) in carcinomas, 7 ml (IQR 4, 11 ml) in autoimmune thyroiditis and 6 ml (IQR 3, 8 ml) in benign goitre post surgery. The weight adjusted L-T4 dose was inversely correlated with thyroid volume in the three diagnostic groups (r= -0.22, p=0.002, n=208).

Three distinct categories of conversion efficiency were defined (s. Methods) as follows, poor converters < 23 nmol/s, intermediate converters 23 to 29 nmol/s and good converters >29 nmol/s deiodinase activity. The poor converters reached significantly (p<0.001) higher
FT4 concentrations in the circulation than intermediate or good converters, but at the same
time showed significantly (p<0.001) lower absolute FT3 levels, compared to the other two
groups (Fig. 2). Whilst the FT3-FT4 dissociation was apparent in all three disease entities,
it was most pronounced in the carcinoma group (n=143) (Fig. 2). The latter group showed
the highest proportion of poor converters (Fig. 2). The converter groups were similar
(p>0.1) in their age, BMI, weight adjusted L-T4 dose and TSH levels except for men being
overrepresented in the good converter group (p<0.01). Converter categories of the
carcinoma group were comparable (p=0.42) in their thyroid residual volumes, which were
below 1 ml in 96% of all cases. In contrast, in the combined group of benign diseases
converter status was significantly associated with thyroid volume (4 (2, 8) vs 7 (4, 11) vs 8
(5, 12) ml, p=0.009). Thyroid volumes differed between the carcinoma group and the
benign diseases (p<0.001), but not between autoimmune thyroiditis and goitre post
surgery (p=0.25, Table 1).

A given weight-adjusted dose suppressed the TSH below the lower reference limit (<0.4
mU/l) in a higher proportion of carcinoma patients than it raised their FT3 level above the
median level typical of the euthyroid controls (>5 pmol/l) (Fig. 3 a, b). Conversely, much
lower doses reached a target of a fully suppressed TSH, compared to the FT3 median
(Fig. 3 a, b). The same tendency is true for a more modest target below 1 mU/l for TSH in
autoimmune thyroiditis or benign disease post surgery, although variation was higher in
this panel (Fig. 3 c, d). Overall, a significantly higher proportion of patients achieved TSH
suppression, compared to FT3 above median by Delong’s test employing receiver
operating characteristic curves (p<0.001).
**Discussion**

In this cohort, dose requirements for L-T4 treated patients varied in a large euthyroid panel and were associated with many influences including gender, age, disease category and thyroid hormone conversion efficiency. However, not all of the treatment conditions necessarily aim at a biochemically euthyroid thyroid state as a comprehensive therapeutical goal, as defined by maintaining the respective reference ranges of all three parameters TSH, FT4 and FT3. Particularly, in the treatment of thyroid carcinomas, for many patients in our sample the target was a lower or suppressed TSH below the reference range, which, as a consequence, raised FT4 levels above the upper reference range in a proportion of these patients. At both comparable levels of TSH suppression or similar FT3 concentrations, athyreotic thyroid carcinoma patients were taking a higher weight-adjusted dose of L-T4. Three remarkable and linked observations from this study were a) a dissociation between FT3 and FT4, b) an apparent disjoint between TSH and FT3, and c) an inverse association between L-T4 dose and conversion efficiency.

The present study was a cross-sectional secondary analysis, not involving a randomised design. As previously reported in a separate communication (22), the primary aim of this prospective observational study was to analyse further the interacting equilibria. While introducing some uncontrolled variations, this allowed for the study of a broader natural spectrum of responses, as observed in consecutive patients. FT3 or FT4 measurements were not compromised in any way by problematic conditions such as the non-thyroid illness syndrome, as the study was conducted in a cohort of otherwise “healthy” out-patients without relevant comorbidity. There was no evidence for a potential bias stemming from a variable time interval between L-T4 intake and blood sampling, which might result in an expected slight temporary elevation of circulating FT4 concentrations, as previously
discussed (22). There were neither linear (p=0.27) nor non-linear (p=0.28) relationships with deiodinase activity.

