Original Article

SEX AND AGE DIFFERENCES IN LEVOTHYROXINE DOSAGE REQUIREMENT

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ABSTRACT

Objective: To examine the performance of weight-based formulae for estimating the levothyroxine dosage requirement in athyreotic patients and to determine whether formula performance is affected by age, sex, or menstrual status.

Methods: In this prospective study, euthyroid study participants aged 18 to 65 years were followed up after total thyroidectomy at 4 time points: 6-8 weeks, 12-16 weeks, 6 months, and 1 year. Patient weight, serum thyrotropin concentration, and levothyroxine dosage required were recorded at each time point. The postoperative starting levothyroxine dosage was 1.7 mcg/kg daily for patients with benign thyroid disease and 2.2 mcg/kg daily for patients with thyroid cancer. Actual body weight was used to calculate the initial dosage. At steady state, adjustments were made in each patient's levothyroxine dosage until the target thyrotropin concentration was reached. The levothyroxine dosage required to achieve this goal was documented.

Results: Fifty patients were included (37 women, 13 men). Formulae based on actual body weight were accurate in achieving a normal thyrotropin concentration in 48% to 75% of participants. Final dosages to achieve normal thyrotropin values were similar in men (1.43 mcg/kg daily) and menopausal women (1.68 mcg/kg daily), but higher in premenopausal women (2.10 mcg/kg daily). When a formula based on ideal body weight was used, the requirement for menopausal women (2.34 mcg/kg daily) was similar to that of premenopausal women (2.44 mcg/kg daily), but the requirement for men (1.73 mcg/kg daily) remained lower than that observed in both female groups.

Conclusions: When actual body weight was used to calculate levothyroxine dosage requirement, premenopausal women appeared to have a greater requirement than either menopausal women or men. When ideal weight was used, the requirement of all women was greater than that of men. Perhaps with formulae using actual weight, this apparent sex difference is masked by the greater weight, older age, or altered hormonal milieu of menopausal women. **(Endocr Pract. 2010;16:71-79)**

Abbreviations:
BMI = body mass index; **IBW** = ideal body weight; **LT_4** = levothyroxine; **TSH** = thyrotropin

INTRODUCTION

The replacement dosage of levothyroxine (LT_4) is affected by body weight (1-5). When initiating LT_4, one approach is to prescribe a treatment dosage based on the patient's pretreatment serum thyrotropin (TSH) concentration (6,7). Another approach is to initiate a midrange starting dosage such as 100 mcg (8) A third approach, particularly used in athyreotic individuals, is to calculate the patient's starting dosage based on body weight (2,9). Dosage titration is generally needed after any of these approaches is applied. Estimates of weight-based dosages for replacement in hypothyroid patients include 1.6 mcg/kg (1-5,9-11), 1.7 mcg/kg (3,5), 1.8 mcg/kg (4,12), 2.0 mcg/kg (12), and 2.1 mcg/kg (4). In contrast, dosages necessary for achieving suppression of serum TSH in patients with differentiated thyroid cancer are generally 2.0 to 2.5 mcg/kg (2,5). Some studies suggest that ideal body weight (IBW), rather than actual body weight, may provide a more

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accurate estimate of dosage requirement (4), particularly in men and older women (13). Furthermore, one of these studies suggests that sex differences in dosage requirement are accounted for by lean body mass (4). In addition, patients with certain deiodinase polymorphisms may require different dosages to achieve a specific TSH level (14).

Factors other than body weight are also known to affect LT_4 dosage requirement. The amount of residual thyroid function affects dosage requirement, such that patients with hypothyroidism due to Hashimoto thyroiditis or radioiodine treatment of Graves disease require a smaller LT_4 dosage to normalize TSH than patients who are completely athyreotic (3,5). Another relevant factor is LT_4 absorption, which is affected by several medical conditions (15-17), multiple medications (18-22), food and beverages (23-25), and timing of LT_4 administration (23,26-28). Medications that alter thyroxine binding or metabolism are another potential cause of altered LT_4 requirement (29,30). Patient age also influences requirement, with requirement decreasing with increasing age (12,13,31,32). Patient adherence to their LT_4 therapy can be a confounding factor when attempting to document a patient's true dosage requirement (33).

