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Levothyroxine Replacement Doses Are Affected by Gender and Weight, But Not Age

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Background: Body weight (BW) and age have been shown to affect the dose of levothyroxine (LT_4) that results in normalization of serum thyroid-stimulating hormone (TSH) in hypothyroid patients. Our objective was to determine whether gender, menstrual status, and ideal BW (IBW) also affect the LT_4 dose required to achieve a serum TSH within the normal range.
Methods: We retrospectively reviewed the charts of patients being treated for primary hypothyroidism who had TSH values within a normal range. We selected patients aged 18–85 years who were taking LT_4 without any confounding medications, and who had no serious chronic conditions. Their LT_4 doses, referred to here as LT_4 dose requirements, based on both BW and IBW were documented. The relationship between gender, menstrual status, age, serum TSH concentrations, and the degree of overweight on LT_4 dose requirements were determined using multivariate analyses.
Results: Women were significantly more overweight than men (ratio of BW/IBW was 1.35 for women vs. 1.17 for men, $p < 0.0001$). LT_4 requirements based on BW did not differ by gender when age was included in the model. However, when degree of overweight was also included, men required lower LT_4 doses than both premenopausal women (1.34 μg/kg vs. 1.51 μg/kg, $p = 0.038$) and menopausal women (1.34 μg/kg vs. 1.49 μg/kg, $p = 0.023$). When examining IBW using a model incorporating age, men also required lower LT_4 doses than both premenopausal women (1.64 μg/kg vs. 1.92 μg/kg, $p = 0.0033$) and menopausal women (1.64 μg/kg vs. 1.90 μg/kg, $p = 0.0024$). Serum TSH concentrations were not significantly different in any of the gender groups. There was no relationship between serum TSH and either age or BW. The initial serum TSH concentration was by design with the normal range, but the concentration within that range was not a significant predictor of the LT_4 replacement dose in any of the models.
Conclusion: In contrast to previous studies suggesting that age affects LT_4 replacement requirements, we found that age-based differences in doses are secondary to differences in BW and gender. In addition, in contrast to prior studies showing that lean body mass, but not gender, affected LT_4 dose, we instead found a significant impact of gender. Gender-based differences in dose requirement only became apparent either when IBW was used to correct for the dose or when degree of overweight was included in the model. Gender differences in LT_4 dose requirement exist, but are masked unless gender-based differences in degree of overweight are also considered.

Introduction

One approach to treatment with levothyroxine (LT_4) in patients with hypothyroidism is to initiate a dose based on the patient's body weight (BW) (1,2). Serum thyroid-stimulating hormone (TSH) can then be checked periodically and the LT_4 dose titrated until the desired serum TSH is reached. Various studies have estimated the magnitude of replacement or suppressive doses of LT_4 in hypothyroid patients based on their BW. These estimates include 1.6 μg (1–8), 1.7 μg (4,6), 1.8 μg (5,9), 2.0 μg (9), and 2.1 μg (5) LT_4 per kilogram actual BW. LT_4 replacement doses in thyroid cancer patients requiring TSH suppression are generally higher and on the order of 2.0–2.56 μg/kg (1,5,6). A study by Santini *et al.* showed that ideal BW (IBW) is a better predictor of LT_4 dose than actual BW and that any gender differences in LT_4 dose requirement were accounted for by lean body mass (5).

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Other factors also play a role in LT_4 dose requirement in individual patients. One such factor is the amount of LT_4 absorbed in the gastrointestinal tract, which is altered by various medical disorders (10–12), several medications (13–16), and food and drink (17–19). The timing of LT_4 administration also has an impact on its absorption (18,20–22). Another factor influencing LT_4 dose requirement is residual thyroid function, which in turn is dependent on the etiology of the hypothyroidism. Treatment of patients with hypothyroidism due to Hashimoto's thyroiditis or radioiodine ablation of Graves' disease requires lesser doses of LT_4 than treatment of patients who have a complete absence of thyroid tissue (4,6). Other factors implicated in modifying LT_4 dose requirement include medications altering thyroxine binding or metabolism (23,24) and patient age, with dose requirements decreasing with increasing age (9,25–27).

