

# Profile of Levothyroxine Replacement Therapy in Graves' Disease Patients with Hypothyroidism Post-Radioactive Iodine Ablation: Focus on Different Weight-Based Regimens

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## Abstract

**Objective.** To evaluate the status of euthyroidism achieved among Thai patients with post-ablative hypothyroidism and to examine the difference between various weight-based daily levothyroxine (LT4) replacement regimens in these patients.

**Methodology.** We conducted a retrospective review of Thai patients with Graves' disease (GD) who developed hypothyroidism following radioactive iodine treatment from 2016 to 2020 at Theptarin hospital. Daily LT4 dose was calculated based on actual body weight (ABW), ideal body weight (IBW), and estimated lean body mass (LBM).

**Results.** We reviewed a total of 271 patient records. Of these, 81.2% were females with a mean age of 40.8±11.7 years, LT4 intake duration of 27.1±14.6 months, and LT4 dose/kg ABW of 1.4±0.5 µg/kg/day. At the final follow-up, 62.4% of patients achieved thyroid-stimulating hormone (TSH) levels within the reference interval, 15.5% had TSH levels over, and 22.1% had TSH levels under the reference range. Obese patients required a lower daily LT4 dose relative to ABW and higher daily LT4 dose relative to IBW to attain euthyroidism (ABW 1.1±0.4 µg/kg/day and IBW 2.0±0.8 µg/kg/day). Estimated daily LT4 dose based on LBM showed a constant dosage of 2.0 µg/kg/day in all BMI categories.

**Conclusions.** Suboptimum LT4 replacement therapy was found in almost half of hypothyroid patients with GD treated with radioactive iodine. Estimated LBM was a better indicator for dosing calculation in these patients compared with ABW and IBW.

**Key words:** post-ablative, hypothyroidism, Graves' disease, in-range TSH, levothyroxine (LT4), lean body mass

## INTRODUCTION

Hyperthyroid Graves' disease (GD) is managed by antithyroid drugs (ATD), radioactive iodine (RAI) or thyroidectomy. RAI is a favorable alternative in many patients who fail to achieve remission from ATD.<sup>1</sup>

In our institute, one-fifth of all GD patients have been treated with RAI over a period of 35 years.<sup>2</sup> Majority (97.1%) developed hypothyroidism due to prescription of a relatively high single fixed dose of RAI to aim for hypothyroidism.

The complexity and challenges of maintaining biochemical euthyroidism in patients with lifelong levothyroxine (LT4) replacement therapy cannot be underestimated given the narrow therapeutic range of LT4.<sup>3-5</sup> The level of TSH is an indicator for monitoring and adjusting the dose of LT4 therapy. Initial dosing can vary greatly depending on the amount of residual thyroid. Most adult patients with

overt hypothyroidism are provided a simple weight-based dose of LT4 at 1.6 µg/kg/day (equivalent to approximately 100–125 µg/day).<sup>6-7</sup> Lower doses of LT4 were suggested from Thai and Singaporean studies, on average 1.1 µg/kg/day.<sup>8-10</sup> After LT4 dose modification, it is recommended to recheck the serum TSH level every 6-8 weeks.<sup>1</sup>

After achieving the optimum dose of LT4, TSH levels should be monitored every 6-12 months. Factors that may affect the dose of LT4 required to maintain euthyroidism include: a reduction in residual thyroid reserve, ageing, obesity, drugs and illnesses.<sup>11-12</sup> Therefore, long-term monitoring is necessary to maintain LT4 replacement therapy. The danger of under-replacement is well recognized but the risks of over-treatment with LT4 (iatrogenic thyrotoxicosis) cannot be overemphasized.<sup>3,13</sup> In patients with low-normal or suppressed serum TSH levels, several studies consistently confirmed an increased risk of atrial fibrillation, osteoporosis, fracture and over-all mortality especially in elderly patients with underlying cardiac conditions.<sup>14-15</sup>

Initial prescription with estimated weight-based dose of LT4 should be followed by a careful dose adjustment and periodic review of drug timing, adherence and concomitant drugs/illnesses that can affect LT4 absorption.<sup>16</sup>