The purpose of the present analysis was to examine the performance of weight-based formulae for estimating LT_4 dosage requirement and to determine whether their performance was affected by age, sex, and menstrual status. An additional hypothesis tested was whether levothyroxine dosage requirements are best predicted by formulae using absolute body weight, IBW, or body mass index (BMI).

METHODS

Study Overview

This article reports additional follow-up data from a study initially designed to examine whether LT_4 therapy after thyroidectomy resulted in deficient triiodothyronine levels compared with levels before thyroidectomy (34). The study prospectively followed patients' clinical course after thyroidectomy. Four time points were used in the analysis. Patient weight, serum TSH concentration, and the LT_4 dosage required by patients were recorded at each time point (Table 1). The study began in January 2004 and was completed by March 2008.

Study Patients

Euthyroid participants of both sexes aged 18 to 65 years were recruited from patients referred to the Department of Otolaryngology-Head and Neck Surgery, Georgetown University Medical Center, Washington, DC, for total thyroidectomy for goiter, nodular thyroid disease, suspected thyroid cancer, or known thyroid cancer. Patients taking medications known to interfere with LT_4 absorption or alter LT_4 binding proteins were excluded from participation. No patients were taking estrogens, progesterone, or testosterone. Other medications leading to exclusion included iodine, propranolol, amiodarone, lithium, dopamine agonists or antagonists, somatostatin analogues, glucocorticoids, phenytoin, carbamazepine, sertraline, rifampin, bile acid sequestrants, antacids, sodium polystyrene sulfonate, cholestyramine, colestipol, and raloxifene. Pregnant or lactating patients were not eligible. Patients with chronic, serious diseases such as cardiac, pulmonary, or renal disease were not eligible for study participation. Patients who wished to participate signed a consent form approved by the Georgetown University Institutional Review Board.

TSH Concentrations and Physical Measurements

The postsurgical serum TSH concentrations determined at time points 1 through 4 are reported in this study. Phlebotomy was performed at between 8 AM and 10:30 AM in a fasting state. The TSH values were determined by the General Clinical Research Center Bioanalytic Core Laboratory using the Dade Dimension RxL Clinical Chemistry Analyzer (Siemens, Wilmington, Delaware). This is a colorimetric immunoassay with a sensitivity of 0.01 mIU/L and an imprecision of less than 6.2% at all concentrations tested; it is calibrated for the range

Table 1
Data Collected at Time Points for Each of 50 Study Participants

Study time points	Time since thyroidectomy and LT_4 initiation	Data recorded		
		Weight	Serum TSH	LT_4 dosage adjustment
1	6-8 weeks	•	•	•
2	12-16 weeks	•	•	•
3	6 months	•	•	•
4	1 year	•	•	•

Abbreviations: LT_4, levothyroxine; TSH, thyrotropin.

0.01-50 mIU/L. The manufacturer's reference range for this third-generation TSH assay was 0.34-4.82 mIU/L. Anthropometric measures included weight and height. Weight was measured using a DS 504 Ohaus scale (Ohaus Corporation, Pine Brook, New Jersey); height was measured with an Accustat Stadiometer (Genentech, San Francisco, California).

