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Levothyroxine Dose Following Thyroidectomy Is Affected by More Than Just Body Weight

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Objectives/Hypothesis: To determine the factors that affect levothyroxine (LT4) requirements following thyroidectomy.

Study Design: Retrospective study.

Methods: This study evaluated 246 participants who had undergone total thyroidectomy and were on a stable dose of LT4. Actual weight–based (AWB) and ideal body weight–based (IBWB) LT4 dose requirements were analyzed, and other confounders including adherence, concurrent medications, comorbidities, female menopausal status, and hormone replacement therapy were examined.

Results: A total of 205 women and 41 men were evaluated, with 48 (20%) benign and 198 (80%) malignant pathology findings. The mean AWB LT4 doses for men and premenopausal women were similar among members of the benign groups and similar among members of the malignant groups. There was a trend for lower dose LT4 in postmenopausal women off hormonal therapy (PM/NH) and on hormonal therapy (PM/H) in the benign group (1.4 and 1.6 μg/kg vs. 1.8 μg/kg in the men and premenopausal women) and a trend for lower dose LT4 in the PM/H women in the malignant group (1.9 μg/kgvs. 2.1 and 2.2 μg/kg in the men and premenopausal women), but they were not significant. However, PM/NH women required significantly less LT4 (1.7 μg/kg) than both the men (2.2 μg/kg) and premenopausal women (2.1 μg/kg) in the malignant group (P=.0006). The IBWB LT4 dosage was not statistically different between groups.

Conclusions: LT4 dosage following thyroidectomy, calculated using actual body weight, can range from 1.4 to 2.2 μg/kg and is dependent on diagnosis (benign vs. malignant), goal TSH, sex, and menopausal status.

Key Words: Thyroidectomy, thyroid nodules, thyroid cancer, thyroid hormone replacement, levothyroxine.

Level of Evidence: 2b.

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INTRODUCTION

Surgical removal of the thyroid gland necessitates replacement with exogenous thyroid hormone medication. Patients with differentiated thyroid cancer (Follicular, Papillary, or Hurthle cell) should be treated with thyroid hormone after total thyroidectomy for two purposes: to correct surgery-induced hypothyroidism and to suppress stimulated growth of persistent or recurrent neoplastic disease by reducing thyroid stimulating hormone (TSH), the main factor regulating the growth and differentiation of thyroid follicular cells.[1] Measurement of serum TSH permits this precise dosage titration of levothyroxine (LT4). TSH goals in differentiated thyroid cancer have been changing but in general are low normal to undetectable serum TSH values depending on initial stage or evidence of recurrence.[1–4] In benign surgically induced hypothyroidism, TSH concentrations are maintained in the normal range with LT4 therapy, and often clinical practice titrates to a tighter TSH goal of 1 to 2μIU/mL.

Not only do original diagnosis and TSH treatment goals affect LT4 dosage for the treatment of hypothyroidism, but many variables including body weight, sex, and concurrent medication usage also affect LT4 requirements. Reports in the literature and frequent current practice estimate a starting actual weight–based (AWB) dose of 1.7 μg/kg.[5,6] Alternatively, other studies have recommended LT4 doses ranging from 1.6 to 2.1 μg/kg.[6–13]

Absorption of thyroid hormone can be diminished when LT4 is administered with other medications, including ferrous sulfate, calcium carbonate, sucralfate, sevelamer, or proton-pump inhibitors (PPIs).[14–16] Alterations in LT4 binding or metabolism can also be seen with androgens and estrogens.[15,17] Differences in sex and an altered hormonal milieu also can play a role.[18] Lean body mass has also been suggested as a potential better estimate than total body weight to determine thyroid hormone replacement.[9] In addition, recent literature suggests AWB formulas provide only an approximate guide to LT4 requirements and further suggests using an ideal body weight–based (IBWB) LT4 dose instead.[18]

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This study used data from the Thyroid Tumor and Cancer Collaborative Registry (TCCR) at the University of Nebraska. The TCCR was jointly funded by the Department of Internal Medicine, the Department of Head and Neck Surgical Oncology, and the Eppley Cancer Center, University of Nebraska Medical Center, Omaha, Nebraska.

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We sought to assess LT4 dose requirements following thyroidectomy for both benign and malignant thyroid disease by taking into consideration all potential variables including actual and ideal body weight, age, sex, TSH goals, medications, female menopausal status, adherence, and radioactive iodine administration for the treatment of thyroid cancer. We used data from the University of Nebraska Medical Center (UNMC) Thyroid Tumor and Cancer Collaborative Registry (TCCR) in Omaha, Nebraska.

