

## Levothyroxine replacement therapy after thyroid surgery

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**Abstract.** *Levothyroxine replacement therapy after thyroid surgery. Introduction and aim:* New entities, such as 'sub-clinical' over- and undersubstitution, are easily diagnosed after thyroid surgery due to improved testing methods, and the incidence of thyroidectomy with lifelong hormone substitution is increasing. Thus, there is a need to review conventional replacement therapy after thyroid surgery. We investigated the adequacy of our thyroid hormone replacement therapy for three months after total-, subtotal-, and hemithyroidectomy using an upper reference limit of thyrotropin (TSH) of 4.6 mU/L.

*Materials and methods:* Eighty-seven patients undergoing thyroidectomy for benign thyroid pathology participated. Levothyroxine (L-T4) treatment began five days after surgery. Preoperatively euthyroid patients received 150 µg L-T4 daily following total thyroidectomy, 100 µg L-T4 after subtotal thyroidectomy, and 50 µg L-T4 after hemithyroidectomy. Preoperatively hyperthyroid patients received 100 µg L-T4 following total thyroidectomy and 50 µg L-T4 following subtotal thyroidectomy. An average of six weeks after surgery, thyrotropin (TSH) was measured (reference limits 0.15-4.60 mU/L), and necessary dose adjustments were made.

*Results:* Of the patients who were preoperatively euthyroid, 45% with total thyroidectomy, 42% with subtotal thyroidectomy, and 17% with hemithyroidectomy required L-T4 dose adjustments. Of the patients who were preoperatively hyperthyroid, 60% of those with total thyroidectomy and all of those with subtotal thyroidectomy required L-T4 dose adjustments.

*Conclusions:* To avoid over- and undersubstitution after thyroidectomy, an optimal replacement therapy dose is necessary. A small majority of our preoperatively euthyroid patients received adequate therapy. Endocrinological follow-up six weeks after surgery revealed the need for L-T4 dose adjustments, especially in preoperatively hyperthyroid patients. When the extent of resection was similar for hyperthyroid and euthyroid patients, the same initial dose of L-T4 was justified.

### Introduction

Following thyroid surgery, levothyroxine (L-T4) therapy is used to replace deficient thyroid hormones and prevent postoperative thyroid hypofunction. Before assays for thyroid stimulating hormone (TSH) were available, the recommended daily dose of L-T4 for patients with primary hypothyroidism was 200 to 400 µg.<sup>1</sup> Due to an increasing tendency to perform total or near-total thyroidectomy for benign thyroid disease and increasingly sensitive assays for TSH, reappraisal of postopera-

tive replacement therapy is necessary. New entities, such as sub-clinical hypo- and hyperthyroidism, are being defined, although their pathological significance in the immediate postoperative setting remains to be established. Some authors advocate narrowing the normal range for serum TSH whereas others defend the limit that we still use (i.e. 4 mU/L).<sup>2,3</sup> Others are investigating the advantages of combining L-T4 with liothyronine for replacement therapy.<sup>4</sup>

The aim of the present retrospective study was to investigate

the adequacy of standard initial postoperative L-T4 replacement therapy in benign thyroid disease. Serum TSH was assayed six weeks after surgery to assess postoperative thyroid function. The target range of TSH was 0.15-4.60 mU/L (reference limits at the time of study). All dose adjustments were made and analysed by an endocrinologist.

