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ORIGINAL ARTICLE

Predicting thyroxine requirements following total thyroidectomy

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Summary

Objective Optimal thyroxine replacement following total thyroidectomy is critical to avoid symptoms of hypothyroidism. The aim of this study was to determine the best formula to determine the initiated replacement dose of levothyroxine immediately following total thyroidectomy.

Design Prospective study. All patients were initiated on 100 μg levothyroxine and titrated to within the reference range for TSH and free T4. Correlations to height, weight, age, lean body mass (LBM), body surface area (BSA) and body mass index (BMI) were calculated.

Patients One hundred consecutive adult patients underwent total thyroidectomy for non-malignant disease.

Measurements Comparison between three methods of levothyroxine dose prediction, aiming for a levothyroxine dose correct to within 25 μg of actual dose required.

Results Correlations were seen between levothyroxine dose and patient age ($r = -0{\cdot}346$, $P < 0{\cdot}01$), bodyweight ($r = 0{\cdot}296$, $P < 0{\cdot}01$), LBM ($r = 0{\cdot}312$, $P < 0{\cdot}01$), BSA ($r = 0{\cdot}319$, $P < 0{\cdot}01$) and BMI ($r = 0{\cdot}172$, $P < 0{\cdot}05$). A regression equation was calculated (predicted levothyroxine dose = [0·943 × bodyweight] + [−1·165 × age] + 125·8), simplified to (levothyroxine dose = bodyweight − age + 125) pragmatically. Initiating patients empirically on 100 μg post-operatively showed that 40% of patients achieved target within 25 μg of their required dose; this increased to 59% when using a weight-only dose calculation (1·6 μg/kg) and to 72% using the simplified regression equation.

Conclusions A simple calculated regression equation gives a more accurate prediction of initiated levothyroxine dose following total thyroidectomy, reducing the need for outpatient attendance for dose titration.

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Introduction

Levothyroxine replacement to within the reference range is key to prevent hypothyroid symptoms following total thyroidectomy for non-malignant disease.[1] However, some patients require several dose adjustments to achieve this.

A number of factors have been found to correlate with levothyroxine requirements including patient age,[2–4] bodyweight,[2–4] lean body mass (LBM)[2,3] and body surface area (BSA).[5] However, no single factor has shown a consistently high correlation with levothyroxine dose to predict the initial dose following total thyroidectomy. Whilst body weight at a replacement dose of 1·6 μg/kg per day is accepted,[1,6–8] it is observed that individuals with similar bodyweights have differing levothyroxine requirements.

There is debate on the reference range for TSH,[9,10] with a suggestion that the upper reference limit should be reduced to 2·5 mIU/l[10], 3·0 mU/l[11] or 4·1 mU/l[12] although others suggest there should be no change. It is suggested that the current TSH reference range is too high as it includes patients with thyroid antibodies that are destined for future hypothyroidism. However, not all population studies that exclude risk factors for thyroid disease report a significant change in the TSH reference range.[13]

The aim of this study was to determine whether a better measure of the prediction of initial levothyroxine replacement could be determined than a dose calculated at 1·6 μg/kg reported in the literature.[1,6–8]

Subjects and methods

One hundred consecutive patients who underwent total thyroidectomy (removal of both thyroid lobes, isthmus and pyramidal lobe[14]) for histologically proven non-malignant thyroid disease (Graves' disease 67 patients, multi-nodular goitre 25 patients, Hashimoto's thyroiditis six patients, toxic multi-nodular goitre two patients) at our institution were recruited into this study (78 women and 22 men; mean age 43 years, range 17–77 years). Patient demographics for weight and height were collected, and LBM, BSA and body mass index (BMI) were calculated. LBM was calculated using the Hume formula[15] [male LBM = (0·32810 × weight in kg) + (0·33929 × height in cm) − 29·5336, female LBM = (0·29569 × weight in kg) + (0·41813 × height in cm) −

43·2933]. BSA was calculated using the Du Bois formula[16] [BSA (m^2) = 0·20247 × Height(m)0·725 × Weight(kg)0·425].