Previous studies from Western countries showed that up to 40% of patients with hypothyroidism from various causes had abnormal serum TSH levels while on LT4 treatment.<sup>13,17-18</sup> In Thailand, there is a paucity of data on the status of serum TSH levels and practice patterns in patients with post-ablative hypothyroidism. LBM was superior to actual body weight (ABW) as a predictor of weight-based dosage from active LT4 pharmacokinetics in the lean body compartment, not in adipose tissue.<sup>19-21</sup> Using ABW to determine a starting LT4 dose in obese patients could lead to supra-therapeutic doses.<sup>22</sup> Ideal body weight (IBW) using the Devine formula which is calculated based on height was also studied as an alternative dosing regimen.<sup>23</sup> However, further validations are warranted to apply estimated LBM or IBW dosing regimens in hypothyroid patients with post-ablative hypothyroidism from RAI ablation.

## OBJECTIVES

The main objective of our study was to evaluate the status of achieved euthyroidism among Thai GD patients with post-ablative hypothyroidism. It also aimed to evaluate the difference between various weight-based daily LT4 regimens (ABW, LBM, and IBW) according to body mass index (BMI) in patients with euthyroidism.

## METHODOLOGY

This was a retrospective study of RAI-treated hyperthyroid GD patients in Theptarin Hospital, Bangkok, Thailand from 2016 to 2020. Patients aged 15 years and above with primary hypothyroidism from RAI ablation were studied. Patients with transient hypothyroidism from RAI, repeated RAI treatment due to relapsed GD, pregnant women and lactating mothers, major illnesses which could affect LT4 absorption, changes in body weight  $\geq 15\%$  in the previous 6 months, and those receiving LT4 therapy less than 6 months were excluded from the study.

In our hospital, a fixed dose of RAI (10-30 mCi) based on estimated thyroid size was prescribed individually to aim for hypothyroidism.<sup>2</sup> In Thailand, there are two brands of LT4 medication available (Eltroxin®, GlaxoSmithKline, United Kingdom and Euthyrox®, Merck, Germany). Euthyrox® is available in 50  $\mu\text{g}$  and 100  $\mu\text{g}$  tablets. No generic drug of LT4 was used in our hospital during the study period. Serum TSH concentrations were measured by electro-chemiluminescent immunoassays (Roche Diagnostics, Indianapolis, USA) with a reference range of 0.3 to 4.2 mIU/L.

Serum TSH levels at the last follow-up visit were retrieved and classified as in-range if a serum TSH value was within

the reference range of 0.3-4.2 mIU/L. The out-of-range TSH group was further divided as over-treatment if the serum TSH level was  $< 0.3$  mIU/L and under-treatment if the serum TSH level was  $> 4.2$  mIU/L. Self-reported compliance with LT4 therapy was retrieved from medical records and categorized into three groups: missed  $<5\%$  dose in the last 1 month; missed  $\geq 5\%$  to  $<15\%$  dose in the last 1 month; and missed  $\geq 15\%$  in the last 1 month. Patterns of LT4 prescription were also collected and categorized as daily dose, alternate day dose, or segmented weekend dose.

BMI was calculated by dividing weight in kilograms by height in meters squared. LBM was calculated based on ABW, height, and gender using the Hume formula<sup>24</sup> and IBW was calculated based on height using the Devine formula (Supplement Table 1).<sup>25</sup> The LT4 dose requirement was calculated as  $\mu\text{g}$  per kilogram ABW, LBM and IBW per day. This study was approved by the Institutional Review Board committee of Theptarin Hospital (EC No.02-2021).

## Statistical analyses

Continuous variables were summarized as mean  $\pm$  standard deviation (SD) or median (interquartile range, IQR) while categorical variables were summarized using counts and percentages. The t-test or analysis of variance was applied to compare differences in means among groups. The Chi-squared test was used to compare differences in percentages between groups. Univariate analysis of variance (ANOVA) was performed to test for differences among demographic parameters in patients with optimal serum TSH levels, patients with over-treatment, and patients with under-treatment. The post-hoc analysis was performed using the Dunnett test. A p-value of  $<0.05$  was considered statistically significant. All analyses were conducted using SPSS Statistical Package, version 20 (IBM Corp., Armonk, NY, USA).

