The American Journal of Surgery (2013) 205, 360-364

The American Journal of Surgery®

Midwest Surgical Association

Levothyroxine replacement dosage determination after thyroidectomy

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KEYWORDS:
Levothyroxine;
Thyroidectomy;
Dose calculation;
Weight;
Thyroid hormone;
Hypothyroidism

Abstract

BACKGROUND: The goal of this study was to identify a simple and effective way of calculating levothyroxine doses for postsurgical hypothyroidism.

METHODS: Levothyroxine dosage was calculated using a weight (μg/kg)-based formula for patients who underwent thyroidectomy for benign disease from 2001 to 2011. Other formulas using age, sex, ideal body weight, body mass index, and body surface area were also evaluated.

RESULTS: Four hundred four patients were included; 85% were women. The mean initial levothyroxine dosage was 1.4 μg/kg, which resulted in thyroid-stimulating hormone normalization in 59%, suppression in 23%, and elevation in 18% of patients. After dose adjustments, the mean therapeutic levothyroxine doses after total thyroidectomy and lobectomy were 1.5 and 1.3 μg/kg, respectively. A regression model incorporating other patient factors did not produce a more reliable dosing regimen.

CONCLUSION: A 1.5- and 1.3-μg/kg dosage calculation based on actual weight is currently the best estimation for levothyroxine replacement therapy after thyroidectomy.

Thyroid hormone replacement therapy in patients undergoing thyroidectomy for benign disease has traditionally been calculated based on actual body weight (μg/kg), a method that was initially derived from patients who were treated for primary hypothyroidism.[1,2] After the initiation of replacement therapy postoperatively, serum thyroid-stimulating hormone (TSH) levels are measured, and levothyroxine dosages are titrated until a normal serum TSH level is achieved. It has been common practice to start patients on a 1.6-μg/kg dose of levothyroxine after total thyroidectomy, a standard dose for thyroid hormone replacement in patients with primary hypothyroidism.[1,2] Although this may provide a simple estimation, the efficacy of achieving a euthyroid state with this method has not been validated in patients who have undergone thyroidectomy. Using actual body weight as a basis for dosage calculation has been questioned given the widespread prevalence of obesity and the effect of body fat composition on drug distribution. As a result, it has been suggested that body mass index (BMI), ideal body weight (IBW), or body surface area (BSA) may be a more accurate predictor of levothyroxine doses than actual body weight.[3,4] Other factors including patient age and sex may affect requirements for thyroid hormone and may be relevant for initial dosage determination.[5,6]

In this study, we sought to evaluate how accurately a 1.6-μg/kg calculation was able to predict the appropriate replacement or "final" levothyroxine dose in patients who underwent thyroidectomy for benign disease. In addition, alternative calculations using patient age, sex, BMI, IBW,

The authors declare no conflicts of interest.

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Manuscript received July 17, 2012; revised manuscript September 10, 2012

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http://dx.doi.org/10.1016/j.amjsurg.2012.10.015

or BSA were studied, and their accuracy of levothyroxine dosage prediction was compared with the simple 1.6-μg/kg calculation.

Methods

The electronic medical records of all patients who underwent thyroidectomy for benign disease between 2001 and 2011 were reviewed. Patients who underwent total thyroidectomy and patients who developed postsurgical hypothyroidism after thyroid lobectomy were included in the study. Patients were excluded if they did not have their initial thyroidectomy performed at MetroHealth Medical Center, Cleveland, OH, or if they failed to follow up postoperativley. Patients with thyroid cancer were excluded because they were treated with TSH-suppressive rather than replacement doses of thyroid hormone. This study was reviewed and approved by the Institutional Review Board at MetroHealth Medical Center.

Preoperative patient demographics including age, sex, body weight (kg), height (m), BMI (kg/m^2), IBW (kg), and BSA (m^2) were collected. IBW was calculated using the Miller formula as follows: for men over 5 feet, 55.7 kg plus 1.39 kg for each additional inch; for women over 5 feet, 53 kg plus 1.33 kg for each additional inch. The extent of thyroidectomy and final pathology of the surgical specimen were obtained. On postoperative day 1, patients who underwent total thyroidectomy were started on levothyroxine with a weight-based calculation of 1.6 μg/kg. Patients were instructed to take their levothyroxine after awakening in the morning and to wait at least 30 to 60 minutes before eating or drinking.

