

Optimization of thyroxine replacement therapy after total or near-total thyroidectomy for benign thyroid disease

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Background: Total or near-total thyroidectomy is increasingly used to treat benign thyroid conditions. Lifelong treatment with thyroxine (T4) is then required, but the optimal dose is difficult to predict. This study investigated factors that might predict the ideal T4 dose, with the aim of reducing delays in achieving normal thyroid function after surgery.

Methods: Data on 98 patients who underwent total or near-total thyroidectomy for benign disease were reviewed retrospectively. Patient and operative variables that might predict time to achieve normal thyroid function and optimal T4 replacement dose were examined. These data were then used to formulate an algorithm for T4 dosage, based on patient weight, that was subsequently applied prospectively to a comparable group of 27 patients.

Results: The median time to achieve normal thyroid function was 14.5 (range 2–120) weeks before introduction of the algorithm, and was greater in patients needing large changes in T4 dose. In multivariate analysis, the best predictors of optimal T4 dose were bodyweight ($r = 0.46$, $P < 0.001$) and age ($r = -0.32$, $P = 0.002$). Subsequent use of a weight-related algorithm improved time to achieve normal thyroid function.

Conclusion: The T4 replacement dosage after total or near-total thyroidectomy is largely influenced by bodyweight. Use of a weight-related algorithm improves patient care compared with use of standard T4 dose-titration methods.

Presented to the Annual Meeting of the British Association of Endocrine Surgeons, Lund, Sweden, September 2004

Paper accepted 12 July 2005

Published online 1 December 2005 in Wiley InterScience (www.bjs.co.uk). DOI: 10.1002/bjs.5157

Introduction

In recent years there has been an increasing tendency to replace traditional subtotal thyroidectomy, which carries an appreciable risk of recurrence, with total or near-total resection in the treatment of benign thyroid disease (Graves' disease and bilateral multinodular goitre). In the hands of experienced endocrine surgeons this more radical approach eliminates recurrence, yet can be achieved with morbidity rates at least as good as those following subtotal resection^{1,2}.

After total thyroidectomy there is a requirement for lifelong thyroxine replacement therapy. Methods for monitoring and adjusting thyroid hormone replacement after surgery vary widely between surgical units, but most use a dose-titration method involving commencement of thyroxine (T4) at an initial empirical dose (commonly

100 µg or 1.3 µg per kg bodyweight)³, and subsequent dose adjustment after thyroid function tests and assessment of patient symptoms. This method can, however, lead to long delays in achieving adequate replacement in some patients.

No published study has specifically examined the issue of thyroxine replacement dosage after total thyroidectomy for benign conditions. Most of the literature on thyroxine dosage relates to treatment of primary hypothyroidism. It has been demonstrated that thyroxine requirements are related to patient age and lean body mass, and that normal thyroid function can be achieved with thyroxine doses of between 1 and 2.2 µg/kg^{4–6}. In primary hypothyroidism the thyroid is still *in situ* and may contribute to thyroid hormone production. These studies may not therefore accurately predict thyroxine requirements after total thyroidectomy. The surgical literature refers only to the

thyroxine dosage required for suppression of thyroid-stimulating hormone (TSH) after thyroidectomy, for example for thyroid cancer or prevention of recurrence of benign goitre^{3,7,8}, but does not address the dosage required to achieve normal thyroid function after total thyroidectomy for benign disease.

The aim of this study was to determine which factors lead to a delay in achieving normal thyroid function after thyroidectomy for benign disease and which best predict optimal thyroxine dosage. The results of this analysis were used to develop an algorithm for optimal thyroxine dosage, which was compared with the standard dose-titration technique.

Patients and methods

The first part of the study comprised a retrospective review of 98 patients (86 women and 12 men; median age 46 (range 18–81) years), who had undergone total or near-total thyroidectomy for Graves' disease or multinodular goitre, with postoperative thyroxine used for replacement only, and normal thyroid function documented after surgery. Patients who had not achieved normal thyroid function were excluded, as were those with differentiated thyroid cancer, owing to their need for TSH suppression.

In this phase of the study a traditional dose-titration method for thyroxine replacement was used. Thyroxine was commenced on the first day after surgery, usually at a 'standard' dose of 100 µg. Patients were seen in the outpatient clinic initially at 4–8 weeks and subsequently according to clinical need, with thyroxine dose titration in increments of 25–50 µg, depending on biochemical thyroid function tests results and patient symptoms. Thyroid hormone levels were assessed using a standard chemiluminescence assay.

