Individually-tailored thyroxine requirement in the same patients before and after thyroidectomy: a longitudinal study

S C Del Duca^{1,*}, M G Santaguida^{1,*}, N Brusca¹, I Gatto¹, M Cellini¹, L Gargano³,
C Verga Falzacappa¹, F M Frattaroli², C Virili¹ and M Centanni^{1,3}

¹Department of Medico-Surgical Sciences and Biotechnologies, 'Sapienza' University of Rome, Corso della Repubblica 79, 04100 Latina, Italy, ²Department of Surgical Specialties and Organ Transplantation 'P. Stefanini', Policlinico Umberto I, 'Sapienza' University of Rome, Rome, Italy and ³Endocrinology Unit, AUSL Latina, Latina, Italy
*S C Del Duca and M G Santaguida contributed equally to this work

Correspondence
should be addressed
to M Centanni
Email
marco.centanni@uniroma1.it

Abstract

Objective: Thyroxine (T₄) requirement after total thyroidectomy for differentiated thyroid carcinoma (DTC) is a debated issue. As most of the studies in the area have been retrospective and/or performed with heterogeneous therapeutic approaches, we designed our study to determine T₄ requirement in the same patients and treatment settings, before and after total thyroidectomy.

Design, patients and methods: This was a longitudinal study including 23 goitrous patients treated with T₄ in an individually tailored fashion. All patients exhibited a stable TSH (median TSH = 0.28 mU/l) at a stable T₄ dose for at least 1 year before surgery (median T₄ dose = 1.50 µg/kg per day). The patients underwent total thyroidectomy based on cancer suspicion or compressive symptoms. Eventually diagnosed as having DTC (pT1b–pT2N0) and following surgical and radiometabolic treatment, they were treated with the same pre-surgical doses of T₄.

Results: Three months after surgery, using the same pre-surgical dose, median TSH increased up to 5.38 mU/l ($P < 0.0001$) and so the T₄ dose had to be increased (median T₄ dose = 1.95 µg/kg per day; +30%; $P < 0.0001$). Once divided by patients' age, we observed that, after thyroidectomy and maintaining the same pre-surgical dose, serum TSH significantly increased both in younger and in older patients (median TSH = 4.57 and 6.11 mU/l respectively). Serum TSH was restored to the pre-surgical level by increasing the dose up to 1.95 and 1.77 µg/kg per day (+25 and +21%) respectively.

Conclusions: Following the same treatment regimen, a thyroidectomized patient requires one-third higher therapeutic T₄ dose than before surgery. Despite this increase, the dose of T₄ needed in our patients remains significantly lower than that previously described in athyreotic patients.

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Introduction

Levothyroxine (L-T₄) sodium is commonly used to restore thyroid function in hypothyroid patients, in the management of non-toxic multinodular goiter (NTMG) or after total thyroidectomy for differentiated thyroid cancer (DTC) (1, 2, 3, 4). The main goal of T₄ treatment is to promptly achieve the therapeutic target, avoiding over- or under-treatments (5), but some patients require several

dose adjustments prior to attaining an adequate pharmacological T₄ homeostasis (6, 7). Despite some reports on the inability of T₄ alone to warrant euthyroidism in all tissues (8), L-T₄ monotherapy is as yet the preferred treatment (9). Oral T₄ is asymmetrically deiodinated to triiodothyronine (T₃) in peripheral tissues and mimics a nearly physiological T₄/T₃ ratio (9, 10). In keeping with

the American Thyroid Association (ATA) and European Thyroid Association (ETA) guidelines, patients with DTC, after total thyroidectomy, should be treated with T₄ according to risk stratification (2, 11). In patients with a low risk of recurrences of DTC, T₄ treatment in semi-suppressive mode is required in the first year after surgery, according to ATA guidelines (2, 5). Several studies dealing with T₄ requirement have been carried out on patients with primary hypothyroidism, with or without thyroid *in situ* (see (6, 9) for a review). Some of these studies focused on factors affecting the therapeutic dose, such as body weight (6, 12), BMI (13), amount of residual thyroid tissue, patients' age and drugs (14, 15, 16), and only a fraction of them examined T₄ requirement after total thyroidectomy (7, 8, 9, 10, 11). However, most of these latter reports were retrospective and/or compared results obtained in different groups of patients (15, 16, 17), and/or in heterogeneous therapeutic settings (7, 16). At best, some authors used empirical and continuously adjusted T₄ doses and mathematical models to predict the post-surgical dose (16, 17). A prospective pre- and post-surgical study on the same patients was carried out by Jonklaas *et al.* (18) who showed similar T₃ levels before and after surgery. However, no conclusions were drawn about T₄ requirements, as patients were not treated before surgery. Therefore, our study was aimed at determining the T₄ requirement in the same treatment setting and in the same patients, before and after total thyroidectomy.