Thyroid Surgery and LT_4 Administration

Thyroidectomy was performed at Georgetown University Hospital, Washington, DC. Study participants were prescribed a name brand of LT_4 after total thyroidectomy. The particular brand was noted, and adherence to the branded product throughout the study was verified. However, not all participants were taking the same brand name. Patients were asked to separate the time of ingestion of multivitamins or calcium supplements from the time of ingestion of their LT_4 by at least 2 hours and to take their thyroid hormone at least 60 minutes before breakfast. Postoperative LT_4 dosage was determined by the patient's pathological diagnosis. Patients with benign disease were initially prescribed 1.7 mcg/kg of LT_4 daily with the goal of achieving a TSH level in the lower two-thirds of the reference range. Dosage adjustments were made at 8-week intervals if the patients' TSH values were less than 0.35 mIU/L or greater than 3.5 mIU/L. Patients with thyroid cancer were prescribed 2.2 mcg/kg of LT_4 daily with the goal of achieving a subnormal or suppressed TSH level. Dosage adjustments were made if the patients' TSH values were 0.35 mIU/L or greater. Absolute body weight, not IBW, was used to calculate dosage. Adherence to LT_4 therapy was assessed with regular clinical visits, telephone contact, and e-mail contact throughout the study. However, formal pill counts were not performed.

Statistical Analysis

Statistical services were provided by the General Clinical Research Center biostatistics core, Georgetown University Medical Center, Washington, DC. The initial formula used for LT_4 replacement in study participants was 1.7 mcg/kg actual body weight. The formula used for LT_4 suppression therapy was 2.2 mcg/kg actual body weight. In both cases, subsequent dosage adjustments were made to achieve the desired TSH level. The LT_4 dosage that achieved the goal TSH level was then used to generate formulae that predicted dosage requirement based on actual body weight, IBW, and BMI at time points 2 and 4. Other covariates considered were sex, hormonal status (premenopausal, menopausal), and age. For women, IBW was calculated as 45 kg plus 2.3 kg for each additional 2.5 cm above 152 cm. For men, IBW was calculated as 48 kg plus 2.7 kg for each additional 2.5 cm above 152 cm (35). BMI was calculated as weight in kg ÷ (height in m)^2.

When the data were normally distributed and had the same variance, *t* tests were used to examine the differences in mean serum TSH values and mean LT_4 requirement between groups. When these assumptions were violated, the Wilcoxon rank sum test was used. A one-way analysis of variance was used to simultaneously compare the mean LT_4 dosage requirement by sex and hormonal status (female, male, premenopausal status, menopausal status). When the normality assumption was violated, the Kruskal-Wallis test was used. A simple linear regression and a correlation were used to examine the linear relationship between dosage and age. When the normality assumption was violated, the Spearman rank correlation was used. Most of the data were not normally distributed. Multiple regression was used to determine whether dosage-age relationships were affected by premenopausal or menopausal status.

Table 2
Characteristics of Patient Groups[a]

Characteristics	Hypothyroid[b]			Thyroid cancer[c]		
	Premenopausal women (n = 12)	Menopausal women (n = 13)	Men (n = 8)	Premenopausal women (n = 7)	Menopausal women (n = 5)	Men (n = 5)
Age, y	41.4	57.9	53.4	37.0	59.1	39.2
Height, cm	168.2	164.4	179.5	163.6	164.4	175.0
Weight, kg	76.3	78.1	85.5	65.3	69.6	82.8
BMI, kg/m^2	27.5	28.4	26.5	24.4	25.9	27.0

Abbreviation: BMI, body mass index.
[a] Data are presented as mean values.
[b] Cause of hypothyroidism was thyroidectomy.
[c] Cause of hypothyroidism was thyroidectomy with or without radioiodine therapy.

RESULTS

The characteristics of the 50 enrolled patients are shown in Table 2. Thirty-seven patients (74%) were female. Serum TSH values did not differ between sexes within the group with normal TSH values or within the group with suppressed TSH values (Table 3). Free thyroxine and total triiodothyronine concentrations (not shown) also did not differ between the study groups.