In L-T4 treatment equilibria typical of the healthy state were found not to be invariant, but profoundly altered (22). Here we disclose further consequences that are associated with alterations in the regulatory patterns in patients under L-T4 therapy. In particular, one aspect relates to L-T4 dose and conversion efficiency. We estimated T4-T3 conversion by calculating the sum activity of peripheral deiodinases (see Methods). The measure is similar to the FT3-FT4 ratio, albeit more precise wherein it accounts for non-linear enzyme saturation kinetics. However, it does not further differentiate global activity by type of deiodinase. Thus, the source of T3 or contribution of various tissues to the T3 plasma pool cannot be discerned. We found that a poor converter status was associated with a higher L-T4 dose and higher serum FT4 levels, but still lower absolute FT3 concentrations, compared to the more efficient converters. This paradoxically relates the higher T4 supply to a worsened rather than improved absolute FT3 level. This is not to say that increasing dose will not raise on average the FT3, but that the dose response varies widely among individuals, and conversion inefficiency in some patients may outweigh the dose effect in terms of achievable absolute FT3 concentrations. How can this be explained? A high L-T4 dose may not invariably remedy T3 deficiency owing to T4-induced conversion inefficiency, but could actually hinder its attainment through the inhibitory actions of the substrate itself and/or reverse T3 (rT3) on deiodinase type 2 activity (27). A study by Cettour-Rose et al. confirmed that rT3 when infused into rats inhibited deiodinase type 2 activity in the pituitary, cerebral cortex and brown adipose tissue, but, interestingly, this had not much impact on circulating T4, T3 and TSH concentrations in the animals (28). However, in this model the rT3 effect was studied under rather artificial conditions in the absence of an abundant T4 supply with elevated FT4 levels that characterizes the treatment situation. In contrast, another recent experimental study has shown that
escalating only the L-T4 dose fails to normalize serum T3 in the rat, and, as a result, irrespective of local variations by type of deiodinase, all organs examined such as the brain, liver and skeletal muscle were hypothyroid at the tissue level in the presence of a normal serum TSH (29). This study suggest ubiquitination may be the limiting factor for T4 alone to restore true tissue euthyroidism in the rodent (29). Lack of TSH stimulation and the absence or functional deficiency of the thyroid gland may also impair T4-T3 conversion (30). Another important consideration is that, just as FT4 and FT3 dissociate under L-T4 therapy, so do TSH and FT3. While a high proportion of patients was able to achieve a target of a suppressed TSH below the lower reference limits or a TSH value <1 mU/l in autoimmune thyroiditis, their FT3 levels at the same time frequently remained below the median FT3 level found in normal subjects. The situation differs from conditions where L-T4 absorption may be impaired and, as a consequence, elevated TSH levels persist (31-33). Thus, not even an L-T4 dose where TSH is fully suppressed and FT4 by far exceeds its upper reference limit can guarantee above average FT3 levels in these patients, indicating an FT3-TSH disjoint. As a consequence, while dose escalation may help some patients who maintained a sufficiently efficient thyroid hormone conversion to raise their FT3 for euthyroidism and well being, the strategy may not be invariably successful in all patients. In two studies, approximately 15% of athyreotic patients could not even raise their FT3 above the lower reference limit on L-T4 (19,20). Another controlled follow-up study after hemithyroidectomy for benign euthyroid goitre suggests that this deficiency may have unwanted clinical consequences. In this study, weight gain after two years in association with a lowered thyroid function within the laboratory reference range was interpreted as a clinical manifestation of a permanently decreased metabolic rate (34). L-T4 dose requirements have been well studied and various regimes based on weight, BMI or more refined algorithms have been proposed to put patients on a presumed adequate dose from the very beginning (10-13,14-16,35-39). Useful as these algorithms
may be for average predictions and initial guidance in the general population, they do not
take into account individual variations in the response to L-T4, such as conversion
efficiency. Dosing strategies solely based on a TSH definition of euthyroidism neglect the
important role of FT3, which has recently emerged as an equally significant parameter in
defining thyroid physiology (20,22,29,30,40,41). Central and peripheral regulatory
mechanisms do not constitute divided levels of control, as has previously been assumed.
Rather they are integrated via feed-forward control of deiodinase activity by TSH and
operate jointly to maintain T3 homeostasis as an overarching goal (30).
While acknowledging the role of genetically determined differences in deiodinase activity
affecting conversion rates, the poor converter status described here appears to emerge
mainly as a consequence of the T4 mono-therapy itself, induced by the mechanisms
discussed above (42-45). Compared to untreated subjects, deiodinase activity and
conversion efficiency tends to be diminished in L-T4 treatment (20,22). However, individual
pre-treatment measurements were not available for comparison. We found conversion
inefficiency to be significantly correlated with low residual thyroid volume and most
prevalent in athyreotic patients. However, differences in deiodinase activities were also
apparent in the absence of a functioning thyroid gland within the group of thyroidectomised
carcinoma patients. Overall, patients differ widely in the degree of the conversion
impairment they suffer. This, in turn, may influence their dose requirements of L-T4, and,
at a comparable weight adjusted L-T4 dose, their levels of TSH suppression and
circulating FT3 concentrations.

