



Appropriate dose of levothyroxine replacement therapy for hypothyroid obese patients

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ABSTRACT

Background: Athyretic patients require a daily levothyroxine (LT4) doses of 1.6–1.8 mcg/kg of actual body weight (BW) to achieve normal thyroid stimulating hormone (TSH) levels. Lean body mass (LBM) calculation may be a more accurate determination of LT4 dose in obese patients. Previous studies were mainly investigated in Caucasians and LBM is markedly different between various ethnic groups. We aim to identify the optimal dose of LT4 replacement therapy in hypothyroid Thai patients including obese subjects.

Methods: We retrospectively reviewed the medical records of Thai adults with hypothyroidism at the thyroid clinic. Patients had been received LT4 (Brand: Euthyrox) at a stable dose ≥ 75 mcg/day for at least 1 year. Patients with thyroid cancer, pregnant, and lactating women were excluded. LBM was calculated by the Hume formula.

Results: Two hundred patients (80% females) with a mean age of 48.6 ± 14.8 years and a body mass index (BMI) of 24.5 ± 4.6 kg/m² were included. Daily LT4 dose/kg of actual BW according to BMI 18.5–24.9, 25–29.9, and ≥ 30 kg/m² were 1.67 ± 0.27 , 1.51 ± 0.28 and 1.39 ± 0.34 mcg/kg, respectively. In contrast, LT4 dose/kg of LBM were 2.31 ± 0.39 , 2.35 ± 0.45 and 2.36 ± 0.51 mcg/kg, respectively.

Conclusions: LBM is considered a better indicator for calculating an appropriate LT4 replacement dose than actual BW in hypothyroid obese Thai patients. The recommended daily dose of LT4 is 2.3 mcg/kg of LBM that could be applied for all ranges of BMI.

Introduction

Hypothyroidism is a state of deficient thyroid hormone production, which is readily diagnosed by laboratory testing and eminently treatable but potentially life-threatening if left untreated. Thyroid hormone replacement therapy with levothyroxine (LT4) has been considered the treatment of choice for all causes of hypothyroidism, either primary hypothyroidism, central hypothyroidism, or rarely peripheral hypothyroidism. The starting daily dose of LT4 depends on the degree of serum TSH elevation and the age of the patient and the co-existing cardiac disease [1]. The aim of replacement therapy of primary hypothyroidism is to render euthyroid through normalization of serum thyroid stimulating hormone (TSH) levels. Patients with overt hypothyroidism usually require a full replacement dose of oral LT4 1.6–1.8 mcg/kg actual body weight (BW)/day to attain an euthyroid state [1–3].

Both over-dosing and under-dosing of LT4, even in subclinical states, could lead to potentially harmful adverse effects. The determination of

the appropriate LT4 dose is challenging in obese individuals [4]. There was consistent evidence that actual BW, ideal BW, and lean body mass (LBM) can affect the LT4 dose requirement [3,5]. If the actual BW is used to calculate an appropriate initial dose of LT4, obese patients may be overtreated [3,5]. LBM is the best predictor of the daily requirements for LT4 because deiodination, converting T4 to T3, has been processed mainly in the muscle components rather than adipose tissue [5,6]. In addition, most metabolic processes of T4, including type 1 deiodinase, glucuronidation, and sulfation in liver, deiodinase type 3 in skin, occur within the LBM [7]. Although hypothyroid obese patients require greater absolute LT4 doses than normal-weight subjects, obese patients require a lower LT4 dose relative to BW to attain the euthyroid state [3,4,8,9]. Higher LT4 dose requirements in severely obese individuals could be attributed to increased LBM, higher distribution volume, delayed gastrointestinal absorption of LT4 (due to motility alterations, concomitant gastritis, and *Helicobacter pylori* infection), and their altered T4 to T3 conversion [5,10–14].

However, there is currently no guideline to recommend LT4 dosing

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in obese patients. Moreover, the results were mainly investigated in Caucasians [15,16,3–5] and ethnic differences in LBM do exist [17–19]. A study from Singapore reported that daily LT4 dosage is lower than in the Western population [20]. Therefore, the primary objective of our study was to identify an appropriate dose of LT4 replacement therapy in hypothyroid obese Thai patients. The study also aimed to evaluate other factors that may affect LT4 replacement dose in these patients.