MATERIALS AND METHODS

The TCCR is a thyroid nodule and cancer registry and biospecimen bank created at the UNMC to provide data, biospecimens, and support services for multidisciplinary research on thyroid nodules and thyroid cancer. All patients give informed consent to be a part of the registry and complete a standardized questionnaire with personal information about themselves, their medical history, their diet and lifestyle habits, past or current environmental exposures, and they re-create their family tree. Data from the medical record including pertinent laboratory and imaging are also added to the TCCR. This study was approved by the UNMC institutional review board and Eppley Cancer Center (at UNMC) Scientific Review Committee.

This is a retrospective analysis of all 264 patients in the UNMCTCCR with thyroid nodules or cancer who underwent total thyroidectomy. Patients were enrolled in the TCCR from March 2008 through September 2010; however, thyroidectomy could have been done any time prior to enrollment. Standard practice at UNMCis to perform a total thyroidectomy for anyone who is a candidate for thyroidectomy; partial thyroidectomy was not done. All subjects provided informed consent to be included in the UNMCTCCR. There were no enrollment restrictions based on sex, child-bearing potential, or ethnicity. Adult subjects were 19 years or older. Patients who were pregnant, had been lactating within the last 6 months, had a history of thyroid cancer treatment within the last 3 months, and those who took triiodothyronine therapy were excluded.

Clinical information obtained from the medical records as patient anthropomorphic data included actual weight, height, calculated body mass index (BMI), and calculated ideal body weightbased on previous literature (female: 45kg plus 2.3 kg for each 2.5 cm above 152cm; male: 48 kg plus 2.7 kg for every 2.5 cm above 152 cm),[18] age, and sex. Laboratory data obtained included TSH levels at a stable LT4 dose (most recent time when TSH was in treatment goal range and dose unchanged at clinic visit), thyroid antibodies (antithyroglobulin or antimicrosomal/TPO) positivity, and thyroid pathology. Information regarding each participant's thyroid cancer or thyroid nodule was obtained from the TCCR or medical record if necessary. Other specific information obtained from participants included stable LT4 dose, adherence (based on physician and self-reported data when documented in medical record), date of thyroidectomy, preexisting hypothyroidism or hyperthyroidism, history of radioactive iodine ablation, comorbidities (including malabsorption, congestive heart failure [ejection fraction <50%], renal insufficiency [glomerular filtration rate (GMR)<60], or other malignancies), menopausal status (females considered postmenopausal ifthey reported menopause, had unknown menopausal status but age >52 years, were taking hormonal replacement therapy, had a history of surgicallyinduced menopause, or reported the presence of vasomotor symptoms), and medication lists (including calcium carbonate/vitamin D, multivitamins, ferrous sulfate, sucralfate, proton pump inhibitors, phosphate binders, estrogens [± progesterone], or androgens).

Descriptive statistics included means, standard deviations, and medians. Ranges for continuous variables, and frequencies and proportions for categorical variables, were used. The independent sample t test was used to compare the AWB LT4 dose (in micrograms per kilogram) and LT4 requirements based on ideal body weight between categorical groups (e.g., sex, etiology). Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models were used to look at the association of more than one factor with weight-based LT4 dosage. ANOVA models included the main effects (e.g., sex, etiology of thyroid disease) and interaction of the main effects. If the interaction term was not statistically significant, then a main-effects ANOVA model was used. The Pearson correlation coefficient was used to look at the association of continuous variables. $P<.05$ was considered statistically significant. SAS software version 9.2 (SAS Institute, Cary, NC) was used for data analysis.

RESULTS

A total of 264 patients were evaluated (2 were excluded owing to lack of initial pathology information; 16 patients were excluded because of TSH levels >5 μIU/mL and lack of stable LT4 dose). Analyses were conducted on 246 patients (205 women, 41 men) with 48 (20%) benign and 198 (80%) malignant pathology findings.

Sex was similar in the benign and malignant groups. The benign cohort was significantly older and heavier (mean age, 51.5 years; BMI=32.5) compared to the malignant group (45.2 years, P=.005; BMI= 29, P=.04). As expected, TSH levels were significantly different between etiologies ($P < .001$), with a mean TSH of 1.3 μIU/mL in the benign cohort and a malignant mean TSH of 0.4 μIU/mL. Overall adherence in taking LT4 between the two groups was not significantly different. The presence of preexisting hypothyroidism and hyperthyroidism before thyroidectomy was statistically different between groups, with 12 of 48 (25%) benign and 18 of 198 (9%) malignant patients having preexisting hypothyroidism ($P = .005$) and 14 of 48 (29%) benign and 11 of 198 (6%) malignant patients having preexisting hyperthyroidism ($P < .0001$) (Table I).

