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

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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.

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 \( T_4 \) according to risk stratification (2, 11). In patients with a low risk of recurrences of DTC, \( T_4 \) treatment in semi-suppressive mode is required in the first year after surgery, according to ATA guidelines (2, 5). Several studies dealing with \( T_4 \) 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 \( T_4 \) 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 \( T_4 \) doses and mathematical models to predict the postsurgical 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 \( T_3 \) levels before and after surgery. However, no conclusions were drawn about \( T_4 \) requirements, as patients were not treated before surgery. Therefore, our study was aimed at determining the \( T_4 \) 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 \( T_4 \) treatment and all patients were treated with the same brand of \( T_4 \). 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 1-\( T_4 \) for at least 1 year; ii) have a low-risk DTC requiring \( T_4 \) 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 1-\( T_4 \) 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 \( T_4 \) 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 \( T_4 \), 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 \( T_4 \) 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

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<tr>
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<tr>
<td>pT2 N0 Mx</td>
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<tr>
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<td>Median TPOAb</td>
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**Table 1** Anthropometric and functional characteristics of patients at baseline.

DTC, differentiated thyroid carcinoma.
L-T4 sodium in tablet form (Eutirox, Bracco, Milan, Italy) and agree 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 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 4P=NS.

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 4P=NS.

i-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.

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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
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 = 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 = 1.33–1.58 µg/kg per day). After surgery, maintaining the same pre-surgical dose, serum TSH significantly increased in all patients but one (P < 0.0001).
with a median T4 dose of 1.77 µg/kg per day. Post-surgical serum TSH significantly increased in all patients but one (median TSH = 0.27 mU/l) in all patients by increasing the T4 dose. In this group, the median daily T4 dose was 1.56 µg/kg per day (IQ1–IQ3 = 1.67–1.96 µg/kg per day; +21%; 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 FT₃ 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 (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

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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.
This additional amount of T4 may be the substrate for the increased by 1/3 as compared with the pre-surgical one. 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 with 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 absence of T3 production from the gland. Despite this fact, these gate-keeper enzymes (31) are alleged to explain why some patients may not fully recover despite an appropriate dose of T4 (8, 33). On this ground, 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). 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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