### Materials and methods

Subjects were 77 female and 12 male patients (mean age 35, range 22-80) that underwent

Table 1  
Protocol for postoperative L-T4

Extent of surgery	Preoperative function	L-T4 replacement therapy
Total thyroidectomy	euthyroid	150 µg/d
	hyperthyroid	100 µg/d
Subtotal thyroidectomy	euthyroid	100 µg/d
	hyperthyroid	50 µg/d
Hemi-thyroidectomy	euthyroid	50 µg/d
	hyperthyroid	0

Table 2  
Number of patients with normal (0.15-4.60 mU/L) TSH levels six weeks after thyroidectomy

Extent of surgery	Preoperatively euthyroid		Preoperatively hyperthyroid	
	adequate substitution; n (%)	total	adequate substitution; n (%)	total
Total	18 (47%)	38	3 (33%)	10
Subtotal	8 (66%)	12	0 (0%)	4
Hemi	17 (94%)	18	5 (100%)	5
	43 (63%)	68	8 (42%)	19

surgery for benign thyroid pathology between 2002 and 2003 in our department. Surgical indications were benign (toxic or non-toxic) goiter, autonomous nodules, and Graves' hyperthyroidism.

Subtotal thyroidectomy consisted of a hemithyroidectomy with a contralateral subtotal lobectomy, leaving about 2 cm<sup>3</sup> of thyroid tissue at the upper thyroid pole. Preoperatively hyperthyroid patients were rendered euthyroid at the time of surgery.

All patients began taking L-T4 on postoperative days 3-5 according to the protocol outlined in Table 1. The initial dose was determined by preoperative thyroid function and the extent of surgical resection. At the initial visit 10-14 days after surgery, no dose changes were made.

All patients had a standard follow-up visit in the Department of

Endocrinology six weeks after surgery. At that time, serum levels of TSH and free T4 index (FT<sub>4</sub>I) were assayed, and necessary adjustments to the L-T4 dose were made. Adjustments were made by dose-titration in increments of 25-50 µg. TSH concentration was measured with a third-generation chemi-illuminometer (Immuno 1, Bayer, Germany). The chemi-illuminometer had a detection limit of 0.01 mU/L, with a functional sensitivity of 0.014 mU/L. Normal TSH values, defined by the manufacturer, were 0.15-4.60 mU/L.

## Results

A summary of the results is shown in Table 2. The majority of preoperatively euthyroid patients were well substituted. Figure 1 shows TSH values of patients (n = 48)

that had euthyroid or hyperthyroid function prior to total thyroidectomy. Forty-seven percent (18/38) of the preoperatively euthyroid patients showed normal thyroid function after surgery. TSH levels of the remaining preoperatively euthyroid patients were distributed symmetrically over low and elevated levels according to a Gaussian distribution. One third of the preoperatively hyperthyroid patients had normal TSH values after surgery, and 50% had elevated TSH values.

A maintenance dose of L-T4 (Figure 2) was obtained in 55% of the preoperatively euthyroid patients and 33% (3/10) of the preoperatively hyperthyroid patients. Figures 3 and 4 show TSH values and L-T4 adjustments for preoperatively euthyroid and preoperatively hyperthyroid patients that had subtotal thyroidectomy (n = 16). All preoperatively hyperthyroid patients required augmentation of the L-T4 dose. Following hemithyroidectomy, 96% (22/23) of the patients required minor dose adjustments (Figures 5, 6). In terms of body-weight, L-T4 levels were between 1.2 and 2.8 µg/kg, with a mean value of 2.1 µg/kg.

## Discussion

The goal of post-thyroidectomy replacement therapy is to restore thyroid function, avoiding over- and undersubstitution by beginning with an ideal dose of L-T4 within seven days after surgery.<sup>1</sup> By definition, an optimal L-T4 replacement dose is a dose that restores TSH concentration to a normal value, with normal or slightly increased serum T4 concentration. According to the literature, the average ideal adult dose

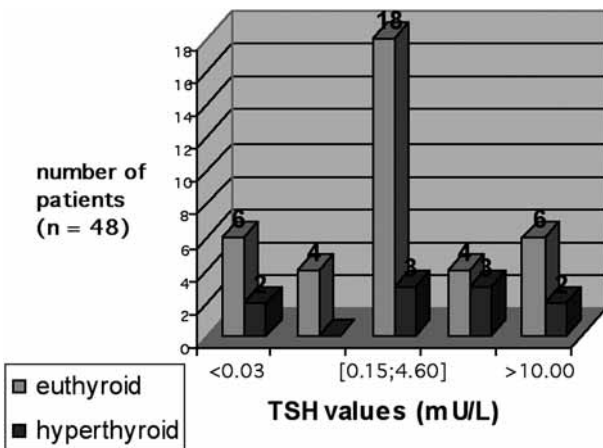


Figure 1

TSH-values: after total thyroidectomy, euthyroid vs hyperthyroid.