A recent secondary analysis examined the impact of gender and age on LT_4 dose requirement (28). This small study suggested that when BW was used, premenopausal women appeared to have a greater dosage requirement than either menopausal women or men. However, when IBW was used, the requirement of premenopausal women became similar to that of their menopausal counterparts, with the lesser requirement of men persisting. This study did not include a full age range for men and was inadequately powered to separate the impact of age, gender, and menstrual status. Therefore, a study having these attributes was performed. The objective of this study was to determine if there were differences in LT_4 dose requirement in hypothyroid patients based on their gender, female menstrual status, weight, degree of overweight, and age.

Methods

Patient selection

This was a retrospective chart review of patients being followed in our endocrine division between July 2007 and April 2010. Data were abstracted between July 2009 and May 2010. Institutional review board approval was obtained before study commencement. Subjects included both men and women between ages 18 and 85 years who carried a diagnosis of primary hypothyroidism. They were required to be on a minimum of 75 μg LT_4 a day for at least 1 year, and to have been consistently euthyroid on a stable dose of LT_4 for the past 6 months before the initial data point. Euthyroidism was defined as a serum TSH within the range of 0.4–3.5 mIU/L. TSH was thus by design with the normal range. Patients taking medications known to interfere with LT_4 absorption or alter LT_4 binding proteins (e.g., estrogen and testosterone) were excluded from participation. Other medications leading to exclusion were iodine, propranolol, amiodarone, lithium, dopamine agonists or antagonists, somatostatin analogues, steroids, phenytoin, carbamazepine, sertraline, rifampin, bile acid sequestrants, antacids, kayexalate, cholestyramine, colestipol, and raloxifene. Times of LT_4, meal, and coffee consumption, if documented in the patient chart, were recorded. Patients taking calcium, iron, and multivitamins were excluded, unless there was documentation in the chart that the consumption of LT_4 and these products was separated by at least 4 hours. Pregnant or lactating patients were not eligible. Patients with chronic, serious diseases such as cardiac, pulmonary, gastro-intestinal, renal, and pituitary disease were ineligible for study participation. Patients were required to have been diagnosed with hypothyroidism at least 12 months prior to when their initial study data were collected. Patients with a fluctuation in weight of >15% in the previous 12 months were excluded from the study.

Data collection

The data collected included subject age, gender, height, BW, menopausal status for women, LT_4 dose, LT_4 brand, time of LT_4 ingestion, TSH and free thyroxine concentration during a time of LT_4 dose constancy, and BW stability. BW was recorded using the endocrine clinic weighing scales and stadiometer; outer garments were removed before obtaining BW. IBW was calculated based on subject height using the Devine formula as follows: for women over 5 feet (152 cm), 100 lb (45 kg) plus 5 lb (2.3 kg) for each additional inch (2.5 cm); for women under 5 feet (152 cm), 100 lb (45 kg) minus 5 lb (2.3 kg) for each additional inch (2.5 cm) under 5 feet; for men over 5 feet (152 cm), 106 lb (48 kg) plus 6 lb (2.7 kg) for each additional inch (2.5 cm). TSH was analyzed by Quest Diagnostics, LabCorp, or Georgetown University Laboratory, as designated by the patient's insurance company. TSH assays used by these clinical laboratories employed a third-generation ultra-sensitive immunochemiluminometric assay with a sensitivity of 0.01 mIU/L (laboratory reference ranges approximately 0.4–4.5 mIU/L). Some patients had more than one TSH value available during the period under examination. The TSH values for each patient were therefore calculated as the mean of the total number of TSH values per patient. A LT_4 dose requirement for each individual patient was then generated as both μg per kilogram BW per day and μg per kilogram IBW per day.