Only 16 patients (32%) had a TSH value at goal at the time of their first thyroid function tests; 34 patients (68%) therefore required a dosage adjustment. The desired TSH goal was achieved in 28 patients (56%) after 12 to 16 weeks of therapy (time point 2, Table 3). Nine of 13 men (69%) had achieved their goal TSH at this time point, compared with only 19 of 37 women (51%). However, by 1 year of therapy (time point 4), 45 of 50 patients (90%) had a TSH value within the desired range (Table 3). Again, more men were at their goal (100%) than women (86%). At both time points 2 and 4, the largest percentage of patients who had not achieved their TSH goal was in the premenopausal group (63% for time point 2 and 16% for time point 4).

Table 3
Patients Reaching Goal Thyrotropin Concentration (Either Normal or Suppressed) at Time Points 2 (12-16 Weeks) and 4 (1 Year)

Variable	Both sexes	All women	Premenopausal women	Menopausal women	Men
	Time point 2, goal of normal TSH				
Patients at goal, No. (%)	18/33 (55)	12/25 (48)	4/12 (33)	8/13 (62)	6/8 (75)
Direction of dosage adjustment, No.					
Increased	7	5	3	2	2
Decreased	8	8	5	3	0
TSH value of patients at goal, mean (SD)	1.09 (0.88)	1.14 (0.95)	1.28 (0.94)	1.08 (0.94)	0.99 (0.73)
	Time point 2, goal of TSH suppression				
Patients at goal, No. (%)	10/17 (59)	7/12 (58)	3/7 (43)	4/5 (80)	3/5 (60)
Direction of dosage adjustment, No.					
Increased	7	5	4	1	2
Decreased	0	0	0	0	0
TSH value of patients at goal, mean (SD)	0.06 (0.06)	0.07 (0.06)	0.12 (0.06)	0.06 (0.06)	0.05 (0.04)
	Time point 4, goal of normal TSH				
Patients at goal, No. (%)	31/33 (94)	23/25 (92)	11/12 (92)	12/13 (92)	8/8 (100)
Direction of dosage adjustment, No.					
Increased	1	1	1	0	0
Decreased	1	1	1	0	0
TSH value of patients at goal, mean (SD)	1.30 (0.93)	1.22 (0.81)	1.01 (0.63)	1.38 (0.90)	1.56 (1.19)
	Time point 4, goal of TSH suppression				
Patients at goal, No. (%)	14/17 (82)	9/12 (75)	5/7 (71)	4/5 (80)	5/5 (100)
Direction of dosage adjustment, No.					
Increased	3	3	2	1	0
Decreased	0	0	0	0	0
TSH value of patients at goal, mean (SD)	0.09 (0.08)	0.09 (0.08)	0.12 (0.09)	0.04 (0.01)	0.10 (0.07)

Abbreviation: TSH, thyrotropin.

The mean LT_4 dosage required for achieving a normal TSH level is displayed according to sex and hormonal status in Table 4. These data are also displayed graphically so that individual patients are identifiable in Figure 1A and as box plots showing the distribution of the data in Figure 1B. When a formula based on actual weight was used, premenopausal women had the largest dosage requirement (2.10 mcg/kg daily), followed by menopausal women (1.68 mcg/kg daily), and men (1.43 mcg/kg daily). The dosage requirement for men was significantly different from the requirement for premenopausal women ($P = .048$), but not different from that of menopausal women.

When a formula based on IBW was used, a different pattern was seen. Premenopausal women required the largest dosage (2.44 mcg/kg daily), menopausal women required a similar dosage (2.34 mcg/kg daily), and men required a considerably smaller dosage (1.73 mcg/kg daily). The dosage requirement in men was again significantly less than the dosage requirement in premenopausal women ($P<.001$). In this case, it was also less than the dosage requirement in menopausal women ($P<.001$).

The correlation coefficients between LT_4 dosage requirement for TSH normalization and weight are shown in Table 5. The weakest correlation between dosage and actual body weight was seen in premenopausal women (correlation 0.21), compared with a correlation of 0.38 for men and a correlation of 0.64 for menopausal women. When the relationship between LT_4 dosage requirement and IBW was examined, the weakest correlation was again in premenopausal women (correlation 0.27), with similar correlations in men and menopausal women (correlations 0.66 and 0.69, respectively).