Study endpoints were the time taken to attain normal thyroid function, defined as TSH level within the normal population range, and the dose of thyroxine needed to achieve this. The time to achieve normal thyroid function was defined as the interval between the date of surgery and the date of the first normal TSH measurement recorded in the patient's case notes. In patients who were thyrotoxic before operation, normal thyroid function was deemed to have been achieved if free thyroid hormone levels were within the normal population range, even when TSH remained suppressed, as long as a subsequent normal TSH level was recorded without any intervening change in thyroxine dose.

Variables examined in relation to the above endpoints were indication for surgery (Graves' disease *versus* multinodular goitre), preoperative thyroid status (toxic *versus*

euthyroid), extent of resection (total *versus* near total), patient age, sex, bodyweight, height and body mass index (BMI). Because the literature suggested that lean body mass may be a better predictor of thyroxine dosage, an 'ideal weight' was calculated for each patient ($\text{height}^2 \times 23$, where 23 is the 'ideal' BMI), as an estimate of lean body mass. Data on all these variables were complete for all patients.

The results from the first part of the study were used to formulate an algorithm for the dosage of thyroxine to be commenced immediately after surgery, and this algorithm was subsequently applied to a consecutive series of 27 patients undergoing total or near-total thyroidectomy for benign disease. Their median age was 50 (range 31–74) years. Postoperative follow-up intervals and thyroxine dose titration were otherwise identical to those in the first phase of the study.

Statistical analysis

Statistical analysis was carried out with StatisticaTM software (Statsoft, Tulsa, Arizona, USA), using the Mann–Whitney *U* test to compare categorical variables and multiple linear regression to examine continuous variables affecting thyroxine dosage. $P < 0.050$ was considered significant.

Results

In the first phase of the study, the time taken to achieve normal thyroid function was highly variable between patients: median 14.5 weeks, interquartile range 8–26 weeks and range 2–120 weeks. This interval was not influenced significantly by any of the patient or operative variables considered, but was dependent on the magnitude of the change in thyroxine dose from baseline (*Fig. 1*).

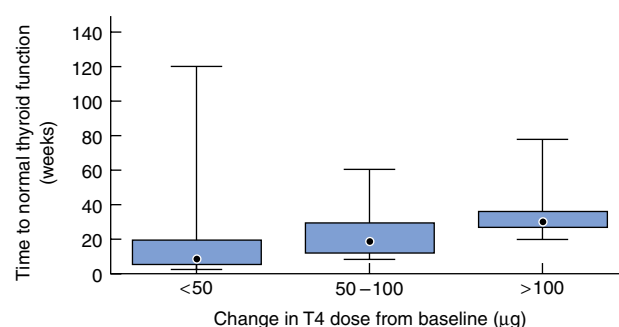


Fig. 1 Time to achieve normal thyroid function before introduction of algorithm in relation to change in thyroxine dose from baseline (final 'ideal' dose minus initial dose). Median, interquartile range and range are represented by points, boxes and whiskers respectively

T4 dose adjustment is usually carried out in 25- μ g increments, because this is the smallest dose available in a single tablet, whereas some patients' optimal daily dose may lie between whole-number multiples of 25 μ g (so requiring a variable daily dose regimen). This applied to five patients, whose median time to achieve normal thyroid function was longer than that for patients whose final T4 dose was a whole-number multiple of 25 μ g (32 *versus* 12 weeks; $z = 2.71$, $P = 0.007$). Use of the weight-related algorithm is likely to identify such patients earlier, as all patients treated after introduction of the algorithm had a final T4 dose within 25 μ g of baseline.

Ninety-one (93 per cent) of the 98 patients were commenced on 100 μ g T4, but in only 36 (36.7 per cent) did this dose result in normal thyroid function; 60 patients (61.1 per cent) required a higher dose. Multivariate analysis indicated that the T4 dose required to achieve normal thyroid function was not influenced independently by indication for surgery, preoperative thyroid function status, extent of resection or patient sex, but was affected by age, bodyweight, height and BMI. Bodyweight proved the best predictor of T4 dose ($r = 0.46$, $P < 0.001$). There was a statistically significant but relatively weaker negative correlation between age and T4 dose ($r = -0.32$, $P = 0.002$), which was independent of bodyweight. Overall, the median T4 dose required to achieve normal thyroid function was 1.69 (range 1.09–3.08) μ g/kg, although the relationship between optimal T4 dose and weight was not uniform across the weight range (Fig. 2).