Six weeks after surgery, all patients who underwent total thyroidectomy and lobectomy with isthmusectomy had their serum TSH measured. The levothyroxine dose was adjusted if the TSH level was not within the normal reference range for the patients (TSH 0.4–5.5 μU/mL). For patients who underwent thyroid lobectomy and isthmusectomy and who were not on levothyroxine before surgery, if the serum TSH level was elevated above the normal range at 6 weeks, levothyroxine therapy was initiated for the treatment of postsurgical hypothyroidism. The starting dosage was determined at the discretion of the surgeon who used a 1.6-μg/kg estimate as a rough guide to help determine what levothyroxine dosage preparation to begin. For lobectomy patients who were on levothyroxine preoperatively, the dose was continued postoperatively until their serum TSH levels were measured 6 weeks later, and adjustments were made if necessary. The final or therapeutic levothyroxine dose was defined as the dose that produced a serum TSH level that was maintained in the normal reference range (TSH 0.4–5.5 μU/mL). The final microgram dose of levothyroxine per kilogram of actual body weight was determined for each patient, and a mean value was calculated for patients who underwent total thyroidectomy and thyroid lobectomy and isthmusectomy respectively.

The final weight-based levothyroxine dosage was compard in patients based on their sex (male vs female), age ($<$55 years vs $\geq$55 years), BMI ($<$30 mg/kg^2 vs $\geq$30 kg/m^2), and extent of surgery (total thyroidectomy vs partial thyroidectomy). Multivariate logistic regression analysis using backward elimination was performed to identify the model that would best predict the final levothyroxine dosage by incorporating patient age, sex, actual body weight, BMI, IBW, and BSA.

Statistical analysis was performed using JMP software (JMP, Cary, NC). The Student *t* test was used for the comparison of continuous variables, whereas the chi-square test was used for the comparison of categoric variables. A P value $<$.05 was considered statistically significant.

Results

Four hundred thirty-four patients were identified during the study period; 30 patients were excluded from the study for either not having had their surgery at MetroHealth or not following up after surgery at all. Eighty-five percent of patients were women, and the mean age was 49 years (range 15–84 years). The average weight, IBW, BMI, and BSA of the group was 85 ± 23 kg, 60 ± 5 kg, 31 ± 8 kg/m^2, and 2.0 ± 0.5 m^2, respectively. Three hundred forty-five patients underwent total thyroidectomy. Fifty-nine of 104 patients underwent thyroid lobectomy and required levothyroxine postoperatively; this included 20 patients who were on levothyroxine before undergoing thyroid lobectomy. The mean initial levothyroxine replacement dose in patients who underwent thyroidectomy was 1.4 μg/kg.

Two hundred eighty patients (70%) were able to achieve a euthyroid state (TSH 0.4–5.5 μU/mL) during the follow-up period; 124 patients failed to follow up after their first blood draw at 6 weeks after surgery when an adjustment was made in their levothyroxine dosage. Of the 280 patients who underwent either total thyroidectomy or lobectomy, 164 (59%) did not require any adjustment from their initial levothyroxine dosage, 63 (23%) patients had initial levothyroxine dosages that were too high, and 53 (18%) patients had initial dosages that were too low. Of the 116 patients who required an adjustment in their levothyroxine dose, 53 (46%) had a normal serum TSH level after a single dosage adjustment. Subanalysis for patients who underwent lobectomy and required levothyroxine replacement showed that this subset had a higher proportion (72%) of achieving euthyroidism after 6 weeks when compared with the total thyroidectomy patients (56%, P = not significant).

The mean final weight-based levothyroxine dosage that was required to achieve a euthyroid state in patients after total thyroidectomy was 1.5 μg/kg and 1.3 μg/kg in patients after thyroid lobectomy and isthmusectomy, respectively. On univariate analysis, patient age, BMI, and extent of surgery were found to be significantly correlated with the final levothyroxine dosage (Table 1). Older patients ($\geq$55 years), obese patients (BMI $\geq$30 kg/m^2), and patients

Table 1 The difference in weight-based levothyroxine dosing when evaluated for patient age, sex, BMI, and the extent of thyroidectomy

	Levothyroxine dose (μg/kg)	*t* test (*P* value)
Age (y)		
≤55	1.5	.01
>55	1.4	
Sex		
Female	1.5	.10
Male	1.4	
BMI (kg/m^2)		
≤30	1.5	.0002
>30	1.4	
Extent of thyroidectomy		
Total	1.5	.00002
Lobectomy	1.3	

BMI = body mass index.

who underwent thyroid lobectomy required lower weight-based levothyroxine therapy. Although sex did not appear to be a statistically significant factor on univariate analysis, there were more male patients who had underdosage (30%) of their initial levothyroxine therapy compared with their female counterparts (18%, $P = .05$).