Statistical methods

Using the means and standard deviations from preliminary data and a significance level of 0.05, a total sample size of 200 was estimated to have 90% power to detect a statistically significant association between BW, gender, and age.

The primary endpoint of the study was to estimate differences in LT_4 dose requirement in hypothyroid patients based on gender, menstrual status in women, actual BW, IBW, and age. We also wished to assess the effect of actual BW versus IBW on dose requirement by examining the effect of degree of overweight on the LT_4 dose that was required to normalize serum TSH.

Continuous variables were summarized as means, standard deviations, minimum, and maximum values. The *t*-test or analysis of variance, as applicable, was used to compare continuous measures among gender groups. Categorical variables were summarized as counts and percentages and analyzed for differences among groups via a chi-square test. Gender was classified into three distinct groups: men, premenopausal women, and menopausal women. For those women in whom the menstrual status was not clearly discernible from the chart, an age cut off of 51 years was chosen (29–31), above which women were considered menopausal. The effect of gender or menstrual status (for women) on LT_4 doses was tested using a general linear model. Both bivariate and multivariate regressions were used.

Multivariate models were generated with LT_4 dose based on either BW or IBW as the dependent variables, and with

gender, TSH value, age, and degree of overweight included as independent variables. TSH was designated as an independent variable as all "normal" TSH values were accepted. While the study population was restricted to patients with normal TSH levels, there was still variability in TSH values that we wished to adjust for by including it in the models. Degree of overweight was calculated as actual BW divided by IBW. The TSH covariate in the models was calculated as the mean of all available TSH values per patient. The *p*-values obtained in the multivariate models showed statistical significance for each variable after adjustment for all other variables in the model. Adjusted mean LT_4 doses by group were reported for each multivariate model. A *p*-value was of <0.05 was considered significant. All analyses were conducted in SAS 9.1 (Cary, North Carolina).

Results

A total of 1015 charts were reviewed; out of these, 248 patients (69 men and 179 women) met the eligibility criteria. The reasons for exclusion of 75% of patients were primarily confounding medications, alterations in LT_4 dose, out of range TSH values, or missing data. Out of the 179 women, 88 were premenopausal and 91 were menopausal. Ten patients were missing data about their menstrual status and were assigned a status based on their age. Most subjects (70%) had Hashimoto's disease as the cause of their hypothyroidism, and mean duration of treatment with LT_4 was 6.7 years. The average dose requirement for patients with Hashimoto's was 1.45 μg/kg, compared with 1.48 μg/kg for other causes (radioactive iodine-induced, radiation-associated, or surgical). The mean number of TSH values per patient during the observation period was 1.5 (55% of patients had one TSH value; 40% had two TSH values).

Table 1 shows the mean age, TSH value, BW, IBW, and degree of overweight for the study subjects divided into their gender/menstrual status groupings. There was no evidence that age differed significantly between men and all women ($p = 0.081$). When looking at the three groups (premenopausal women, menopausal women, and men) separately, there was a statistically significant difference in age between the groups ($p < 0.0001$). On average, male patients were younger than menopausal women (53.0 vs. 60.5 years) and older than premenopausal women (53.0 vs. 38.2 years). There was no evidence of a significant association between mean TSH value and the three gender groups ($p = 0.79$). Etiology of hypothyroidism ($p = 0.41$) and LT_4 brand ($p = 0.20$) also did not differ between groups.

There were, however, significant differences in the BW, IBW, and degree of overweight among the gender groups. Looking at BW, pair-wise comparisons revealed that men were significantly heavier than both groups of women ($p < 0.0001$ for men vs. premenopausal women, $p = 0.003$ for men vs. menopausal women), but the two groups of women did not differ. Pair-wise comparisons of IBW revealed that men were significantly different from both groups of women ($p < 0.0001$ for both), but the two groups of women, again, did not differ. Degree of overweight was significantly higher in women (premenopausal and menopausal groups combined) than in men (1.35 vs. 1.17, $p < 0.0001$). When comparing all three groups, the difference was significant as well ($p < 0.0001$). Further analysis revealed that men were significantly less overweight than each female group (1.17 vs. 1.30, $p = 0.0371$ and 1.17 vs. 1.40, $p < 0.0001$ for premenopausal and menopausal women, respectively). There was no correlation between serum TSH and either age or BW ($p = 0.76$ and 0.61 respectively).