The weight-related algorithm developed for calculation of postoperative T4 dose (in 25- μ g intervals, for simplicity of dosage) is shown in Table 1. The cohort

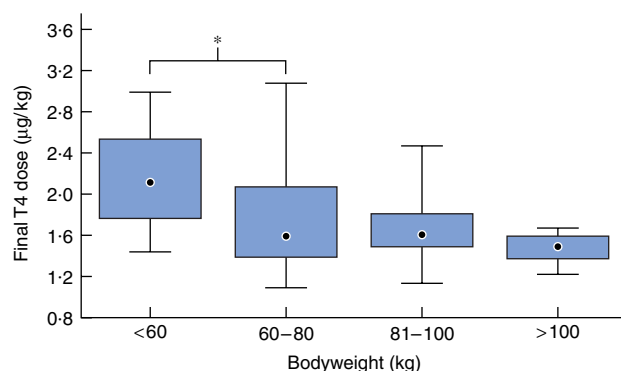


Fig. 2 Effect of bodyweight on final weight-adjusted T4 dose before introduction of algorithm. Median, interquartile range and range are represented by points, boxes and whiskers respectively. * $z = 3.45$, $P < 0.001$ (Mann–Whitney U test)

Table 1 Weight-related algorithm for calculation of postoperative T4 dose

| Patient weight (kg) | T4 dose (μ g) |
|---------------------|--------------------|
| ≤ 53 | 100 |
| 54–86 | 125 |
| 87–108 | 150 |
| > 108 | 175 |

of patients treated after introduction of the algorithm was well matched with the earlier group with respect to baseline characteristics, particularly age and bodyweight.

The algorithm was adhered to correctly in 26 of 27 patients, and resulted in use of higher initial doses of T4 (median 100 μ g before introduction of algorithm *versus* 125 μ g afterwards; $z = -6.23$, $P < 0.001$). There was a corresponding reduction in subsequent changes of T4 dose from baseline (median (interquartile range (i.q.r.)) 25 (–25 to 125) *versus* 0 (–25 to 25) μ g respectively; $z = 4.57$, $P < 0.001$). As a result, time to achieve normal thyroid function was significantly reduced after introduction of the algorithm (median (i.q.r.) 8 (6–16) *versus* 14.5 (8–26) weeks respectively; $z = 2.18$, $P = 0.029$).

Discussion

Thyroxine replacement therapy is instituted to restore thyroid function to normal after total or near-total thyroidectomy for benign thyroid disease. It is important to achieve this promptly because over- or under-replacement results in troublesome symptoms, and in Graves' disease may be associated with worsening of ophthalmopathy⁹.

This study demonstrated that standard T4 dose-titration methods may result in prolonged delays in achieving normal thyroid function, particularly when the final, optimal dose of T4 is much greater than the dose commenced immediately after surgery. This is because titration of the T4 dose is usually undertaken in small increments of 25–50 μ g, with an interval of several weeks before thyroid function tests can meaningfully be repeated. Reducing these delays can be achieved only by determining which factors influence optimal T4 dose for each individual.

Much of the previous literature on T4 requirements has focused on primary hypothyroidism^{4–6,10} and these studies may not accurately predict T4 requirements after total thyroidectomy. The present results nonetheless confirm previous findings of a relationship between T4 dose and bodyweight and age. Moreover, the finding of a negative

correlation between T4 dose expressed with respect to bodyweight and weight itself¹⁰ was also confirmed in the present report. Thus, lighter patients required proportionally greater doses of T4 per unit bodyweight than heavier patients, although the latter patients required higher absolute T4 doses.

Some studies in primary hypothyroidism have shown that the T4 requirement is more closely related to lean body mass than bodyweight alone^{11,12}, but accurate assessment of lean body mass requires complex techniques such as body impedance measurements that are not routinely available in clinical practice. The present study demonstrated that estimates of lean body mass based only on routine anthropometric measurements are no better predictors of T4 requirement after thyroidectomy than bodyweight alone, so for routine practice bodyweight alone is the simplest predictive factor.

Optimal weight-adjusted doses of T4 in this study were higher (median 1.69 µg/kg) than baseline doses used in many endocrine units (100 µg or 1.3 µg/kg)³, and were greater than expected particularly in leaner patients (median 2.12 µg/kg for patients weighing less than 60 kg). A T4 dose algorithm based on bodyweight, such as that developed in the present study, is therefore recommended, but an initial empirical dose of 125 µg T4 might be preferred if a standard dose-titration technique is used.

This study also demonstrated that there is a large interindividual variation in optimal T4 dose, only part of which can be explained by bodyweight and/or age. Patient compliance with replacement therapy may be an important factor in this respect. Although the principal determinant of delay to normal thyroid function is the need for large changes in T4 dose during follow-up after surgery, some of the longest delays nonetheless occurred in patients whose change in T4 dose was small (*Fig. 1*), implying irregular compliance during this time interval.

Acknowledgements

The authors thank Miss C. Nockolds for assistance in data collection.

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