The LT_4 dosage required for achieving a low or suppressed TSH value is displayed according to sex and hormonal status in the lower section of Table 4. The dosage based on actual body weight for both sexes combined was 2.2 mcg/kg daily. When using a formula based on actual body weight, premenopausal women had the largest dosage requirement (2.43 mcg/kg daily), followed by similar requirements in both menopausal women and men (1.99 and 2.02 mcg/kg daily). When a formula based on IBW was used, premenopausal women required the largest dosage (2.98 mcg/kg), followed by menopausal women (2.56 mcg/kg daily) and men (2.36 mcg/kg daily). None of these dosage requirements were statistically different, but in each case the magnitude of the requirement followed the same pattern as that for the patients treated to achieve a normal TSH.

Table 4
Levothyroxine Dosage Required for Either Normal Serum Thyrotropin or Thyrotropin Suppression Based on Actual Body Weight, Ideal Body Weight, or Body Mass Index[a,b]

Dosage calculation	Both sexes	Premenopausal women	Menopausal women	Men	*P* value
	Goal of normal TSH				
Daily dosage per kg actual body weight	1.76 (0.48)	2.10 (0.55)	1.68 (0.39)	1.43 (0.27)	.048[c,e]
Daily dosage per kg ideal body weight	2.19 (0.49)	2.44 (0.43)	2.34 (0.46)	1.73 (0.22)	<.001[d,f]
Daily dosage per kg/m^2 (BMI)	5.06 (1.33)	5.71 (1.43)	4.69 (1.33)	4.96 (0.95)	.5[f]
	Goal of TSH suppression				
Daily dosage per kg actual body weight	2.15 (0.47)	2.43 (0.57)	1.99 (0.33)	2.02 (0.38)	.2[f]
Daily dosage per kg ideal body weight	2.63 (0.54)	2.98 (0.51)	2.56 (0.37)	2.36 (0.49)	.3[e]
Daily dosage per kg/m^2 (BMI)	6.07 (1.41)	6.56 (1.67)	5.38 (1.21)	6.26 (0.99)	.8[f]

Abbreviations: BMI, body mass index; TSH, thyrotropin.
[a] Patients whose TSH levels were not at goal were excluded from analysis.
[b] Values are expressed as mean (standard deviation).
[c] *P* value is for men vs premenopausal women.
[d] *P* value is for men vs all other groups.
[e] Compared using one-way analysis of variance.
[f] Compared using Kruskal-Wallis test.