Materials and Methods

Study population

A retrospective chart review of primary hypothyroid Thai patients who received LT4 replacement therapy were followed in the thyroid clinic at Ramathibodi Hospital during January 2013 - April 2017. Subjects included adults aged >18 years old with an established diagnosis of primary hypothyroidism from chronic autoimmune thyroiditis (Hashimoto's thyroiditis), after near-total/total thyroidectomy and/or radioiodine treatment. They had been receiving a minimum LT4 daily dosage of 75 mcg for at least 1 year, and have been consistently euthyroid on a stable dose of LT4 for the past 6 months. A stable euthyroid state was defined as a stable serum TSH within the manufacture's reference range (0.35–4.94 mIU/L). We avoided the efficacy variations of LT4 in patients who received the same brand of LT4; Euthyrox® (Merck, Germany) throughout the study evaluation period. We excluded patients with missing data; pregnant or lactating patients; history of acute illness within 3 months; underlying conditions of cardiac, liver, and kidney diseases; malabsorption syndrome; and hypothalamic-pituitary disease. Furthermore, patients with greater than 15% weight fluctuation in the last 1 year were excluded. Patients with thyroid cancer were also excluded because they required a higher dose of LT4 due to suppression of serum TSH levels [21].

The study was approved by the Human Research Ethics Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Data collection

The data included age, sex, actual BW, height, etiology of hypothyroidism, serum TSH concentrations, concurrent medications, and daily LT4 dosage. BW and height were recorded using weighing scales and a stadiometer at the thyroid clinic. Body mass index (BMI) was calculated by dividing weight in kg by height in meters squared. Ideal BW was calculated based on subject height using the Devine formula [22]. LBM was calculated based on actual BW, height, and gender using the Hume formula [23]. The calculations for each formula are as follows:

$$\begin{aligned} \text{Devine formula Ideal BW (men)} &= 50\text{kg} + 0.9 \text{ kg} \times (\text{height, cm} - 152) \\ \text{Ideal BW (women)} &= 45.5\text{kg} + 0.9 \text{ kg} \times (\text{height, cm} - 152) \end{aligned}$$

$$\begin{aligned} \text{Hume formula LBM (men)} &= (0.32810 \times \text{BW, kg}) + (0.33929 \times \text{height, cm}) - 29.5336 \\ \text{LBM (women)} &= (0.29569 \times \text{BW, kg}) + (0.41813 \times \text{height, cm}) - 43.2933 \end{aligned}$$

Serum TSH was measured at our institution by an automated analyzer with an immunochemiluminometric assay (Abbott Diagnostics, Abbott Park, IL, USA) with the manufacture's reference range, 0.35–4.94 mIU/L.

Statistical analysis

Continuous variables are presented as means and standard deviations. Categorical variables are expressed as counts and percentages. Pearson correlation analysis was used to determine correlations between two variables. Univariate and multivariate analyses were used to calculate factors that affected with daily LT4 dose/kg. A *p*-value of < 0.05 was considered statistically significant. The analysis was performed using STATA 13 (StataCorp LLC, College Station, TX, USA).

Results

Medical records of 1,104 hypothyroid patients who received LT4 were reviewed. After exclusion, analyses were performed on 200 patients who met the eligibility criteria. The mean age of the cohort was 48.6 ± 14.8 years with 80% females. The mean actual BW, ideal BW, and LBM were 62.8 ± 13.1 kg, 55.5 ± 8.7 kg, and 42.7 ± 6.9 kg, respectively. The mean BMI was 24.5 ± 4.6 kg/m². Forty-two percent of participants were classified as obese (BMI ≥ 25 kg/m²), according to the Asia-Pacific obesity classification [24]. The etiologies of primary hypothyroidism were from postradioiodine treatment (53.5%), chronic autoimmune thyroiditis (31%), and postthyroidectomy (15.5%). Calcium carbonate was given in 10.5% of participants.