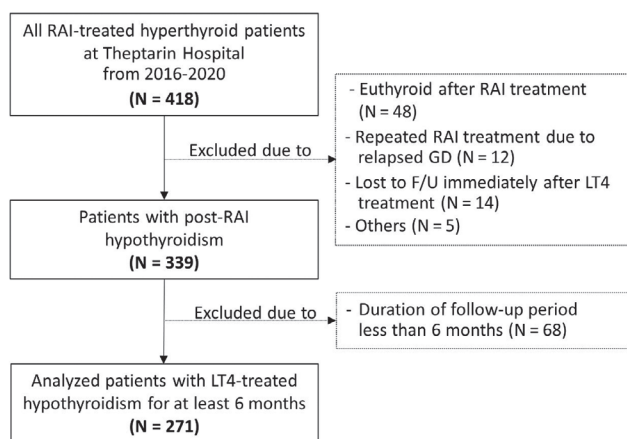
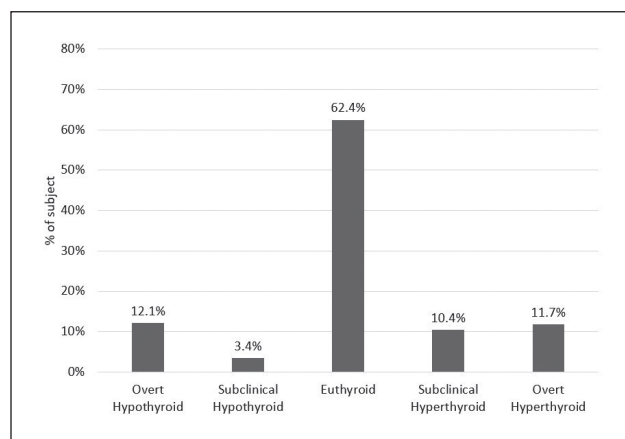
## RESULTS

A total of 418 charts were reviewed and 271 patients met the inclusion criteria (Figure 1). The baseline demographic data and patterns of LT4 prescription are presented in Table 1. In the cohort, the mean age was  $40.8 \pm 11.7$  years (8.5% were  $\geq 60$  years of age); females comprised 81.2%; the mean BW was  $60.9 \pm 12.6$  kgs, the mean BMI was  $24.4 \pm 4.2$   $\text{kg}/\text{m}^2$  and the mean duration of LT4 treatment was  $27.1 \pm 14.6$  months. The mean weekly LT4 dose was  $620 \pm 222$   $\mu\text{g}/\text{week}$ . The mean daily LT4 dose/kg of ABW was  $1.4 \pm 0.5$   $\mu\text{g}/\text{kg}/\text{day}$ ; mean daily LT4 dose/kg of LBM was  $2.0 \pm 0.7$   $\mu\text{g}/\text{kg}/\text{day}$ ; and the mean daily LT4 dose/kg of IBW was  $1.6 \pm 0.6$   $\mu\text{g}/\text{kg}/\text{day}$ . Three percent (3.3%) of all patients report missing LT4 dose  $\geq 15\%$  of LT4 in the last month.

Only 62.4% of the patients achieved normal serum TSH range at the last follow-up. Serum TSH levels were above the reference range (TSH  $> 4.2$  mIU/L) in 15.5% and were under the reference range (TSH  $< 0.3$  mIU/L) in 22.1%. The detailed distribution of thyroid status at the last visit