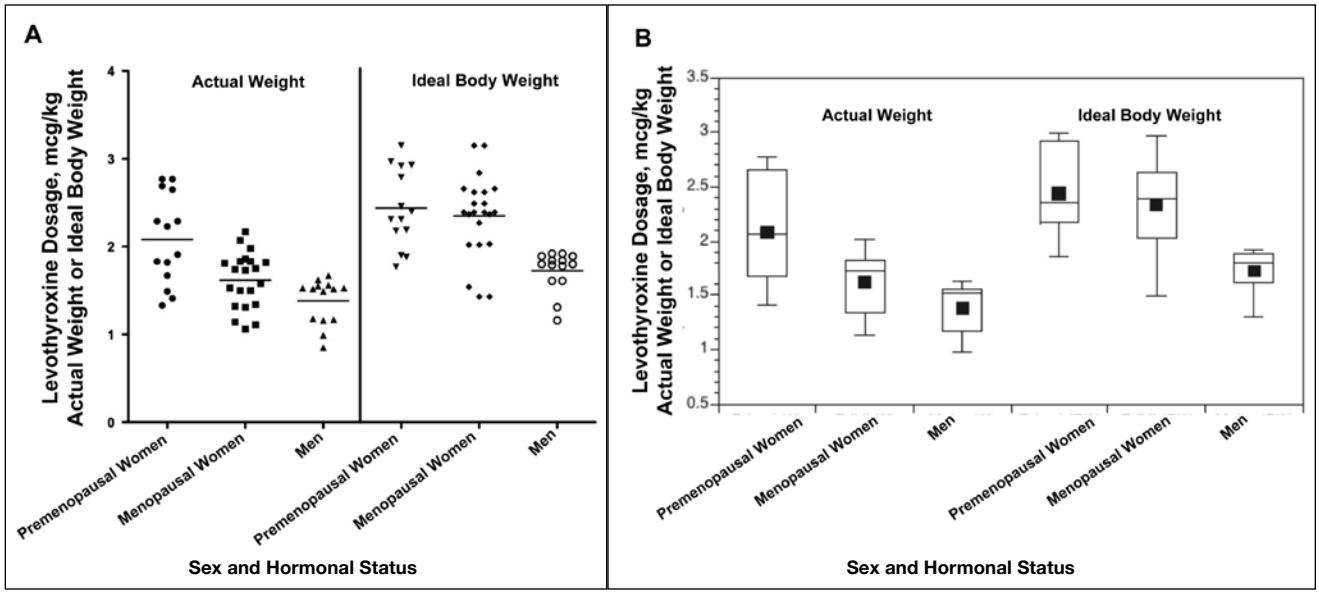

Fig. 1. Levothyroxine dosage required to normalize serum thyrotropin according to sex and hormonal status. *Panel A*, The horizontal line represents the mean. *Panel B*, The horizontal line in the middle of each box indicates the median, while the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers above and below the box mark the 90th and 10th percentiles, respectively. The filled square inside the box indicates the arithmetic mean.

Figure 2 shows the relationship between participant age and the LT_4 dosage that was required for TSH normalization based on actual body weight and IBW at time points 2 and 4. The relationship between age and dosage was statistically significant for the LT_4 dosage required to normalize TSH using actual body weight and also IBW (P = .045). As expected, menopausal women clustered in the older age group, whereas the premenopausal women clustered in the younger age group. The men in the study with benign histologic findings were mostly in the age group older than 40 years and therefore clustered with the menopausal women. The relationship between the age of participants and the LT_4 dosage required for achieving a low or suppressed TSH based on actual body weight and IBW at time points 2 and 4 was not statistically significant (data not shown), although the trend was similar to that observed for patients with normal TSH concentrations.

Table 5
Relationship Between Levothyroxine Dosage Required to Normalize Serum Thyrotropin Concentration and Actual Body Weight and Ideal Body Weight

Study group	Correlation coefficient
Dosage based on actual body weight	
Premenopausal women	0.21
Menopausal women	0.64
All women	0.49
Men	0.38
Dosage based on ideal body weight	
Premenopausal women	0.27
Menopausal women	0.69
All women	0.57
Men	0.66

DISCUSSION

The weight-based dosage required to normalize TSH for both sexes was 1.7 mcg/kg daily, which is similar to one of the figures quoted in the literature (3,5). The weight-based dosage needed to achieve a low TSH for both sexes was 2.2 mcg/kg daily, which is, again, similar to one of the figures quoted in the literature (2,5). However, this analysis also shows a surprisingly high failure rate in achieving the desired TSH level with the use of a formula based on actual body weight after thyroidectomy. This may be partially due to the lower TSH goal of 3.5 mIU/L or less that was used in this particular study for the patients in whom a normal TSH was desired. All patients required at least 1 additional dosage adjustment to achieve their goal serum TSH value. A small percentage of patients (10%) had still not achieved the desired TSH value after 7 dosage adjustments over 1 year of therapy.