Mean stable daily LT4 dose was 1.6 ± 0.3 mcg/kg actual BW/kg. According to the etiology of hypothyroidism, requirements of daily LT4 dosages were chronic autoimmune thyroiditis 1.69 ± 0.32 , postthyroidectomy 1.67 ± 0.29 , and postradioiodine treatment 1.56 ± 0.37 mcg/kg. Daily LT4 dose/kg actual BW according to BMI < 18.5, 18.5–24.9, 25–29.9, and ≥ 30 kg/m² were 2.27 ± 0.55 , 1.67 ± 0.27 , 1.51 ± 0.28 , and 1.39 ± 0.34 mcg/kg, respectively. Daily LT4 dose/kg ideal BW were 1.75 ± 0.29 , 1.70 ± 0.31 , 1.90 ± 0.39 and 2.10 ± 0.45 mcg/kg. There was no significant difference in the mean TSH levels (2.04 ± 1.26 mIU/L) and daily LT4 dose/kg LBM (2.30 ± 0.40 mcg/kg) across various BMIs (Table 1).

The relationship between the daily LT4 dose/kg and BMI was analyzed by Pearson correlation analysis (Fig. 1). There was a significant negative correlation between daily LT4 doses per actual BW and BMI ($r = -0.50$, *p*-value < 0.0001). While the correlation between daily LT4 dose per ideal BW and BMI were significantly positive ($r = 0.41$, *p*-value < 0.0001). The minimal but significant association was demonstrated when the daily LT4 dose per LBM was correlated with BMI ($r = -0.03$, *p*-value < 0.0001).

Due to very high collinearity between BW, BMI, and LBM, redundant variables (BMI and LBM) were removed from the analysis. Univariate analysis of multiple variables and daily LT4 dose per actual BW revealed that actual BW (*p*-value < 0.001) and age (*p*-value = 0.02) were significantly correlated with daily LT4 dose per actual BW (Table 2). Multivariate analysis of daily LT4 dose per actual BW found that actual BW was strongly negative associated with daily LT4 dose per actual BW ($\beta = -0.54$, *p*-value < 0.001) and age ($\beta = -0.20$, *p*-value = 0.001). Also,

male sex ($\beta = 0.14$, *p*-value = 0.03) was positively associated with daily LT4 dose per actual BW (Table 2).

Discussion

In the present study, we confirm that BW, either actual BW, ideal BW, and LBM, affect LT4 dose requirement. In comparison with actual BW and ideal BW, the daily LT4 dose per kg LBM was quite constant through

Table 1
Mean daily levothyroxine (LT4) dose calculated based on actual body weight, ideal body weight, and lean body mass according to different body mass indexes.

N = 200	Body mass index, kg/m ²				p-value
	< 18.5	18.5–24.9	25–29.9	≥ 30	
Number of patients	10	107	59	24	
Female, n (%)	10 (100%)	87 (81.3%)	47 (79.7%)	16 (66.7%)	0.152
Age (years)	37.7 ± 14.1	48.0 ± 14.8	50.1 ± 14.0	51.7 ± 15.5	0.062
Mean kg	41 ± 5.6	56.5 ± 7.4	69.1 ± 6.7	84.3 ± 12.6	< 0.001
Mean BMI (kg/m ²)	16.6 ± 2.0	21.9 ± 1.8	27.0 ± 1.4	33.2 ± 3.1	< 0.001
Etiology of hypothyroidism, n (%)					0.131
Postradioiodine treatment	4 (40%)	54 (50.5%)	34 (57.6%)	15 (62.5%)	
Chronic autoimmune thyroiditis	6 (60%)	39 (36.4%)	13 (22.0%)	4 (16.7%)	
Postthyroidectomy	0 (0%)	14 (13.1%)	12 (20.3%)	5 (20.8%)	
Mean TSH (mIU/L)	2.48 ± 1.33	2.06 ± 1.21	1.88 ± 1.22	2.17 ± 1.56	0.497
Daily LT4 dose/actual BW (mcg/kg/day)	2.27 ± 0.55	1.67 ± 0.27	1.51 ± 0.28	1.39 ± 0.34	< 0.001
Daily LT4 dose/ideal BW (mcg/kg/day)	1.75 ± 0.29	1.70 ± 0.31	1.90 ± 0.39	2.10 ± 0.45	< 0.001
Daily LT4 dose/LBM (mcg/kg/day)	2.66 ± 0.49	2.31 ± 0.39	2.35 ± 0.45	2.36 ± 0.51	0.095