Patients and methods

A total of 1538 Caucasian outpatients living in a mild iodine-deficient area, with NTMG, were examined in our referral center for thyroid diseases from 2008 to 2012. About half of them required T₄ treatment and all patients were treated with the same brand of T₄. Of these, 158 patients underwent thyroid surgery because of cancer suspicion or compressive symptoms (19). All these patients underwent total thyroidectomy and, of these, 83 patients had thyroid cancer. Among these, 36 patients had a diagnosis of papillary thyroid carcinoma (PTC) with a low risk of recurrence (2). Twenty-three patients (19 women and four men; median age = 51 years) were eligible for our study according to the following criteria: i) they have had NTMG treated with an individually tailored semi-suppressive dose of L-T₄ for at least 1 year; ii) have a low-risk DTC requiring T₄ treatment in semi-suppressive mode (2). Exclusion criteria were: i) a history of hyperthyroidism or toxic nodular goitre as well as the presence of autonomously functioning areas in the thyroid scan; ii) the recent

use (<6 months) of drugs known to interfere with thyroid homeostasis (20); iii) the presence of concomitant gastrointestinal disorders (gastritis related to *Helicobacter pylori* infection, atrophic gastritis, coeliac disease, lactose intolerance, etc.) known to increase L-T₄ requirement (21, 22, 23); iv) being pregnant.

Among the 23 patients enrolled, 18 patients had a pT2 N0 PTC and five patients had a pT1b N0 PTC, according to the TNM classification from the International Union against Cancer. According to ATA guidelines for the follow-up of DTC at low risk of recurrences (2), all these patients received radioiodine (RAI) treatment after surgery (30 mCi) and T₄ therapy had been reinstituted in a semi-suppressive dose fashion (target serum thyroid-stimulating hormone (TSH) = 0.1–0.5 mU/l).

All patients were disease-free after 1 year from the RAI ablation (undetectable serum thyroglobulin and a negative neck ultrasonography). Clinical features of the study patients are described in Table 1.

Study design

All patients with NTMG were treated with an individually tailored dose of T₄, as previously described (21, 22, 23, 24) and in semi-suppressive mode (target serum TSH = 0.1–0.5 mU/l) (2). The individually tailored dose is the dose of T₄ which is administered following a standardized assumption procedure and titrated on the basis of patient's age, weight, BMI, the amount of residual thyroid tissue and the ability to absorb the hormone (12, 14, 15, 21, 22, 23, 24). All patients were treated with the same brand of oral

Table 1 Anthropometric and functional characteristics of patients at baseline.

Characteristics	Values
Patients, <i>n</i>	23
Median age (years)	51
Sex, <i>n</i>	
Male	4
Female	19
Weight (kg)	
Before surgery	66
After surgery	66
DTC (TNM class), <i>n</i>	
pT1b N0 Mx	5
pT2 N0 Mx	18
Median TSH	
Without T ₄	1.20 mU/l
With T ₄ pre-surgery	0.28 mU/l
Median TPOAb	27 U/ml

DTC, differentiated thyroid carcinoma.

Figure 1

Median TSH value ($n=23$ patients) in pre-surgical period (with and without thyroxine therapy) (A and B) and in post-surgical period (with and without increased thyroxine dose) (C and D). Mann–Whitney non-parametric test has been used for statistical analysis. B vs C *** $P<0.0001$; C vs D *** $P<0.0001$; B vs D # $P=NS$.

L-T₄ sodium in tablet form (Eutirox, Bracco, Milan, Italy) and agreed to take T₄ under fasting conditions, abstaining from eating or drinking anything other than water for at least 1 h after treatment. Before surgery, once target TSH had been reached, the dose of T₄ was not changed and serum TSH was measured every 6 months. All these goitrous patients were followed for at least 1 year before surgery (mean period of treatment 4 ± 2 years). Compliance of enrolled patients was checked at every control and confirmed by the stability of serum TSH at constant dose.