Table 2 shows the LT_4 dose requirement based on BW and IBW according to gender groups. When looking at LT_4 dose based on BW, there was a different requirement across individual groups. With respect to pair-wise group comparisons, there initially appeared to be a different requirement for premenopausal women compared to menopausal women ($p = 0.0074$). However, after adjusting for age, this difference was no longer significant (*p*-value 0.34). Etiology of hypothyroidism and brand name of LT_4 did not affect dose requirement (*p*-values = 0.56 and 0.66, respectively), and so all etiologies and brand names were combined in the multivariate analyses. Time of LT_4 ingestion with respect to food and coffee could only be ascertained in 10% and 3% of patients, respectively, and so was not analyzed.

When a multivariate model employing gender (men vs. premenopausal women vs. postmenopausal women), age, and mean TSH value as independent variables was employed to predict LT_4 dose based on BW, none of the independent variables in this model were significant predictors (see Table 3). Specifically, there was no difference in the effect of gender (men vs. premenopausal women vs. postmenopausal women) ($p = 0.33$), age ($p = 0.22$), or mean TSH value ($p = 0.36$) on LT_4

Table 1. Descriptive Statistics for Study Subjects Showing Age, Thyroid-Stimulating Hormone Concentration, Body Weight, Ideal Body Weight, and Degree of Overweight According to Gender Groups

	Age (years)	*Mean TSH concentration (mIU/L)*	*BW (kg)*	*IBW (kg)*	*Degree of overweight (BW/IBW)*
Gender (mean ± SD)					
Men ($n = 69$)	53.0 ± 14.4	1.78 ± 1.05	88.1 ± 22.5	74.8 ± 6.8	1.17 ± 0.26
All women ($n = 179$)	49.5 ± 13.9	1.69 ± 1.22	75.5 ± 19.8	56.1 ± 5.8	1.35 ± 0.34
Premenopausal women ($n = 88$)	38.2 ± 7.3	1.72 ± 1.38	74.1 ± 19.5	57.1 ± 6.0	1.30 ± 0.34
Menopausal women ($n = 91$)	60.5 ± 9.1	1.65 ± 1.05	77.2 ± 20.1	55.3 ± 5.5	1.40 ± 0.34
All ($n = 248$)	50.5 ± 14.1	1.71 ± 1.17	79.0 ± 21.3	61.3 ± 10.4	1.30 ± 0.33
p-Value for significance					
Men compared with all women (pairwise comparison)	0.081	0.58	<0.0001	<0.0001	<0.0001
All 3 groups compared (ANOVA)	<0.0001	0.79	<0.0001	<0.0001	<0.0001

TSH, thyroid-stimulating hormone; BW, body weight; IBW, ideal body weight; ANOVA, analysis of variance; SD, standard deviation.

Table 2. Mean Levothyroxine Dose Calculated Based on Actual Body Weight and Ideal Body Weight According to Gender Groups

	LT4 dose/actual BW (μg/kg)	*LT4 dose/IBW (μg/kg)*
Gender (mean [unadjusted] ± SD)		
Men ($n = 69$)	1.42 ± 0.38	1.62 ± 0.40
All women ($n = 179$)	1.47 ± 0.43	1.92 ± 0.50
Premenopausal women ($n = 88$)	1.56 ± 0.42	1.98 ± 0.52
Menopausal women ($n = 91$)	1.38 ± 0.42	1.86 ± 0.47
All ($n = 248$)	1.46 ± 0.42	1.83 ± 0.49
p-Value for significance		
Men compared with all women (pairwise comparison)	0.40	<0.0001
All 3 groups compared (ANOVA)	0.0075	<0.0001
Men compared with premenopausal women (pairwise comparison)	0.074	<0.0001 (after age adjustment 0.0029)
Men compared with menopausal women (pairwise comparison)	0.80	0.0059 (after age adjustment 0.0021)
Premenopausal and menopausal women compared (pairwise comparison)	0.0074 (after age adjustment 0.34)	0.20

LT4, levothyroxine.

dose based on BW. With respect to TSH, there was no significant relationship between serum TSH and the LT_4 dose based on BW (regression coefficient −0.0206, $p = 0.35$).