**Table 1.** Baseline characteristics of the study population

Characteristics	Total (n = 271)	Optimal-treated group (n = 169)	Over-treated group (n = 60)	Under-treated group (n = 42)	p-value
Present age (years)	40.8 ± 11.7	41.4 ± 11.7	39.5 ± 12.7	40.1 ± 10.4	0.527
< 40 years	52.0%	51.6%	51.7%	54.8%	0.994
40–59 years	39.5%	39.6%	40.0%	38.1%	
≥ 60 years	8.5%	8.9%	8.3%	7.1%	
Gender					<b>0.046</b>
Male	18.8%	14.8%	21.7%	31.0%	
Female	81.2%	85.2%	78.3%	69.0%	
Body weight (kg)	60.9 ± 12.6	60.0 ± 11.4	59.9 ± 12.9	66.3 ± 15.4	<b>0.010</b>
Body mass index (kg/m <sup>2</sup> )	24.2 ± 4.2	24.3 ± 4.1	23.8 ± 3.9	25.6 ± 4.7	0.092
< 18.5	3.0%	3.6%	3.3%	0%	0.087
18.5 – 24.9	57.9%	57.4%	70.0%	42.8%	
25.0 – 29.9	29.5%	30.1%	20.0%	40.5%	
≥ 30.0	9.6%	8.9%	6.7%	16.7%	
Ideal Body Weight (kg)	54.7 ± 8.2	54.3 ± 7.9	54.0 ± 8.7	57.3 ± 8.3	0.073
Lean Body Mass (kg)	42.7 ± 6.8	42.1 ± 6.2	42.0 ± 7.2	45.6 ± 8.0	<b>0.009</b>
Duration of GD Before RAI (Months)	45.7 ± 63.6	45.3 ± 60.4	54.2 ± 72.7	35.3 ± 62.2	0.335
Dose of Radioactive Iodine (mCi)	19.0 ± 5.8	18.8 ± 5.9	19.1 ± 5.5	19.5 ± 6.0	0.825
Duration of Hypothyroidism before the start of LT4 therapy (months)	1.4 ± 2.0	1.3 ± 1.5	1.8 ± 3.3	1.1 ± 1.0	0.140
Nadir TSH before the start of LT4 therapy (uIU/mL)	38.4 ± 34.2	34.7 ± 30.2	46.8 ± 40.7	40.4 ± 36.4	0.070
Patterns of LT4 intake (%)					<b>0.038</b>
Same dose daily	43.5%	42.6%	35.0%	59.5%	
Alternate day dose	14.1%	14.8%	10.0%	16.7%	
Segmented weekend	42.4%	42.6%	55.0%	23.8%	
LT4 dosage (mcg/kg of ABW)	1.4 ± 0.5	1.4 ± 0.4	1.4 ± 0.5	1.6 ± 0.5	<b>0.045</b>
LT4 dosage (mcg/kg of IBW)	1.6 ± 0.6	1.6 ± 0.5	1.5 ± 0.5	1.9 ± 0.6	<b>0.004</b>
LT4 dosage (mcg/kg of LBM)	2.0 ± 0.7	2.0 ± 0.6	1.9 ± 0.7	2.3 ± 0.7	<b>0.010</b>
LT4 dosage per week (mcg)	620.1 ± 221.6	605.9 ± 207.9	567.5 ± 185.1	752.4 ± 272.8	<b>&lt;0.001</b>
Duration of LT4 (months)	27.1 ± 14.6	28.3 ± 14.8	25.7 ± 13.1	24.1 ± 15.1	0.165
LT4 compliance					<b>&lt;0.001</b>
Missed < 5%	81.2%	83.4%	81.7%	71.4%	
Missed 5–14 %	15.5%	15.4%	16.7%	14.3%	
Missed ≥ 15 %	3.3%	1.2%	1.6%	14.3%	

**Figure 1.** Flow diagram of patients in the present study.**Figure 2.** Thyroid status of studied patients at the last visit.

is summarized in Figure 2. The median serum TSH level in patients with optimal treatment was 1.45 mIU/L (0.79, 2.41), in the undertreated it was 7.02 mIU/L (5.43, 12.68), while in the overtreated it was 0.09 mIU/L (0.03, 0.19).

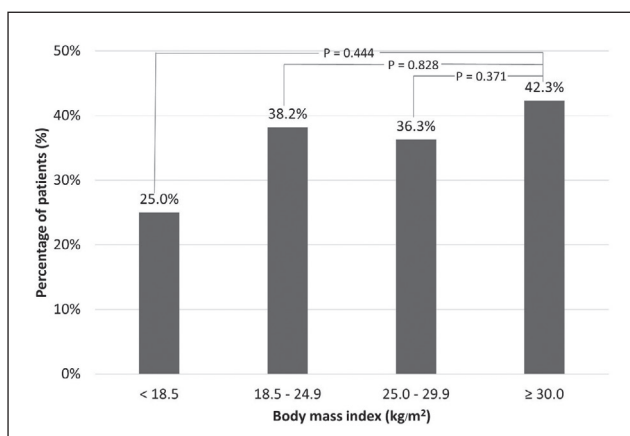
As shown in Table 1, 81.2% of patients adhered to their daily LT4 treatment in the last month. Regarding patterns of LT4 prescription, 43.5% were on the same daily LT4 dosing regimen; 42.4% were on the segmented weekend

dosing regimen; while 14.1% were on the alternate daily dosing regimen. There was no statistical significance found between patterns of LT4 prescription and in-range serum TSH levels.