After surgery and radioiodine treatment, T₄ treatment has been restarted at the same presurgical dose with identical criteria for T₄ assumption and TSH and thyroid hormones checked every 3 months. When necessary, the dose of T₄ has been subsequently increased to reach the therapeutic target. The dose of T₄ required to obtain the therapeutic goal was normalized by patient's age and body weight both during pre and post surgical period. So far, we compared the T₄ requirement in the same patients, before and after total thyroidectomy.

Study has been conducted upon written informed consent and as part of the diagnostic and therapeutic workup of the patients involved, according to the local ethical rules and to the guidelines in the Declaration of Helsinki.

Methods

Serum TSH, free T₄ (FT₄) and free T₃ (FT₃) levels were analyzed at the same time. Serum TSH levels were measured by commercial kit (Thermo Scientific, BRAHMS

TSH RIA, Hennigsdorf, Germany) (normal range: 0.4–4.0 mU/l; sensitivity: 0.04 mU/l; intra-assay and inter-assay variation were 2.5 and 4.1%, respectively). Levels of serum FT₄ were detected by commercial kit (Thermo Scientific, BRAHMS FT₄ RIA) (normal range: 10–25 pmol/l, which is the equivalent of 0.78–1.94 ng/dl), as the levels of serum FT₃ (normal range 3.5–8.1 pmol/l or 2.3–5.3 pg/ml). Serum anti-thyroid peroxidase antibodies were measured by commercial assay (Thermo Scientific, BRAHMS anti-TPO) (normal range: <60 U/ml).

The diagnosis of NTMG

The diagnosis of NTMG was based on clinical and ultrasonographical features, normal serum iodothyronines and TSH, the absence of serum antiperoxidase antibodies, normal radioiodine uptake and thyroid scan. All patients had goitre WHO stage 1A or 1B and at least 2 nodules > 1 cm (21).

Thyroid surgery

Total thyroidectomy was performed at 'Sapienza' University of Rome, Policlinico Umberto I, Rome, Italy, by a highly experienced head and neck surgeon (Fabrizio Frattaroli, MD).

Completeness of thyroidectomy was checked by neck ultrasound, performed almost 6 months after surgery. No patients had evidence of thyroid tissue remnant >0.5 ml.

Statistical analysis

Data are expressed as a median with relative interquartile range (IQR). The median values were compared using the

Figure 3

Median T₄ dose/weight in all patients before and after thyroidectomy. Mann–Whitney non-parametric test has been used for statistical analysis.

Mann–Whitney test for non-parametric data. Kruskal–Wallis non-parametric tests were used to test independence of more than two samples at a 0.05 level of significance. Dunn's Multiple Comparison Post Test was used to compare single groups. INSTAT Graphpad prism 5 software (2007) for Windows was used in the statistical analysis.

Results

A total of 23 patients with NTMG in treatment with T₄ underwent total thyroidectomy and DTC was histologically diagnosed. None of them was hypothyroid at the baseline (median serum TSH=1.20 mU/l; median serum FT₃=3.3 pg/ml and FT₄=1.06 ng/dl). Once treated for NTMG, at a median dose of T₄ of 1.50 µg/kg per day (IQ1–IQ3=1.33–1.58 µg/kg per day), these patients exhibited a stable TSH at stable T₄ dose for at least 1 year. In the last control before surgery these patients had a median TSH of 0.28 mU/l (IQ1–IQ3=0.19–0.55 mU/l) and a median serum FT₄ of 1.46 ng/dl and FT₃ of 3.11 pg/ml. Following total thyroidectomy and radiometabolic procedures, T₄ treatment had been resumed at the presurgical dose in each patient and thyroid function was tested within 3 months after the treatment restart.