Abbreviations: BW, body weight; kg, kilogram; LBM, lean body mass; LT4, levothyroxine.

various BMIs. This is the simplest approach to calculate the appropriate LT4 dose by using a single dosing coefficient. The recommended calculated daily dose of LT4 is 2.3 mcg/kg of LBM that could be generally applied to all ranges of BMIs, especially in hypothyroid obese patients. Currently, most medical calculators are easy to use and available online, and the calculation of LBM by Hume formula requires only BW, height, and gender. The actual BW and age were negatively correlated with the daily LT4 dose per actual BW. In contrast, male was positively correlated with the daily LT4 dose per actual BW.

LBM, the difference between actual BW and fat mass, is known to play an important role in metabolic functions. It is comprised of body cell mass, extracellular water, and nonfatty intercellular connective tissue. Related, but not identical to LBM is an ideal BW. The anthropometric calculation of the ideal BW differs from that of LBM in that the ideal BW is based only on height and not on the actual BW [22]. Using the ideal BW, all patients of the same gender and height would receive the same dose. Obese people are at risk of overdose if dose calculations are made using actual BW. Consideration of LBM is particularly relevant in patients who are obese, because of the relatively large divergence of LBM and actual BW. There is substantial evidence of pharmacokinetic studies to suggest that LBM is a better predictor of drug dosage than actual BW in obese patients [25]. If weight is used to determine a starting dose in obese patients, actual BW may lead to overdosing. Therefore, LT4 dose to be administered in obese hypothyroid patients is more accurately based on LBM [5,26].

Our results were consistent with the previous data that a higher BMI required a lower LT4 dose/kg actual BW [15] and a higher dose/kg ideal BW [4,15]. In contrast, LT4 dose/kg LBM was more stable across various BMIs [15]. However, our recommendations are not applicable to some cases because the variations may increase in underweight patients (BMI <18.5 kg/m²; our study) or morbidly obese (BMI ≥40 kg/m²) [15]. This