In the post-hoc analysis, the undertreated group was found to have a significantly lower actual body weight compared with the optimally-treated group ( $p = 0.007$ ). Moreover, the undertreated group had a higher daily LT4 dose compared

**Table 2.** Baseline characteristics grouped by body mass index (BMI) in participants who achieved euthyroidism after LT4 replacement

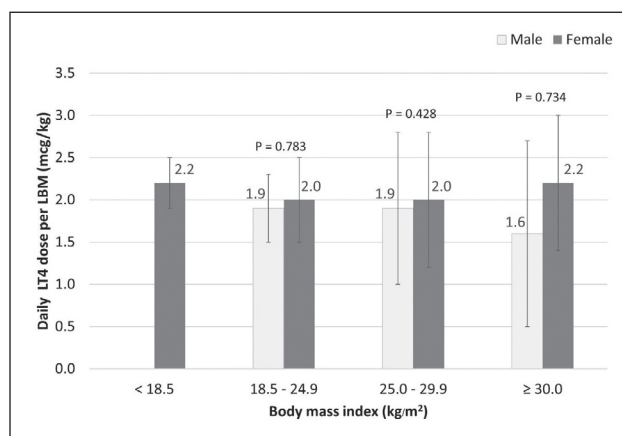
Characteristics	Body mass index (kg/m <sup>2</sup> )				p-value
	< 18.5 (n = 6)	18.5 – 24.9 (n = 97)	25.0 – 29.9 (n = 51)	≥ 30.0 (n = 15)	
Present age (years)	31.2 ± 3.5	41.1 ± 11.1	43.1 ± 12.2	41.1 ± 14.6	0.010
Gender					0.606
Male	0.0%	13.4%	17.6%	20.0%	
Female	100.0%	86.6%	82.4%	80.0%	
Body weight (kg)	46.1 ± 3.9	54.9 ± 7.5	66.3 ± 9.2	76.7 ± 13.1	<0.001
Ideal Body Weight (kg)	52.4 ± 6.8	54.3 ± 7.8	54.7 ± 8.4	53.8 ± 7.1	0.660
Lean Body Mass (kg)	37.1 ± 4.1	40.6 ± 5.4	44.2 ± 6.3	47.0 ± 6.7	<0.001
Duration of GD Before RAI (Months)	17.0 ± 15.1	47.7 ± 67.1	46.1 ± 51.1	38.4 ± 55.1	0.624
Dose of Radioactive Iodine (mCi)	18.3 ± 2.6	18.6 ± 5.9	19.0 ± 6.1	19.7 ± 6.9	0.790
Duration of Hypothyroidism before the start of LT4 therapy (months)	0.8 ± 0.8	1.4 ± 1.6	1.2 ± 1.4	0.9 ± 1.0	0.211
Nadir TSH before the start of LT4 therapy (uIU/mL)	37.4 ± 32.1	31.4 ± 27.9	40.8 ± 34.4	35.9 ± 30.3	0.876
Patterns of LT4 intake (%)					0.800
Same dose daily	50.0%	39.2%	45.1%	53.3%	
Alternate day dose	0.0%	14.4%	17.6%	13.4%	
Segmented weekend	50.0%	46.4%	37.3%	33.3%	
LT4 dosage (mcg/kg of ABW)	1.8 ± 0.2	1.4 ± 0.3	1.3 ± 0.5	1.2 ± 0.5	0.002
LT4 dosage (mcg/kg of IBW)	1.6 ± 0.2	1.5 ± 0.3	1.7 ± 0.7	2.0 ± 0.8	<0.001
LT4 dosage (mcg/kg of LBM)	2.2 ± 0.3	2.0 ± 0.4	2.0 ± 0.8	2.1 ± 0.9	0.397
LT4 dosage per week (mcg)	575.0 ± 74.2	572.6 ± 140.7	636.9 ± 271.2	728.3 ± 300.7	<0.001
Duration of LT4 (months)	35.8 ± 18.7	29.6 ± 14.4	25.9 ± 15.6	25.6 ± 11.9	0.093



**Figure 3.** Percentage of out-of-reference range serum TSH values at the last visit in different BMI categories.

with the optimally-treated group ( $p < 0.05$ ) regardless of the weight-based regimen. The number of patients who missed LT4  $\geq 15\%$  in the last month was also found to be higher in the undertreated compared with the optimally-treated group (14.3% vs. 1.2%,  $p = 0.011$ ).