Despite the median weight (66 kg) and the T₄ dose before and after surgery was identical to presurgical period, only 2/23 patients reached the target TSH, while in the remaining 21 patients a significant increase of serum TSH has been observed. The overall median TSH was 5.38 mU/l (IQ1–IQ3=3.63–7.87 mU/l; $P < 0.0001$)

(Fig. 1). To maintain the therapeutic goal, as required both for DTC risk stratification and for the design of the study, T₄ dose had been adjusted in the 21 patients and, within three to 6 months period, the individual TSH was in the expected range. The median TSH value was then comparable to the presurgical one (0.21 mU/l; IQ1–IQ3=0.13–0.44 mU/l; $P = \text{NS}$) (Fig. 1). To obtain this goal, the individual T₄ dose was increased in these patients to a different extent (Fig. 2). After 1 year, the median daily dose of T₄ was 1.95 µg/kg per day (IQ1–IQ3=1.71–1.98 µg/kg per day), significantly higher than the presurgical one by 30% (1.50 vs 1.95 µg/kg per day; $P < 0.0001$) (Fig. 3). To note, the median values of serum FT₄ and FT₃ were not changed throughout the study and were not affected by the increased T₄ dose ($P = 0.5111$; $P = 0.4076$, respectively) (Fig. 4). More specifically, only two patients out of 23 showed FT₃ values below normal and none showed subnormal FT₄. Since T₄ metabolism is slowed down in elderly patients (12) and the dose of T₄ should be accordingly reduced, age may represent a confounding factor. So far, patients were subdivided into two age-related groups: under 50 years of age ($n = 11$) and 50 years of age or older ($n = 12$) and the pre- and post-surgical dose has been compared accordingly. Clinical features of these patients are described in Table 2.

Prior to surgery, a median TSH of 0.34 mU/l has been obtained in younger patients using a median T₄ dose of 1.56 µg/kg per day (IQ1–IQ3=1.38–1.61 µg/kg per day). After surgery, maintaining the same pre-surgical dose, serum TSH significantly increased in all patients but one

Figure 4

Median FT₃ and FT₄ values during the pre-surgical period (with thyroxine therapy) and in post-surgical period (with and without increased thyroxine dose). ANOVA Kruskal–Wallis test has been used for statistical analysis.

Table 2 Clinical features of patients divided by age.

	<50 years	>50 years
Patients (n)	11	12
Median age (years)	38	61
Sex (male/female)	2M/9W	2M/10W
Weight (kg)	63	69
Median L-T ₄ dose		
Pre-surgery (µg/kg per day)	1.56	1.46
Post-surgery (µg/kg per day)	1.95	1.77
Median TSH		
With T ₄ pre-surgery (mU/l)	0.34	0.21
With T ₄ post-surgery (mU/l)	0.18	0.27
Median FT ₃		
With T ₄ pre-surgery (pg/ml)	3.00	3.14
With T ₄ post-surgery (pg/ml)	3.12	3.16
Median FT ₄		
With T ₄ pre-surgery (ng/dl)	1.50	1.38
With T ₄ post-surgery (ng/dl)	1.63	1.39

(median=4.57 mU/l; $P=0.0022$). T₄ treatment was then increased and serum TSH was restored to normal (median=0.18 mU/l) in all patients by increasing the median T₄ dose up to 1.95 µg/kg per day (IQ1–IQ3=1.87–1.98 µg/kg per day; +25%; $P=0.0003$) (Fig. 5a). In patients aged 50 years or older, median presurgical TSH was 0.21 mU/l and was attained with a median T₄ dose of 1.46 µg/kg per day (IQ1–IQ3=1.23–1.52 µg/kg per day). Post-surgical serum TSH significantly increased in all patients but one (median TSH=6.11 mU/l), and again it was restored to presurgical levels (0.27 mU/l) by increasing the T₄ dose. In this group, the median daily T₄ dose was 1.77 µg/kg per day (IQ1–IQ3=1.67–1.96 µg/kg per day; +21%; $P=0.0002$) (Fig. 5b). In these age-related groups of patients, serum FT₄ levels were also similar prior to surgery and after the increase of the T₄ dose ($P=NS$). On the contrary, we observed that postsurgical FT₃ values were lower in three out of 11 young patients (27%) and in seven out of 12 older patients (58%) as compared to presurgical values. Despite these apparent differences, the median pre- and post-surgical FT₃ levels were not statistically different in both age-related groups ($P=0.7621$ and $P=0.2185$ respectively).