Initial analysis evaluating all patients of both benign and malignant etiologies showed that the overall AWB LT4 doses for benign to be 1.62 μg/kgand malignant 1.99 μg/kg ($P < .0001$). The most common medication reported for the entire study group was calcium/vitamin D (143 of 246, 58%), which was equally distributed in the benign and malignant cohorts ($P = 1.0$). This was followed by multivitamin use in 44% of the study population (also equally distributed between etiologies, $P = 1.0$). PPIs were used by 19% of the study participants, and 30% (14 of 47) of these patients had benign etiology compared to 70% with malignant disease ($P = .06$). Renal insufficiency (GFR < 60) was the most common medical illness seen (19 of 246, 8%) in our study population, with six (32%) of these patients having benign thyroid disease and the other 13 (68%) thyroid malignancy. Ten other malignancies besides thyroid cancer were seen in the study in 16 of 246 (7%) patients; seven of 16 (44%) of these patients had benign thyroid pathology compared to nine of 16 (56%) with malignancy. Overall, no significant difference was seen in the mean AWB LT4 dose among patients who used any

TABLE I.
Descriptive Statistics by Etiology.

	Benign, n = 48, 20%	Malignant, n = 198, 80%	*P*
Male, no. (%)	6/48 (13)	35/198 (18)	.52
Female, no. (%)	42/48 (87)	163/198 (82)	.52
Age (±SD), yr	51.5 (±14.4)	42.2 (±13.6)	.005
BMI(±SD)	32.5 (±9.6)	29.3 (±7.6)	.04
TSH (±SD), μlU/mL	1.3 (±1.1)	0.4 (±0.6)	.0001
Adherence to LT4 medication, no. (%)	37/48 (77)	161/198 (81)	.054
Preexisting hypothyroidism, no. (%)	12/48 (25)	18/198 (9)	.005
Preexisting hyperthyroidism, no. (%)	14/48 (29)	11/198 (6)	.0001

SD = standard deviation; BMI =body mass index (calculated as weight in kilograms divided by the square of the height in meters); TSH = thyroid-stimulating hormone; LT4 = levothyroxine.

medications and those that did not use medications (calcium/vitamin D, $P = .81$; PPI, $P = .29$) or had renal insufficiency (GFR< 60; $P = .89$) in both the benign and malignant groups.

Of the 205 women evaluated, 121 (59%) were premenopausal, and 84 (41%) were postmenopausal. In the benign group, 17 of 121 were premenopausal, and 25 of 84 were postmenopausal; in the malignant group, 104 of 121 were premenopausal and 59 of 84 were postmenopausal women. Hormone use differed between premenopausal and postmenopausal groups. In the premenopausal group, 32 of 121 (26%) took oral contraceptives (estrogen plus progesterone). Of these 32 women, four (13%) had benign pathology and 28 (87%) had malignant disease. Hormone therapy use in postmenopausal women was present with estrogen alone in 12 of 84 (14%) women, including six (50%) with benign thyroid disease and the other half with malignancy. Combination estrogen and progesterone was used by 18% (15 of 84) of postmenopausal women, which included one woman with benign thyroid etiology and 14 of 15 (93%) with malignant etiology.

Of the 198 malignant patients, three-fourths (147 of 198) in the study were AJCC TNM stage I, compared with 5% stage II, 11% stage III, and 9% stage IV. Radioactive iodine (RAI I-131) ablation therapy was administered to 88% (175 of 198) of malignant patients. Further analysis showed patients who received RAI I-131 ablation needed a higher AWB LT4 dose (2.0 μg/kg vs. 1.7 μg/kg) compared to those not ablated after adjusting for TSH (P=.02).

Thyroid etiology, sex, and menopausal status (male, premenopausal female, and postmenopausal female) were independently associated with AWB LT4 dose (P=.002 for all) in a multivariate model that also included age. Further analysis was done dividing women in both etiology cohorts into premenopausal, postmenopausal on hormonal therapy (PM/H) (estrogen or estrogen + progesterone), and postmenopausal not taking hormones (PM/NH). In patients with malignant disease, overall significant differences in AWB LT4 dose between males, premenopausal women, and postmenopausal women were seen; specifically, between males and PM/NH (2.2 μg/kg vs. 1.7 μg/kg, P=.0006) and premenopausal and PM/NH (2.1 μg/kg vs. 1.7 μg/kg, P=.005) (Table II). There was not a statistically significant difference in the mean LT4 dose between the foursex/menopausal groups with benign etiology when using actual weight (P=.08); however, there was a trend for lower LT4 dose in the postmenopausal groups (PM/NH= 1.4 μg/kg; PM/H= 1.6 μg/kg vs. 1.8 μg/kg in men and premenopausal women). The IBWBLT4 dosewas

TABLE II.
Levothyroxine Dose Requirements After Total Thyroidectomy.