All patients were started empirically on 100 μg levothyroxine and the dose increased every 6 weeks to ensure that the TSH (0·5–4·6 mU/l) and serum thyroxine (10–24 pmol/l) were within the reference ranges. Patients were asked to take their thyroxine once daily in the morning. Patients were reviewed 6 weeks post-operatively until their TSH and serum thyroxine were within the reference range; additional dosage alteration based on symptoms was undertaken as part of this study.

Statistical analysis of data, including correlation, multiple stepwise regression and analysis of variance (ANOVA), was carried out using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was indicated when $P < 0·05$.

Results

Mean weight was 74·5 kg (range 44–121), mean BMI was 27 kg/m^2 (range 17–45), mean LBM was 49 kg (range 34–70) and mean BSA 1·8 m^2 (range 1·4–2·4).

The median levothyroxine dose was 150 μg (standard deviation 46). The mean TSH was 2·1 mU/l (standard error of mean 0·1), and the mean free T4 was 16 pmol/l (standard error of mean 0·3).

Levothyroxine replacement dose correlated with age of patient ($r = -0·346$, $P < 0·01$), LBM (0·312, $P < 0·01$), BSA (0·319, $P < 0·01$), bodyweight (0·296, $P < 0·01$) and BMI (0·172, $P < 0·05$).

There was no significant association between gender and thyroxine dose.

The mean thyroxine dose per kilogram (kg) bodyweight was 2·00 μg/kg (standard deviation 0·61). The data of patient age and bodyweight were divided into quartiles. The mean TSH for the 1st, 2nd, 3rd and 4th age quartiles was 2·0, 2·4, 2·0 and 2·0 mU/l, respectively (the differences in mean TSH between groups were not statistically significant: ANOVA $F = 0·866$, $P = 0·461$). The mean TSH for the 1st, 2nd, 3rd and 4th weight quartiles was 2·3, 2·0, 2·2 and 1·9 mU/l, respectively (the differences in mean TSH between groups were not statistically significant: ANOVA $F = 0·617$, $P = 0·606$). Comparison between quartiles revealed that thyroxine dose per kg bodyweight was inversely related to age and total bodyweight (Figs 1 and 2, respectively). Comparison of the interquartile mean values of thyroxine dose per kg bodyweight revealed that this relationship was significant for both age (ANOVA $F = 4·221$, $P = 0·008$) and bodyweight (ANOVA $F = 5·946$, $P = 0·001$).

Multiple stepwise regression revealed that patient age and bodyweight produced the best regression model: Predicted thyroxine dose = (0·943 × bodyweight) + (−1·165 × age) + 125·8. For this model, R (multiple correlation) = 0·47 (strength of correlation), ANOVA $F = 13·5$ $P < 0·001$ (confirming that the variation explained by the model was not because of chance) and the residual standard deviation was 40·4. As the factors used to multiply both bodyweight and age approximate to one, a simplification of this equation became: Predicted thyroxine dose = Weight − Age + 125.

The assumption of ANOVA (normality of residuals) was examined by the Shapiro–Wilk test after fitting the regression model.

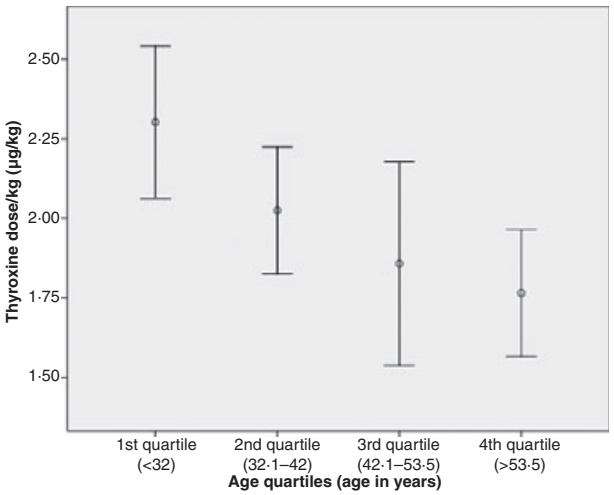

Fig. 1 Patient age and mean thyroxine dose per kg bodyweight (error bars represent 95% confidence interval).