A different pattern was found when examining IBW (see Table 2). LT_4 dose based on IBW was found to be significantly different between men and women ($p < 0.0001$) with men exhibiting lower dose requirements than women (1.62 μg/kg vs. 1.92 μg/kg). Pair-wise comparisons revealed that LT_4 dose based on IBW differed significantly between men and premenopausal women ($p < 0.0001$), as well as men and menopausal women ($p = 0.0059$), with men requiring lower doses than both groups of women. These differences persisted even after adjusting for age (*p*-value 0.0029 for premenopausal women vs. men and *p*-value 0.0021 for menopausal women vs. men).

Table 3. Multivariate Model Predicting Levothyroxine Dose Per Actual Body Weight or Ideal Body Weight with Gender (Men vs. Premenopausal Women vs. Menopausal Women), Age, and Mean Thyroid-Stimulating Hormone Value as Independent Variables

Model	*LT4 dose/actual BW*	*LT4 dose/IBW*
Independent variables	p-*Value in model*	p-*Value in model*
Gender	0.33	0.0003
Age	0.22	0.11
Mean TSH	0.36	0.10
Gender	*Adjusted mean (LT4 dose in μg/kg actual BW) based on model*	*Adjusted mean (LT4 dose in μg/kg IBW) based on model*
Men	1.43	1.64
Premenopausal women	1.53	1.92
Menopausal women	1.41	1.90
Pairwise comparison		p-*Value for comparison*
Men vs. premenopausal women	—	0.0033
Men vs. menopausal women	—	0.0024
Premenopausal vs. menopausal women	—	0.97

When using multivariate regression analyses (see Table 3), the gender effect on LT_4 requirement based on IBW was statistically significant ($p = 0.0003$). The effects of age and serum TSH on LT_4 dose requirement, however, were not significant. With respect to TSH, there was no significant relationship between serum TSH and the LT_4 dose based on IBW (regression coefficient −0.042, $p = 0.10$). Looking at pair-wise comparisons (see Table 3), men exhibited lower LT_4 requirements based on IBW than both premenopausal women (1.64 μg/kg vs. 1.92 μg/kg, $p = 0.0033$) and menopausal women (1.64 μg/kg vs. 1.90 μg/kg, $p = 0.0024$). There was no difference in LT_4 dose requirement based on IBW between the premenopausal and menopausal women (*p*-value 0.97).

As shown in Table 1, there were significant differences in degree of overweight between the genders. We postulated that degree of overweight might better reflect differences in body composition between genders than either BW or IBW. We, therefore, further analyzed the data while including degree of overweight as an independent variable in the model. Additionally, in the model for LT_4 dose based on BW a squared term for degree of overweight was included in all models, to account for the slight curvature in the relationship between LT_4 dose/BW and degree of overweight. This squared term was not included in the models for LT_4 dose based on IBW, as in this case the relationship between dose and degree of overweight appeared to be linear.