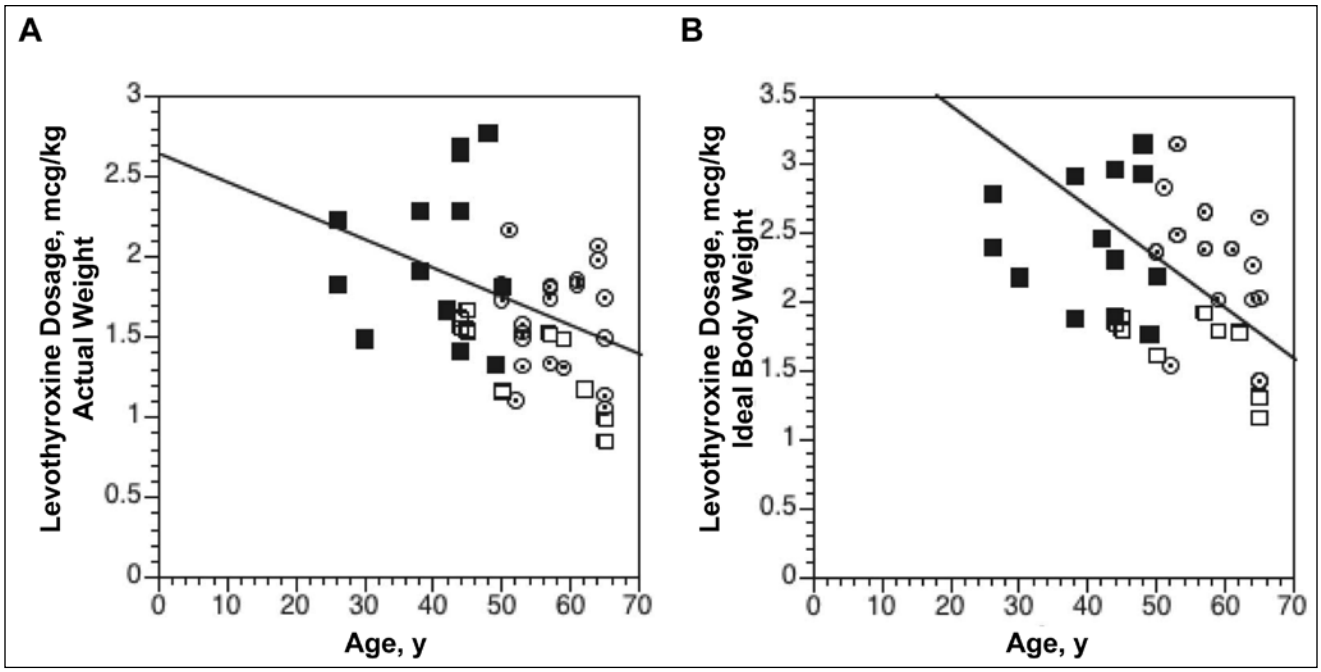

Fig. 2. Levothyroxine dosage required to normalize serum thyrotropin according to patient age. Filled squares indicate premenopausal women, dotted circles indicate menopausal women, and open squares indicate men. *Panel A*, Actual body weight. Correlation coefficient, 0.50. *Panel B*, Ideal body weight. Correlation coefficient, 0.58.

When actual body weight was used to document LT_4 dosage requirement, the premenopausal female group required a higher dosage to reach their target TSH than both men and menopausal women. The requirements for men and menopausal women, however, were similar. This was seen more clearly with the group of patients being treated to achieve a normal TSH, perhaps because the group being treated to achieve TSH suppression was too small to allow a significant effect to be demonstrated. The differences in dosage requirements were not related to different TSH means achieved within the sex or hormonal status groups, as the TSH means were not statistically different between groups. Previous data have suggested that between-sex differences in dosage requirements were accounted for by differences in lean body mass (4). With the current data, when the dosage requirement was documented based on IBW, the requirement for menopausal women increased and became similar to the requirement for premenopausal women. Thus, these data show that different dosage requirements within the female hormonal subgroups can be removed by normalizing according to IBW. This suggests that the lesser requirement of menopausal women for LT_4 based on actual weight may be accounted for by weight gain in the menopausal period. However, even after adjustment using IBW, the difference between the sexes remained, perhaps implicating other factors such as hormonal influences or LT_4 metabolism.