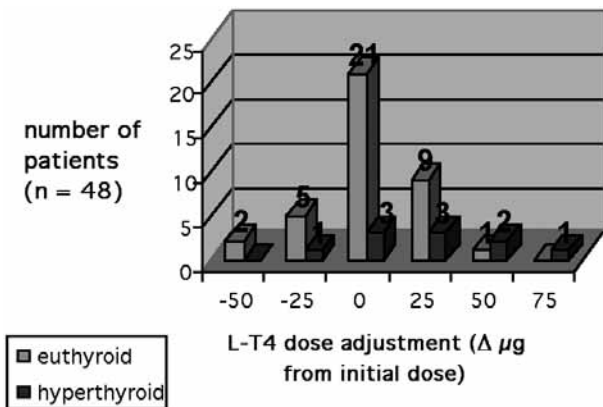


Figure 2

L-T4 dose adjustment after total thyroidectomy, euthyroid vs hyperthyroid.

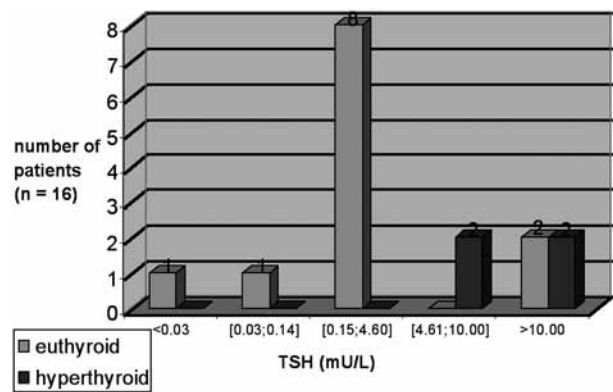


Figure 3

TSH-values: after subtotal thyroidectomy, euthyroid and hyperthyroid.

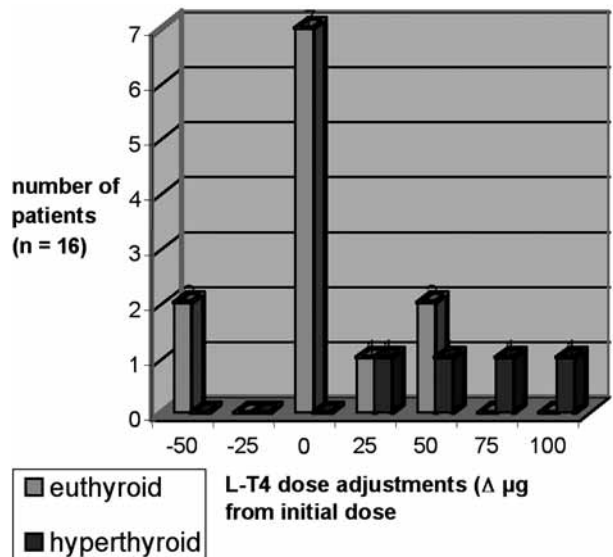


Figure 4

L-T4 dose adjustment after subtotal thyroidectomy, euthyroid (and hyperthyroid).

of L-T4 is 1.68 μg/kg daily.<sup>5</sup> We used TSH concentration and need for dose adjustment to evaluate the adequacy of L-T4. Free T4 (FT<sub>4</sub>I) measurements and clinical symptoms have an unacceptable lag period for this purpose.<sup>6</sup>

Our results revealed that only a small majority of patients were well substituted by the standard L-T4 dose six weeks after surgery. At that time, the dose could be adjusted by dose-titration.