In a multivariate model predicting LT_4 dose based on BW with gender, age, mean TSH, degree of overweight, and degree of overweight squared as explanatory variables (see Table 4), men exhibited lower LT_4 dose requirements than

Table 4. Multivariate Model Predicting Levothyroxine Dose Per Actual Body Weight or Ideal Body Weight with Gender (Men vs. Premenopausal Women vs. Menopausal Women), Age, Mean Thyroid-Stimulating Hormone Value, and Degree of Overweight as Independent Variables

Model	*LT4 dose/actual BW*	*LT4 dose/IBW*
Independent variables	p-*Value in model*	p-*Value in model*
Gender	0.0084	0.016
Age	0.064	0.12
Mean TSH	0.061	0.12
Degree of overweight	<0.0001	<0.0001
Degree of overweight squared	0.0002	—
Gender	*Adjusted mean (LT4 dose in μg/kg actual BW) based on model*	*Adjusted mean (LT4 dose in μg/kg IBW) based on model*
Men	1.34	1.70
Premenopausal women	1.51	1.93
Menopausal women	1.49	1.84
Pairwise comparison	p-*Value for comparison*	p-*Value for comparison*
Men vs. premenopausal women	0.023	0.018
Men vs. menopausal women	0.038	0.15
Premenopausal vs. menopausal women	0.95	0.63

both premenopausal ($p = 0.023$) and menopausal women ($p = 0.038$). Degree of overweight was a significant covariate, as was the squared term, which suggests the presence of a nonlinear relationship between LT_4 dose based on BW and degree of overweight. A greater degree of overweight was associated with a lower LT_4 dose requirement ($p < 0.0001$). There was a trend for both age and mean TSH to be significant covariates. Regarding the relationship between serum TSH and LT_4 dose, the regression coefficient was -0.036, ($p = 0.06$).

In a multivariate model predicting LT_4 dose based on IBW with gender, age, mean TSH, and degree of overweight as explanatory variables (see Table 4), men exhibited lower LT_4 dose requirements than premenopausal women ($p = 0.018$). Compared with the model examining dose based on BW, there was no longer a significant difference between men and menopausal women. Degree of overweight was a significant covariate, with higher degree of overweight being associated with a higher LT_4 dose ($p < 0.0001$). (A higher LT_4 requirement based on IBW is seen with higher degrees of overweight as IBW is in the denominator for both dose requirement [LT_4 dose/IBW] and degree of overweight [BW/IBW]. This is in contrast to the situation with LT_4 dose/BW. In this case LT_4 dose/BW has BW as the denominator, but degree of overweight [BW/IBW] has BW as the numerator.) There was no relationship between TSH and LT_4 dose based on IBW (regression coefficient -0.038, $p = 0.12$).

Discussion

In the present analyses we show that gender, menstrual status, and degree of overweight all can, under various circumstances, affect LT_4 dose requirement based on either BW or IBW. Moreover, when all these variables are considered together in multivariate analyses, age did not affect LT_4 dose requirement, and there was no relationship between the serum TSH values, all of which were within the normal range, and the LT_4 doses that patients were taking. Therefore, the novel findings from our study are the following: (i) age does not affect apparent LT_4 dose requirements when BW and gender are considered and (ii) the effect of gender on LT_4 dose requirement is not removed by accounting for gender differences in lean body mass.

An effect of BW on LT_4 dose is consistent with various prior studies (1–9). The finding that IBW affects LT_4 dose is consistent with a prior study suggesting that lean body mass impacts LT_4 dose (5). This effect of IBW on LT_4 dose requirement suggests that LT_4 metabolism is partly accomplished in the lean body compartment, presumably the muscle compartment, and that adipose tissue has a less important effect on LT_4 requirement. Our new finding is that the LT_4 dose requirement based on IBW is different across genders. This suggests either that the proportion of lean body mass differs by gender, or that other body compartments may differentially drive LT_4 requirement in the various gender and menstrual groups. The greater requirement for LT_4 based on IBW in women versus men suggests that other body compartments, and/or other gender-related factors increase LT_4 requirement in women.

It is well known that thyroxine production rates in individuals with endogenous thyroid function are under tight control, are affected by a variety of situations, and can be studied using multicompartment models (32–34). If gender was one of the factors that affected thyroxine production, it would be possible that the different dose requirements seen in this study are a reflection of gender-specific physiological needs.