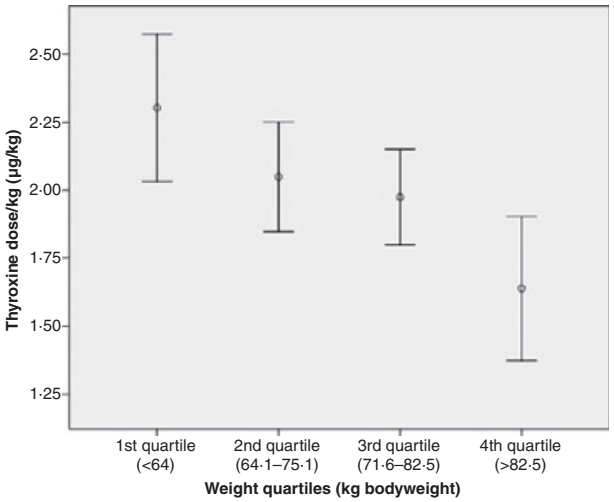

Fig. 2 Body weight and mean thyroxine dose per kg (error bars represent 95% confidence interval).

For the regression model, the residuals followed a normal distribution ($P = 0·46$, Shapiro–Wilk test). Raw thyroxine dose did not follow a normal distribution. We present this data by box and whisker plots (Figs 3 and 4).

A comparison of three methods of thyroxine dose prediction was carried out, and the results can be seen in Table 1. These figures illustrate that when initiating patients empirically on 100 μg thyroxine post-operatively, 42% of patients achieved target within 25 μg of their required dose; this increased to 59% when using a weight-only dose calculation (1·6 μg/kg) and to 72% using the simplified regression equation.

The predicted thyroxine dose according to the mean thyroxine dose per kilogram for our cohort (2·0 μg/kg per day) was also calculated. Using this method, 27 patients would have had the correct thyroxine dose and a further 33 would have been within 25 μg of

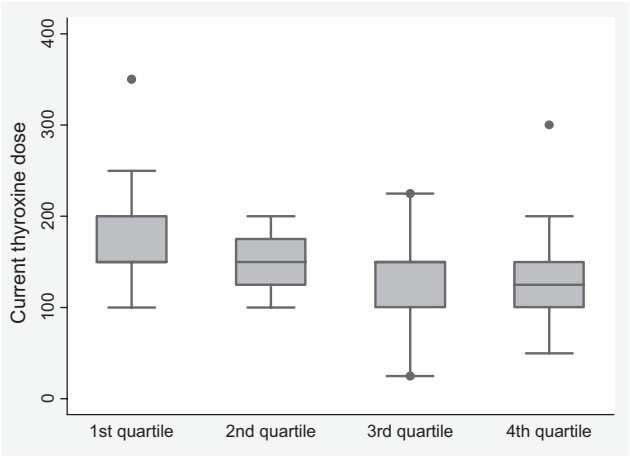

Fig. 3 Thyroxine dose (μg) by age quartiles.

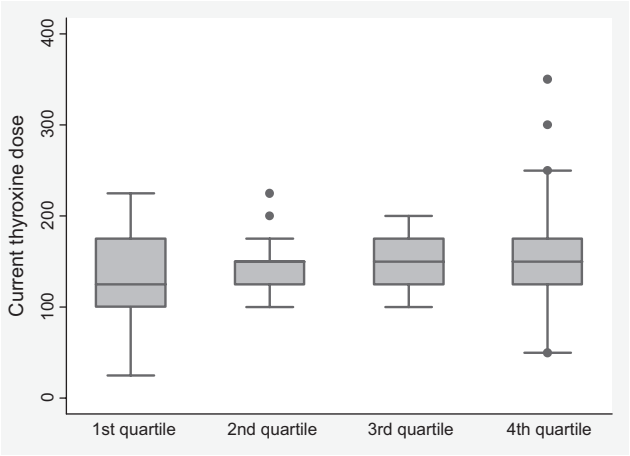

Fig. 4 Thyroxine dose (μg) by weight quartiles.