A multivariate logistic regression analysis using backward elimination was performed to identify the model that would best predict the final levothyroxine dosage (μg) by incorporating patient age, sex, actual body weight, BMI, IBW, and BSA. Among the multiple models that were generated with the best R^2 score of .45, there was not 1 model (Table 2) with a better prediction for the final levothyroxine dose than the 1.5-μg/kg dosing for total thyroidectomy patients and 1.3 μg/kg for the thyroid lobectomy patients.

Comments

Levothyroxine replacement therapy for postsurgical hypothyroidism has been determined using a 1.6-μg/kg dosing regimen that was originally developed for the treatment of patients with primary hypothyroidism.[1] The purpose of this study was (1) to evaluate how accurate the 1.6-μg/kg dosing regimen was in producing a normal serum TSH level in patients who had partial or complete removal of the thyroid gland; (2) to determine whether other demographic factors affect levothyroxine dosing; and (3) to investigate whether the incorporation of other factors will help improve the accuracy of the initial thyroid hormone dosage determination. This was particularly important in our patient population because 30% of our patients failed to show up for subsequent serum TSH measurement and follow-up evaluation after an initial dosage adjustment at 6 weeks. Therefore, achieving a euthyroid state without the need for 1 or more dosage adjustments, serum TSH measurements, and office visits is a laudable goal.

Table 2 Various formulas for levothyroxine dose calculation generated by backward logistic analysis using patient factors

Levothyroxine dose (μg) =
1. 40 + actual weight (kg)
2. 55 + actual weight (kg) − 0.5 × age
3. 70 + actual weight (kg) − 0.4 × age + 10 (female) (1 = female, 0 = male)
4. 60 + 2.5 × BMI − 0.5 × age
5. 80 × BSA − 0.5 × age − 20

BMI = body mass index; BSA = body surface area.

In our study, we found that the best initial thyroid hormone dosage determination in patients who underwent total thyroidectomy and thyroid lobectomy with isthmusectomy was based on 1.5-μg/kg and 1.3-μg/kg estimation using actual body weight, respectively. Multiple formulas incorporating other factors were not able to provide a better prediction of the levothyroxine dose that resulted in euthyroidism defined by a serum TSH level in the normal range. Contrary to other studies, post-thyroidectomy patients did not require higher weight-based levothyroxine dosing when compared with patients who were treated for primary hypothyroidism.[3,7]

Although there was no alternative calculation that proved to be better than the weight-based dosing for patients who underwent thyroidectomy, we were able to identify some patients who might benefit from a lower levothyroxine dose than the 1.5 μg/kg- or 1.3-μg/kg dosing regimens. These include patients who are older than 55 years or have a BMI ≥30 kg/m^2. In clinical practice, this can be translated into picking a lower prescription dosage preparation when the calculated dosage is in between 2 prescription strengths. Premenopausal women have been shown to require the highest levothyroxine dosing when compared with men and postmenopausal women.[4–6] There was inadequate power to draw a firm conclusion regarding the effect of sex on levothyroxine replacement therapy in this study because the percentage of men was small. However, our study did confirm that older patients required less weight-based dosing. Similarly, patients who were obese required less levothyroxine when compared with their nonobese counterparts; this is likely because the fat cells are metabolically less active. Our findings are corroborated by Jonklaas[6]; his patients had a mean BMI of 27 kg/m^2 and required higher weight-based levothyroxine dosing (1.8 μg/kg) than our patients whose mean BMI was 32 kg/m^2.

The gastrointestinal absorption of levothyroxine may be affected by other medications being taken at the same time (eg, calcium supplements). Patients who take calcium supplements are often excluded from studies evaluating primary hypothyroidism[4] but that is not possible in surgical patients. Oral calcium is commonly given to patients

undergoing thyroidectomy postoperatively for the treatment of transient hypocalcemia. Patients are instructed to allow at least a 4-hour interval between levothyroxine and calcium supplements. The limitations of this study are that it was retrospective and it was difficult to discern if patients followed the instructions to correctly time their calcium intake. Therefore, we were not able to draw any conclusions regarding whether or not calcium supplementation affected the initial levothyroxine dosing and the patients' ability to achieve a euthyroid state.