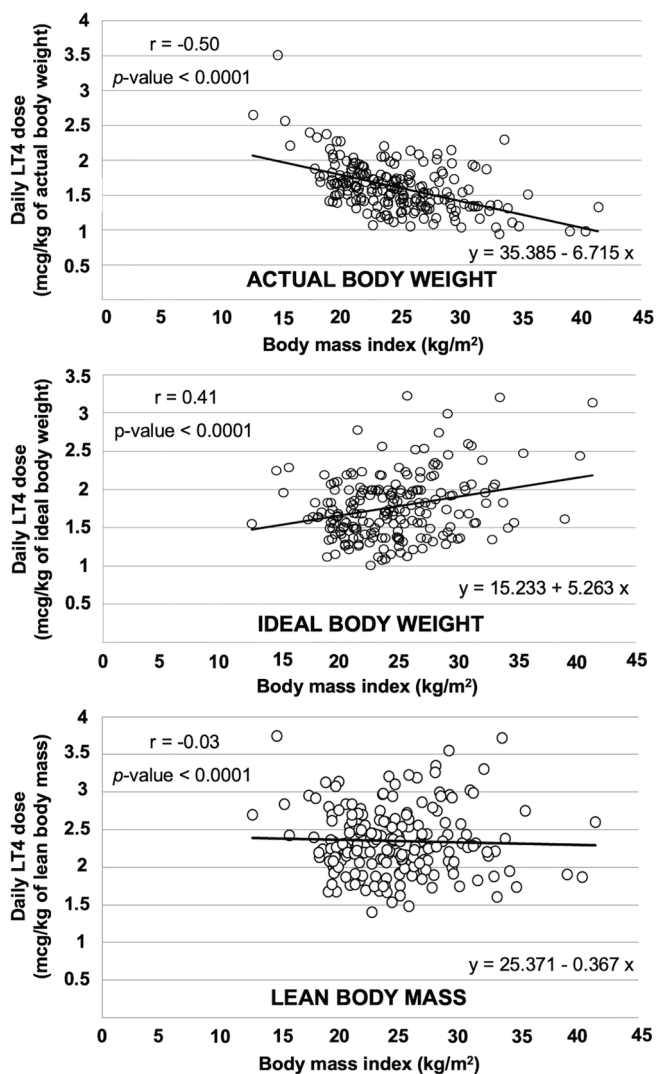


Fig. 1. Correlations between the daily LT4 dose per kg actual body weight (upper panel), LT4 dose per kg ideal body weight (middle panel), LT4 dose per kg lean body mass (lower panel), and body mass index.

might have occurred by chance from small proportion of cohorts. Also, the estimation of LBM using Hume formula was derived from the population that included obese subjects for only 5.4% [23].

Age and gender differences in LT4 dose requirement based on actual BW exist. Men and younger adults require a higher dose of LT4, as a consequence of a higher LBM [5,27]. These results are consistent with previous reports [28,29]. Individualized dosing of LT4 based on the

Table 2
Univariate and multivariate analyses of levothyroxine dose per actual body weight, with body weight, age, and sex as independent variables.

Univariate Analysis		Daily LT4 dose/kg of actual BW		
N = 200	β	Coefficient	p-value	95% CI
BW	-0.49	-0.13	< 0.001	-0.16, -0.01
Age	-0.16	-0.03	0.02	-0.01, -0.00
Male	-0.89	0.08	0.22	-0.19, 0.44
Multivariate Analysis		Daily LT4 dose/kg of actual BW		
N = 200	β	Coefficient	p-value	95% CI
BW	-0.54	-0.15	< 0.001	-0.20, -0.03
Age	-0.20	-0.06	0.001	-0.10, -0.01
Male	0.14	0.12	0.03	0.02, 0.24

Abbreviations: BW, body weight; CI, confidence interval; LT4, levothyroxine.

patient's LBM is recommended.

This study is limited by its retrospective nature. The prospective validation is necessary. We cannot assess compliance with dosing. Many cases with missing data were excluded, introducing a selection bias. This retrospective study did not allow us to collect the menopausal status or estrogen therapy. Premenopausal women may require greater LT4 doses than either postmenopausal women or men [3,28,29]. Estrogen therapy also increases the higher doses of LT4 to maintain the same serum TSH [30]. The patients with severe obesity (BMI \geq 30 kg/m²) were only 12% of the cohort. The LBM was calculated from the formulas, not measured from direct body composition assessment. However, the calculations are more practical use than direct measurement in clinical practice. The amount of residual functioning thyroid tissue may affect the LT4 dosage. Higher doses of L-T4 generally are required in athyreotic patients (total thyroidectomy and radioiodine remnant ablation in differentiated thyroid cancer) compared with patients with functioning residual thyroid tissue (i.e., chronic autoimmune thyroiditis or after radioiodine ablation for Graves' disease) [31,32]. Our study excluded patients with thyroid cancer because TSH suppression is mostly applied with these patients. In addition, the results can be easily compared to prior studies that excluded patients with malignant thyroid conditions [4,8,15,16,33,34]. Previous studies mostly included hypothyroid patients after thyroidectomy.

Conclusions

We conclude that LBM is considered a better indicator for calculating an appropriate LT4 replacement dose than actual BW and ideal BW, especially in hypothyroid Thai patients with obesity. Recommended daily dose of LT4 is 2.3 mcg/kg of LBM that could be applied to all ranges of BMI. We believe that an estimate of LBM may be helpful to shorten the time required to attain a stable LT4 dose.

Ethical approval

The study was approved by the Human Research Ethics Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRedit authorship contribution statement

Ganista Ratanapornsompong: Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. **Chutintorn Sriphrapradang:** Conceptualization, Methodology, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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