We speculate that L-T4 induced conversion inefficiency could prevent some vulnerable
subjects from reaching true tissue normality on T4 mono-therapy alone. Those were not
analysed separately in the numerous earlier T3/T4 trials and could be possible candidates
for a combined T3/T4 treatment option, as recognized by some authors and the guidelines of the European Thyroid Association (46,47).

As a limitation, this study addresses biochemical treatment responses, but did not evaluate patient reported outcomes or biomarkers of thyroid hormone action. Whether conversion efficiency and the resulting differences in relationships between TSH, FT4 and FT3 are clinically useful markers of dosing inadequacy requires further well-designed prospective studies. Patient satisfaction, complaints and symptoms play an essential part in the clinical assessment. However, owing to considerable inter-individual variation these measures apparently lack statistical power in a trial setting and have not been clearly linked to prognosis. For example, even a change in thyroid function as profound as the transition from the hypothyroid to the euthyroid state may be associated with only modest improvements in thyroid-related quality of life measures in patients with autoimmune thyroiditis (48). As a result, a trial size of several thousand subjects may be required to produce a credible result with adequate discriminatory power. Additionally, the exact outcome would depend on the overall makeup of the panel as regards the mixture of T4-T3 conversion capabilities. Possible long-term consequences of the observed biochemical alterations such as the altered FT3-FT4 ratio are also presently unknown.

The findings of the present study have several clinical implications. Firstly, they recognize thyroid hormone conversion efficiency, as defined by the calculated global deiodinase activity or more simply the T3-T4 ratio, is an important determinant of L-T4 dose requirements and the biochemical response to treatment. Secondly, in view of a T4-related FT3-TSH disjoint FT3 measurement should be adopted as an additional treatment target. Thirdly, in cases where an FT3-FT4 dissociation becomes increasingly apparent following dose escalation of L-T4 an alternate treatment modality, possibly T3/T4 combination
therapy, should be considered, but further randomized controlled trials are required to
assess the benefit versus risk in this particular group.

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Declaration of Interest

JWD is co-owner of the intellectual property rights for the patent “System and Method for
Deriving Parameters for Homeostatic Feedback Control of an Individual” (Singapore
Institute for Clinical Sciences, Biomedical Sciences Institutes, Application Number
201208940e20120895). All other authors declare that there is no conflict of interest that
could be perceived as prejudicing the impartiality of the research reported.

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Legends To Figures

**Fig. 1 a,b.** TSH (a) or FT3 (b) versus weight adjusted L-T4 dose in three groups of patients on thyroid hormone replacement, with autoimmune thyroiditis (n=96), after surgery for benign goitre (n=111) or thyroid carcinoma (n=143).

Between group differences in both panels were significant (p< 0.01) and remained so after adjusting for volume (not shown, p<0.01), as evidenced by linear models with diagnostic group as covariate. For further details see text.

AIT refers to autoimmune thyroiditis, goitre to goitre post surgery for benign nodular thyroid disease.

**Fig. 2 a,b,c.** FT3 (a), FT4 (b) and TSH (c) levels in L-T4 treated patients stratified by disease and conversion efficiency.

The disease entities were closely associated with categories of thyroid volume (see Table 1 and text).

Red box (first) refers to poor converters (calculated deiodinase activity <23 nmol/s), green (second) to intermediate converters (deiodinase activity 23 - 29 nmol/s) and blue (third) to good converters (deiodinase activity >29 nmol/s).

Remarkably, absolute FT3 concentrations were lowest in the poor converter group in all disease categories, while FT4 levels were highest in the poor converters.

An asterix indicates significant difference by Wilcoxon test, compared to each first group, *p<0.05, **p<0.001.

**Fig. 3 a-d.** Probability plot of weight adjusted L-T4 dose to a) suppress TSH below its lower reference limit (0.4 mU/l) or b) raise FT3 above the median of euthyroid controls (>5 pmol/l) in the carcinoma patients (n=143), and c) suppress TSH <1 mU/l or d) elevate FT3
above 5 pmol/l in benign disease (patients with autoimmune thyroiditis, n=75 and nodular thyroid disease post surgery, n= 111).