In conclusion, we found that the simple calculation of 1.5 and 1.3 μg/kg of actual body weight after total thyroidectomy and thyroid lobectomy with isthmusectomy, respectively, was the best formula for determining an initial dose of levothyroxine that was most likely to result in a serum TSH level in a normal range. Using this formula, almost 60% of patients would achieve a euthyroid state within 6 weeks of surgery. Another 20% of patients would require only 1 dosage adjustment before the serum TSH level was in the normal range. However, based on the results of the study, we recommend choosing the lower of the 2 potential prescription strengths of levothyroxine for patients who are older than 55 years or patients who have a BMI $\geq$30 kg/m^2 when weight-based dosage calculations are in between 2 prescription strengths. Our study provides preliminary insight into the calculation of thyroid hormone replacement therapy in patients with postsurgical hypothyroidism. A prospective study will help confirm the results we have found in this study.

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Discussion

David F. Schneider, M.D. (Madison, WI): I just want to congratulate Dr McHenry and his colleagues on a very useful article on how to properly dose thyroid hormone after thyroidectomy. It is interesting that you have included patients who both had a total thyroidectomy as well as a thyroid lobectomy, and I think that it can be a little more challenging when a patient has native thyroid tissue still present, especially for patients who have underlying thyroiditis like Hashimoto thyroiditis. Do you know what proportion of the patients had a lobectomy? Also, for those patients was it more difficult to sort of get them euthyroid in terms of the length of time that it took you to become euthyroid? I am just wondering which terms in your multivariate analysis were significant, if any, such as BMI? Finally, you divided your patients using a BMI of 30, which I am assuming is because 30 defines obesity. Our group and others have found, like you have, that more obese patients require less thyroid hormone, and very thin patients actually require more. Therefore, I was wondering how did your weight-based calculation work at the extremes of BMI?.

Christopher R. McHenry, M.D. (Cleveland, OH): I cannot give you an exact number of the patients who had thyroiditis in our lobectomy group, but what I can tell you is that as a group we found that patients who underwent thyroid lobectomy actually achieved a euthyroid state with fewer adjustments in their doses of levothyroxine compared with patients who underwent total thyroidectomy. Approximately 20% of our patients who underwent lobectomy were actually on levothyroxine preoperatively. Then, they required dosage adjustments postoperatively. Because of the retrospective nature of the study, I do not know the actual cause of the hypothyroidism, and, as a result, I cannot specifically address your question if thyroid hormone dosing was more difficult in patients with thyroiditis. In answer to your second question, on univariate analysis, an age greater than 55 and BMI greater than 30 were predictors of lower levothyroxine dosage requirement. In the backward linear regression model that we use, we included age, sex, BMI, IBW, actual weight, and BSA. However, we were unable to really produce a better formula for estimating levothyroxine dosage than 1.5 and 1.3 μg/kg based on the actual body weight for total thyroidectomy and thyroid lobectomy. The average BMI in our patients was 31, so we chose to divide patients into groups based on their BMI of $\leq$30 or $>$30 just based on the definition of obesity. An increased BMI was predictive of a lower dosage requirement of levothyroxine in the univariate analysis as I mentioned, but its incorporation into various formulas did not really produce a better estimate of levothyroxine dosage requirement. In summary, what we now do is we take 1.5 μg/kg of the actual body weight or 1.3 μg/kg of the actual body weight after a lobectomy (1.5 for total thyroidectomy and 1.3 after thyroid lobectomy), and then we determined the total micrograms. Then, we look at the different formulations, and for patients who are older than 55 or who have a BMI greater than 30, we would choose the lower strength to try to adjust for those factors.

Scott M. Wilhelm, M.D. (Cleveland, OH): With regard to age, I routinely drop patients, especially in that elderly

category for risk of atrial fibrillation and things like that. Is that anything that you have seen in your practice in terms of elderly patients, dropping the dose specifically based for potential cardiac arrhythmia risks?

Dr McHenry: Ultimately, the dose will not change, but that is a significant point. In fact, what we will sometimes do and what my endocrinology colleagues will do is they will not start them on the full dose immediately. They will start them on a lower dose initially and then progressively increase the dose. And I do not know if that is any different. That is just my anecdotal experience. I have not done that. I have used this same approach for all patients.