	Benign	Malignant
Actual-weight LT4 dose requirements, μg/kg (±SD)		
Men	1.8 (± 0.05)	2.2 (±0.6)*
Premenopausal women	1.8 (±0.4)	2.1 (±0.6)†
Postmenopausal women on hormonal therapy	1.6 (±0.07)	1.9 (±0.5)
Postmenopausal women not taking hormones	1.4 (±0.3)	1.7 (±0.4)*,†
Ideal-body-weight LT4 dose requirements, μg/kg (±SD)		
Men	2.4 (±0.4)	2.7 (±0.7)
Premenopausal women	2.5 (±0.7)	2.9 (±1.3)
Postmenopausal women on hormonal therapy	2.4 (±0.9)	2.4 (±0.9)
Postmenopausal women not taking hormones	2.3 (±0.7)	2.4 (±0.7)

*P = .0006; men versus postmenopausal women not taking hormones.
†P = .005; premenopausal women versus postmenopausal women not taking hormones.
LT4 = levothyroxine; SD = standard deviation.

similar across thyroid etiology and sex/menopausal status after controlling for age ($P = .24$ in benign cohort, $P = .1$ in malignancy).

DISCUSSION

Because TSH goals are different for patients with well-differentiated thyroid cancer and those with benign disease, we expected that the weight-based dose for replacement of thyroid hormone following thyroidectomy would be different between these groups. When dosing LT4 following total thyroidectomy for benign disease, the TSH target is usually mid-normal range. However, LT4 dosing after total thyroidectomy for malignant disease is often higher because TSH goals are lower. In general, LT4 is dosed to attain a low normal TSH or suppressed TSH, depending on the stage, but also to avoid overt hyperthyroidism. Our data confirm that these different treatment goals were attained, as evidenced by our mean TSH values in the benign group of 1.3 μIU/mL and mean TSH in the malignant group of 0.4 μIU/mL. Most of the literature on LT4 dosage relates to treatment of primary hypothyroidism,[12] with only a small number of studies specifically addressing the issue of surgically induced hypothyroidism from either benign or malignant pathologies. Given that the treatment goals are different, we aimed to examine weight-based LT4 dosage after total thyroidectomy for both benign and malignant conditions. Overall, the weight-based doses of thyroid hormone replacement in the malignant groups were higher than the same groups with benign etiology (i.e., in men, the malignant group mean LT4 was 2.2 ± 0.6 vs. the benign group mean of 1.8 ± 0.5) (Table II). These results were similar to previous literature showing that thyroid cancer patients required approximately 30% greater LT4 dose compared to hypothyroidism from benign disease.[7]

In the malignant groups, men and premenopausal women required the highest dose of LT4 compared to postmenopausal women overall. There was a trend for lower requirements in postmenopausal women on hormone therapy that was not statistically different, but the men and premenopausal women requirements were significantly higher than the postmenopausal women on no hormone therapy. This is in contrast to a recent study that showed pre- and postmenopausal women required a higher AWB dose of LT4 compared to men with both benign and malignant etiologies.[18] A possible explanation for the differences seen is that our study has a larger sample size and broader age range. Other studies[9] have reported men requiring higher absolute values of LT4 compared to females when based on lean body mass; however, there was no difference when corrected for body weight. Differences in LT4 dosage in premenopausal and postmenopausal women have been explained by differences in hormonal milieu.[18] Studies have reported an increased need for LT4 in women with hypothyroidism during estrogen therapy.[17] Our data support this given the significant differences in AWB LT4 requirements between premenopausal women and PM/NH. Another consideration affecting the dose difference of LT4 between menopausal groups of women is age, because LT4 requirements are known to progressively decrease with age.[11,19] However, our results showed statistical difference between the sex/menopause groups after controlling for age, and there was no difference in the LT4 requirements between premenopausal women and PM/H; thus, hormone status likely played the greatest role.

Overall, IBWB LT4 requirements between sex/menopause groups for each etiology were not statistically different. IBWB calculations already take into account sex, as separate formulas exist for males and females. The actual IBWB calculations used in this study were the same as those in recent studies[18] and are among the most commonly used formulas, giving greater accuracy to the findings. Another explanation for the more accurate prediction obtained using IBWB calculations is that body composition in the postmenopausal period changes because of a relative decrease in lean body mass with age compared to an increase of visceral fat mass.[9] Overall, similar trends were seen when comparing IBWB LT4 dosage to using actual body weight, although this was not statistically significant. For example, malignant patients required more LT4 as compared to benign patients. Also using IBWB calculations for LT4 dosage in this study, PM/NH required the least amount of LT4 in both etiologies compared to the other three sex/menopause groups.

CONCLUSION

LT4 dosage following thyroidectomy, calculated using actual body weight, should be determined based on operative diagnosis (benign vs. malignant) and appropriate treatment goals, sex, and menopausal status. All these factors can influence the AWB dose requirements for patients undergoing thyroidectomy and need to be considered to optimally dose LT4. In contrast, LT4 requirements using ideal body weight are not statistically different, making weight-based calculation of LT4 dose using IBW another reasonable option.

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