A novel finding from our study was that the effect of age on LT_4 requirements appeared to be mediated by other factors. Several studies have suggested that advancing age leads to a decreased LT_4 dose requirement (9,25–28), but most of these studies did not include IBW and gender in their analyses. Only three studies included gender (25,26,28) and these studies either documented the age-related decline in LT_4 dose in men only (26), showed the effect in only men and menopausal women (25), or were unable to separate the effects of age and gender (28). In this study it appears that the decreased LT_4 requirement with advancing age may be mediated by alterations in BW, body composition, and, in women, hormonal status, as age was not a significant influence in multivariate analyses. For example, it could be postulated that at an older age, reduced BW and altered degree of overweight both result in reduced LT_4 requirement.

In women hormonal status does not appear to drive LT_4 dose requirement based on BW, as requirements did not differ between premenopausal and menopausal women after adjustments had been made for age, serum TSH, and degree of overweight. Perhaps surprisingly, this suggests that the ambient estrogen levels in premenopausal women did not lead to increased LT_4 requirement compared with menopausal women.

It may be unexpected that there was not a significant relationship between serum TSH concentrations and LT_4 doses in patients who would generally be considered to have achieved ideal LT_4 replacement. It might be expected that lower LT_4 doses would be associated with higher serum TSH values. Such an effect would be likely if the study design encompassed a wide range of LT_4 doses and did not specify that patients have a serum TSH within the normal range. The selection of study subjects with a relatively narrow range of TSH values (0.4–3.5 mIU/L) might have made such a relationship difficult to ascertain. There was a trend toward a relationship of lower LT_4 doses being associated with higher serum TSH values only for the analyses based on BW and incorporating degree of overweight. It is possible that the study was underpowered to discern a TSH-LT_4 dose relationship. Alternatively, there could be a true variation across patients in the dose of LT_4 required to achieve the euthyroid state.

In addition, perhaps such a finding could be better shown with within-patient data rather than across-patient data, as different patients are likely to have different pituitary set points. Only 100 patients (40%) of patients in this analysis had two TSH values available, so this issue could not be examined further. We suspect that etiology of hypothyroidism was not significant in this analysis due to the small number of patients with an etiology other than Hashimoto's hypothyroidism.

One of the interesting facets of these data is that even in multivariate analyses, there were different dose requirements between genders. When degree of overweight was not incorporated in the analysis, men had lower dose requirements than either premenopausal or menopausal women based on IBW. However, their requirement did not differ when it was based on their BW. When degree of overweight was included in the analysis, men had lower requirement than both female groups based on BW. However, when dose requirement based on IBW was considered, the only difference in requirement was between men and premenopausal women. Thus, gender-based differences in dose requirement only become apparent either when IBW is used to determine dose or when degree of overweight is included in the model. These findings suggest that gender differences in LT_4 dose requirement exist, but are masked unless gender-based differences in IBW or degree of overweight are also considered.

The limitations of the study are primarily based on its retrospective nature and the need to exclude many patients. The retrospective study design did not allow us control over several factors. These factors include weighing patients in standardized clothing, prescribing a specific brand name of LT_4, controlling time of ingestion of LT_4, or employing a central laboratory for TSH measurements. During our chart review we excluded 75% of patients, primarily because their LT_4 dose had been changed or because they were taking medications that affected LT_4 absorption, binding, or metabolism. These exclusions improve the accuracy and reliability of the data, but also reduce its generalizability.

However, under conditions of a stable LT_4 dose, stable BW, and absence of confounding medications, we conclude that LT_4 dose is primarily driven by a patient's IBW, gender, menstrual status, and degree of overweight. This finding provides a basis for studying the physiologic underpinnings that determine an individual patient's LT_4 dose requirement. This knowledge may eventually improve the ability to predict a patient's dose requirement and thus more quickly attain a euthyroid status when initiating LT_4 therapy. It may also enhance our ability to maintain euthyroidism in our patient population.

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Disclosure Statement

The authors have nothing to disclose.

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