Discussion

There is a general consensus that an increased need for T₄ is observed in patients following thyroidectomy (7, 15, 16, 17). However, the quality of evidence in the guidelines prepared by the ATA task force was only moderate (25), because of the differences in the design of the studies, in the characteristics of patients and in the standardization of treatments. Also, a wide range of daily T₄ requirements

and very high doses were reported (see (25) for review). Some of these limitations were overcome in our study in that: i) all patients were treated and stabilized before surgery using an individually tailored dose and the compliance of patients was carefully checked; ii) the need for T₄ has been measured for the first time in the very same patient before and after thyroidectomy with identical criteria for T₄ assumption; iii) all patients were treated with a semi-suppressive T₄ dose whose target is a narrow TSH range. This approach increased the reliability of our results, namely the daily T₄ requirement in the same patients, thus avoiding interindividual variability. So far, in our prospective study, a remarkably lower daily T₄ requirement has been noticed. An increased dose of T₄ by about 30% was sufficient to attain target TSH in our patients after thyroidectomy. This increase has been ascribed to the need for replacement of direct glandular T₃ production (26), which in post-surgical athyreotic patients is no longer available. In our study, following total thyroidectomy, patients also received radioiodine treatment for DTC, allegedly leading to the absence of functional thyroid tissue. The absence of thyroid-derived T₃ in these patients led some authors to assume that a partial T₃ deficiency may be an issue during L-T₄ treatment after surgery (8, 26). However, in a prospective study carried out in the same patients before and after thyroidectomy, no difference has been shown by comparing FT₃ levels before and after replacement T₄ dose (18). This suggests that T₃ administration may be not needed to maintain serum T₃ values at their endogenous pre-surgical levels. According to Jonklaas *et al.* (18), our present data confirm the lack of differences in median T₃ values before and after surgery, following an individually tailored T₄ treatment. However, we noticed that, mainly in the older group, some patients showed apparently lower

Figure 5

Median T₄ dose/weight before and after thyroidectomy (a) in patients aged <50 years and (b) in patients aged >50 years. Mann–Whitney non-parametric test has been used for statistical analysis.

Clinical Study	S C Del Duca, M G Santaguida and others	T ₄ dose in thyroidectomized patients	173:3	356
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FT₃ concentrations as compared to the pre-surgical levels. Although not conclusive, this finding suggests that some patients may show an incomplete recovery of thyroid homeostasis after thyroidectomy, despite an appropriate T₄ treatment. In fact, certain reports suggested an incomplete ability of T₄ treatment to warrant euthyroidism in all tissues of some patients (8, 27, 28), despite a serum TSH concentration in the expected range. In fact, serum TSH mirrors the feedback effect of thyroid hormones at the pituitary level, but different tissues may not be able to attain a sufficient intracellular T₃ (27, 28, 29). Escobar-Morreale *et al.* (27) even suggested that athyreotic patients may have a differential organ responsiveness to suboptimal thyroid hormone concentrations. Now, the question arises about the crucial role of D2 in the conversion of T₄ in T₃ in peripheral tissues (29, 30). In fact, these gate-keeper enzymes (31) are alleged to counteract the loss of thyroid-derived T₃ with an increase of extrathyroidal type 2 deiodinase activity (29, 30). A type 2 deiodinase polymorphism has been described in patients where a defective D2 activity was associated with an increased need for T₄ (32). However, it seems not sufficient to explain why some patients may not fully recover despite an appropriate dose of T₄ (8, 33). On this ground, some studies analyzed the effects of combined T₃/T₄ treatment in hypothyroid patients, including those who have undergone thyroidectomy (10, 27, 28, 33, 34), but mostly failed to show advantages when compared with L-T₄ therapy alone (10, 25, 34).

In summary, our study provided evidence for the first time and in a consistent human model that, after total thyroidectomy, the therapeutic dose of T₄ must be increased by 1/3 as compared with the pre-surgical one. This additional amount of T₄ may be the substrate for the peripheral deiodinase network to compensate for the absence of T₃ production from the gland. Despite this increase, the individually tailored T₄ requirement in our patients remains significantly lower than previously described, thereby reducing the risk of over-treatment.

Declaration of interest

The 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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Author contribution statement

M Centanni and L Gargano designed the study; S C Del Duca, C Virili and I Gatto selected the patients; F M Frattaroli performed surgical procedures; S C Del Duca and M G Santaguida wrote the manuscript; N Brusca and M Cellini provided a critical literature research; C Verga Falzacappa performed number supervision and statistical analysis; C Virili, M G Santaguida and M Centanni performed the revision of the final version.

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Clinical Study	S C Del Duca, M G Santaguida and others	T ₄ dose in thyroidectomized patients	173:3	357
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