Substitution with our standard protocol (Table 1) resulted in pre-

dictable thyroid function in preoperatively euthyroid patients. For example, 83% of the hemithyroidectomy patients were correctly substituted with the initially prescribed dose of L-T4. On the other hand, dose adjustments were usually necessary for patients with a history of hyperthyroidism. The initial dose of L-T4 was acceptable in only 30% of the preoperatively hyperthyroid patients after total thyroidectomy and in none of those patients after subtotal thyroidectomy (Figures 3,4).

In contrast to traditional views in endocrine surgery literature, we performed a near-total resection for Graves' hyperthyroidism in order to avoid recurrence. In euthyroid goiters a remnant size of less than 4 g leads to hypothyroidism in 27-99% of patients.<sup>7</sup> On the other hand, a comparable remnant volume following surgery for a hyperfunctional thyroid is believed to fulfil the physiological need of thyroid hormones, which is the rationale for leaving that volume. A striking finding in the

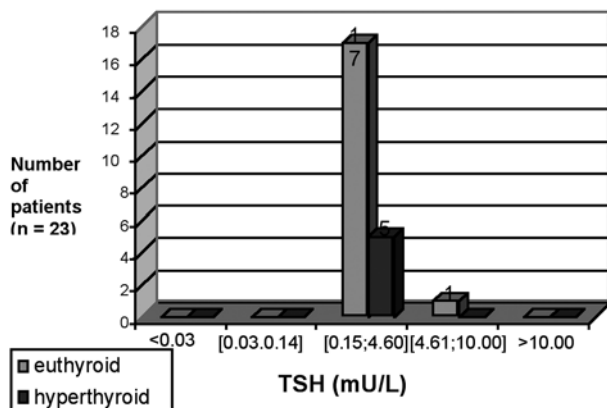


Figure 5

TSH-values: after hemithyroidectomy, euthyroid and hyperthyroid.

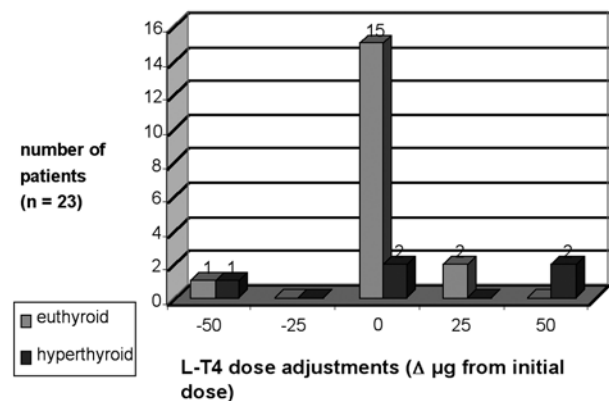


Figure 6

L-T4 dose adjustment after hemithyroidectomy, euthyroid and hyperthyroid.

present study was that all patients required dose increments after subtotal thyroidectomy for hyperthyroidism that left a smaller volume of the thyroid intact. This could indicate that our larger resection was associated with less remnant thyroid function. However, this was not supported by statistical analysis (Figure 3).

Regarding the increasing use of total and near-total resection in preoperative hyperthyroid patients, we propose following the protocol that was used in our preoperatively euthyroid patients. Furthermore, a study is currently underway at our Institute to investigate our protocol with long-term follow-up, using narrower TSH reference ranges, as recently promoted in the endocrine literature (i.e., 0.5-2.0 mIU/L).<sup>2</sup> Our preliminary results show that, long term, only one-third of our preoperatively euthyroid total thyroidectomy patients were appropriately substituted with the current protocol. These findings concur with a recent study by Olubowale *et al.*<sup>8</sup> that suggests starting with 125 μg L-T4 when a standard dose-titration technique is used. It remains to be seen if their proposed

weight-related algorithm is valid for our population, and analysis is ongoing. In the present study, we did not intend to explore a narrower TSH reference rate after thyroid surgery.