Table 1. Comparison between three methods of thyroxine dose prediction

	Patients with correct initial thyroxine dose (%)	Patients with correct thyroxine dose to within 25 μg (%)
Empirical dose 100 μg	21	42
1·6 μg/kg bodyweight	25	59
Weight − Age + 125	28	72

the correct dose. Thus, a total of 60% of patients would have required no or only one dose change.

Dose prediction efficacy of 1·6 μg/kg and the simplified regression equation were compared with patients in the highest (4th) and lowest (1st) quartiles of age and weight. The simplified regression equation was superior in predicting thyroxine replacement dose to within 25 μg (75% *vs* 60% for age 1st and 4th quartiles and 64% *vs* 54% for weight 1st and 4th quartiles).

Discussion

The simplified regression formula that was derived resulted in a significant improvement for the prediction of final levothyroxine replacement dose in patients undergoing total thyroidectomy for non-malignant disease. In this patient cohort, it correctly predicted the thyroxine dose to within 25 μg in over 70% of patients. The formula was a better predictor than a weight-only dose calculation (1·6 μg/kg) and an initial empirical dose of 100 μg. These data are in accord with others that show that the mean levothyroxine dose per kilogram bodyweight was inversely proportional to overall bodyweight[17] and inversely proportional to age.[4]

Therefore, although many authors quote or calculate a mean dose of thyroxine per kilogram of approximately 1·6–1·7 μg/kg,[5–8,18] it is clear from our results and those of others that this figure changes according to the patient's age and their overall weight. It seems logical therefore that these factors should be taken into account when predicting thyroxine requirements.

The replacement dose of levothyroxine may vary with the cause of hypothyroidism.[19] This is likely to be due to endogenous thyroxine production from residual thyroid tissue. We controlled for this by studying patients with benign thyroid disease who underwent total thyroidectomy only (rather than a combination of total, subtotal or near-total thyroidectomy).

Studies examining levothyroxine replacement following thyroid surgery for benign thyroid disease are few. Two such studies reported that when commenced on a post-operative dose of 100 μg (n = 98) and 150 μg (n = 38), 37% and 47% of patients achieved optimal levothyroxine dose, respectively.[17,20] In this study, when started on 100 μg levothyroxine, 21% of patients were adequately replaced, whilst if our patients had been commenced on 150 μg (the median dose for our patient cohort), 31% of patients would have been adequately replaced.

A recent randomised study involving 60 patients who underwent total thyroidectomy for benign thyroid disease compared empirical dosing (starting dose 75–150 μg) with dose according to bodyweight (1·6 μg/kg per day) and LBM (2·5 μg/kg per day).[21] When measured in terms of the least number of medical visits required to achieve biochemical euthyroidism, the empirical dosing and dosing according to LBM were best with a median of 2 and 1·5 visits, respectively. The authors do not comment on the percentage of patients adequately replaced on their initial dose.

The time taken for patients to achieve optimal levothyroxine replacement from the time of their surgery has been found to be highly variable (median 14·5 weeks, range 2–120 weeks) and dependent on the magnitude of change in dose from baseline,[17] emphasizing the importance of accurate levothyroxine dose prediction. Optimum levothyroxine replacement leads to less use of resources, such as physician appointments and blood tests, and is likely to improve patient satisfaction.

In conclusion, a simple formula was a better prediction of the optimal initial replacement dose of levothyroxine following thyroidectomy for benign thyroid disease, although prospective studies are needed to confirm this.

Disclosure statement

The authors have nothing to declare.

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