Two other studies, in addition to the one examining lean body mass (4), also examined the impact of sex (13,31). None of these studies examined the impact of hormonal status. In one study addressing both age and sex, only men were found to have an age-related decline in their LT_4 requirement (31). In the other study, the age-related decline in LT_4 requirement was only documented in older menopausal women, but not in premenopausal women (13). This finding of decreased LT_4 requirement in older persons (6,12,13,31) was confirmed in this analysis. In the present study, the decreased LT_4 requirement with age appears to be mostly due to a decreased requirement in postmenopausal women compared with premenopausal women. However, the number of men in the study was small and did not allow for a separate analysis. In addition, the full age range was not represented in male participants. Within the group of patients in whom the goal was normalization of TSH, male patients fell mostly in an older age group (>40 years). This confounded the ability to test whether the reduced LT_4 requirement was driven by hormonal alterations or advancing age. We could not confirm the finding that the decreased LT_4 requirement with age was solely due to alterations in body composition as suggested by 2 previous studies (4,13), as the age-dosage relationship persisted when IBW was used. Perhaps the decreasing requirement with age is also due to other factors related to LT_4 metabolism or clearance.

It is notable that premenopausal women seemed to have greater variability in their LT_4 requirement than men and menopausal women, as is reflected in the poor correlation between actual weight and dosage. Perhaps this variability

in dosage requirement in premenopausal women and the disparate LT_4 requirement according to sex and hormonal status partly accounts for the poor performance of the usual weight-based formulae. The correlation between LT_4 dosage requirement and IBW is better than that between dosage and actual weight in every group, although the correlation for premenopausal women remained poor. The better correlation when IBW is used supports the use of IBW to estimate LT_4 dosage requirement. Metabolism of LT_4 takes place in many peripheral tissues (36) including liver, kidney, and, in some species or circumstances, adipose tissue. The fact that IBW best predicts LT_4 dosage within each sex suggests that the predominant processes relevant to LT_4 metabolism are occurring within the "lean body mass" compartment. Thus, adipose tissue would appear to have limited impact on LT_4 requirement.

The novel finding from these data is that men require a lower LT_4 dosage than women to achieve a particular TSH goal. Menopausal women initially appear to require a lower LT_4 dosage too, but this is corrected by calculating the dosage based on IBW, suggesting that the apparent reduction in dosage requirement is due to increased adiposity. The poor performance of formulae based on body weight or IBW may be because LT_4 dosage requirements are affected by sex, hormonal status, and age. To most accurately predict LT_4 dosage requirements, these data suggest that a formula based on IBW rather than actual body weight should be used. Furthermore, performance would be improved by using a different formula for men and women. For example, dosage requirement would be approximately 2.4 mcg/kg IBW for women and 1.7 mcg/kg IBW for men if the goal were to achieve a normal TSH level. If actual body weight were used to estimate LT_4, these data would suggest that both sex and hormonal status should be taken into account. If sex is not included in a formula of LT_4 dosage estimation, a BMI formula may be the most uniformly predictive across sex and hormonal status. A formula that also includes patient age may possibly have an improved predictive value. However, the small number of patients in this study and the narrow range of ages in the male group did not permit determination of whether sex, hormonal status, and age were independent effects. Future larger studies with a population that includes both sexes, adequate numbers of premenopausal and menopausal women, and a wider range of patient ages could examine this question.

CONCLUSION

Weight-based formulae only provide an approximate guide to LT_4 requirement. When actual body weight is used, premenopausal women appear to have a greater dosage requirement than either menopausal women or men. When ideal weight is used, the dosage requirement of all women is greater than that of men. Perhaps with formulae using actual weight, this apparent sex difference is masked by the greater weights, older age, or altered hormonal milieu of menopausal women.

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DISCLOSURE

The author has no multiplicity of interest to disclose.

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