Normally, hypothyroidism occurs 2-44 weeks after total thyroidectomy. Using TSH concentrations as a parameter, 26% (n = 23) of our patients developed postoperative hypofunction despite replacement therapy. Only seven of those patients showed 'typical' clinical symptoms of overt hypothyroidism (i.e., slow speech, depression, hair loss, and weight gain). The others displayed 'subclinical' thyroid hypofunction. Note that 'atypical' symptoms like dullness of alertness, insomnia, and fatigue are commonly observed in a normal postoperative setting, even with normal thyroid function.

Subclinical primary hypothyroidism is defined by elevated TSH concentration and normal levels of serum free thyroxine (FT4).<sup>9,10</sup> Many studies have investigated the clinical significance of subclinical hypothyroidism.<sup>9-11</sup> The annual conversion rate of subclinical to overt hypothyroidism is

approximately 5% among patients with hyperthyroidism that is treated with iodine-131 or surgery.<sup>12</sup> The exact clinical impact of subclinical features in the immediate postoperative phase is not known, and requires further prospective investigation.

Replacement L-T4 may have adverse effects, including nervousness, palpitations, atrial fibrillation,<sup>13</sup> and exacerbation of angina pectoris.<sup>8</sup> The meta-analysis (n = 1,250) performed by Uzzan *et al.*<sup>14</sup> indicated that over-substitution with L-T4 contributes to the development of osteoporosis in postmenopausal women.

Fifteen of 87 patients (17%) in our cohort had low TSH values. Thirteen of those had a total thyroidectomy, and two had subtotal thyroidectomy (Figures 1,2). Of the total thyroidectomy patients, eight required a dose adjustment due to suppressed TSH values, whereas the others had subnormal TSH levels, but no dose adjustment was needed since thyroid function was expected to normalise.

Some patients report feeling better when they take a daily dose of thyroxine that is 50 μg in excess

of that required to normalise TSH secretion.<sup>6</sup> Thus, it is necessary to instruct our patients not to over-treat, since symptoms like fatigue and weight gain are normal after surgery and are not necessarily due to undersubstitution.

Recently, a combination of L-T4 and liothyronine was suggested to be superior to L-T4 treatment alone.<sup>15</sup> Most investigators continue to endorse L-T4 as the choice for replacement therapy for hypothyroidism.<sup>4</sup> At our Institute, we treat with L-T4 alone.

Finally, regarding replacement therapy after hemithyroidectomy, 74% of the patients received adequate thyroid substitution. We need to stress that Belgium is a region of endemic mild iodine deficiency.<sup>16</sup> The recommended urinary iodide concentration for adults is 100-200 µg/L. In Belgium the concentration is 50-60 µg/L.<sup>16</sup> This argues for lifelong substitution with 50 µg L-T4 in hemithyroidectomy patients to avoid thyroid dysfunction and nodule recurrence. Following hemithyroidectomy for toxic adenomas in preoperatively hyperthyroid patients, our protocol does not call for any hormone replacement.

## Conclusions

The initial postoperative dose of L-T4 was adequate for a small majority of patients in the present study. When using a standard initial dose technique (not weight-related), more than half of the subtotal thyroidectomy patients needed minor dose adjustments six weeks after surgery. This underlines the importance of endocrinological follow-up and the need to adjust initial dose.

When the extent of resection is similar for hyperthyroid and euthyroid patients, the same initial dose of L-T4 is justified.

A small majority of our preoperatively euthyroid patients received adequate L-T4 therapy. Nevertheless, endocrinological follow-up six weeks after surgery revealed the need for L-T4 dose adjustments, especially in preoperatively hyperthyroid patients.

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