Probability plots were created by logistic regression. The shaded areas indicate the confidence interval surrounding the fitted curve. The TSH targets were more frequently reached at a lower dose than the FT3 target (see Results).
### Table 1. Characteristics of study group (n=353)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (IQR) or Percentage</th>
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</thead>
<tbody>
<tr>
<td>Gender (female, male)</td>
<td>280 (79%), 73 (21%)</td>
</tr>
<tr>
<td>Age (years) in women vs men</td>
<td>56 (46, 66)</td>
</tr>
<tr>
<td>Disease aetiology (%)</td>
<td>autoimmune thyroiditis 27%,</td>
</tr>
<tr>
<td></td>
<td>benign thyroid disease after surgery 32%,</td>
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<tr>
<td></td>
<td>thyroid carcinoma¹ 41%</td>
</tr>
<tr>
<td>Surgery, radioiodine treatment (%)</td>
<td>73%, 42%</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.5 (24.1, 30.8)</td>
</tr>
<tr>
<td>Dose (µg/d)</td>
<td>100 (75, 150)</td>
</tr>
<tr>
<td>Weight-adjusted daily dose (µg/kg/d)</td>
<td>1.47 (1.09, 1.72)</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>0.64 (0.12, 1.47)</td>
</tr>
<tr>
<td>FT3 (pmol/l)</td>
<td>4.80 (4.40, 5.30)</td>
</tr>
<tr>
<td>FT4 (pmol/l)</td>
<td>18.6 (16.2, 21.1)</td>
</tr>
<tr>
<td>TPO-Ab (U/l)</td>
<td>450 (48, 1300), positive 65%, n=97</td>
</tr>
<tr>
<td>FT3-FT4 ratio</td>
<td>0.26 (0.24, 0.29)</td>
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<tr>
<td>Deiodinase activity (nmol/s)</td>
<td>24.3 (21.8, 27.1)</td>
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<td>Thyroid volume (ml) - total group</td>
<td>2 (0, 7)</td>
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<tr>
<td></td>
<td>7 (4,11)</td>
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</tr>
</tbody>
</table>

¹82% of the thyroid carcinoma patients had a higher TNM stage than 1 and ²96% had no detectable residual thyroid volume by ultrasound after total thyroidectomy and radioiodine treatment.

For referencing purpose, parameters in 146 disease-free individuals from the same study were as follows, median age 38 (26, 49) years, TSH 1.62 (1.12, 2.25) mU/l, FT3 5.0 (4.8, 5.2) pmol/l, FT4 14.0 (13.0,15.1) pmol/l, calculated deiodinase activity 32.8 (30.0, 36.2) nmol/s, thyroid volume 10 (8,13) mL (22).
Table 2. Beta coefficients in a linear model of covariates predicting dose of L-T4 in the euthyroid panel

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male vs female</td>
<td>0.22 (0.11, 0.33), p&lt;0.001</td>
</tr>
<tr>
<td>Disease aetiology</td>
<td></td>
</tr>
<tr>
<td>autoimmune vs malignant disease</td>
<td>-0.33 (-0.47, -0.19), p&lt;0.001</td>
</tr>
<tr>
<td>benign goitre vs malignant disease</td>
<td>-0.34 (-0.48, -0.20), p&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>-0.26 (-0.37, -0.15), p&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.33 (0.22, 0.44), p&lt;0.001</td>
</tr>
<tr>
<td>Deiodinase activity</td>
<td>-0.27 (-0.39, -0.15), p&lt;0.001</td>
</tr>
</tbody>
</table>

The multivariable model was simultaneously fitted with the parameters listed, all of which were significant predictors of L-T4 dose in univariate models. All variance inflations factors were <1.2.
Carcinoma  AIT  Goitre

FT3 (pmol/L)

n  66   69   8   31   49   16   32   56   23

*  **  **  **  **  **  **  **
Carcinoma
AIT
Goitre

lnTSH (mU/L)

<table>
<thead>
<tr>
<th></th>
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<th>AIT</th>
<th>Goitre</th>
</tr>
</thead>
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<tr>
<td>n</td>
<td>66</td>
<td>69</td>
<td>8</td>
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</tr>
</tbody>
</table>
dose per kg effect plot

L-T4 Dose (ug/kg BW/d)

Probability of FT3 >5 pmol/L

L-T4 Dose (ug/kg BW/d)