The comparisons of the percentages of patients with TSH levels out-of-reference range between BMI  $\geq 30$  kg/m<sup>2</sup> versus BMI 25-29.9 kg/m<sup>2</sup>, BMI  $\geq 30$  kg/m<sup>2</sup> versus BMI 18.5-24.9 kg/m<sup>2</sup>, and BMI  $\geq 30$  kg/m<sup>2</sup> versus BMI  $< 18.5$  kg/m<sup>2</sup> are shown in Figure 3. There was no statistically significant difference between percentages of serum TSH out of reference range between the two BMI categories. In obese patients with BMI  $\geq 30$  kg/m<sup>2</sup>, 26.9% had TSH levels under the reference range while 15.4% had TSH levels lower than the reference range.



**Figure 4.** Comparison of gender differences in daily LT4 dose requirement based on lean body mass (LBM), stratified by BMI category.

To determine the appropriate LT4 dosage in relation to the various categories of BMI, a subgroup analysis in patients with in-range serum TSH levels was performed (Table 2). Obese patients with BMI of  $\geq 30$  kg/m<sup>2</sup> had significantly lower daily LT4 dose per ABW and IBW but not per LBM compared with the other BMI categories ( $p < 0.05$ ). Patients who were more obese had lower daily LT4 dose with the LT4 dosing strategy based on ABW. All patients with BMI  $\geq 18.5$  kg/m<sup>2</sup> ( $p = 0.815$ ) had a constant daily dose of 2.0-2.2  $\mu\text{g}/\text{kg}$  with the daily LT4 dosing strategy based on LBM. In contrast, obese patients required a higher daily LT4 dose with the LT4 dosing strategy based on IBW compared with lower BMI categories ( $p < 0.05$ ). We found no gender difference in LT4 dose requirement based on LBM in each of the BMI stratum (Figure 4).



## DISCUSSION

While LT4 replacement therapy seems to be straightforward, its optimal use can be challenging. As LT4 is usually administered over a patient's lifetime, physicians need to understand the various factors that can affect LT4 dose and absorption. Apart from this, they will have to meticulously titrate the patient's LT4 dose to prevent adverse effects of suboptimum therapy. In this study, almost 40% of patients with RAI-treated hypothyroidism had suboptimum LT4 replacement. For initial dose estimation, lean body mass might be a better indicator for weight-based calculation in obese patients. No baseline parameter was found to be associated with in-range or out-of-range serum TSH levels. It is interesting that the percentage of over-replaced LT4 patients was greater than the percentage of under-replaced patients.

The main determining factors of LT4 requirement are the etiology of hypothyroidism, age, gender, body weight, and lean body mass.<sup>3,5</sup> Generally, hypothyroidism due to Hashimoto's thyroiditis or post-ablative treatment of GD require lower doses of LT4 compared to patients who completely lack thyroid tissue following total thyroidectomy. Unfortunately, most previous studies on dosing strategies did not specify the cause of hypothyroidism or selected only post-thyroidectomy patients. The optimal daily LT4 dose was suggested to be 1.5-1.8 µg/kg/day.<sup>6</sup> In 2005, the seminal study from Italy found that LBM was a better predictor of the daily LT4 requirement than total body weight in thyroid cancer patients who underwent thyroidectomy and RAI remnant ablation.<sup>20</sup>

The concept of LBM as a predictor of drug dosage has been studied much earlier where dual energy x-ray absorptiometry precisely evaluated body composition.<sup>19</sup> Recently, a study among Thai patients with various causes of hypothyroidism also demonstrated the usefulness of estimated LBM as calculated by the Hume formula in obese patients.<sup>10</sup> The daily LT4 dose of 2.3 µg/kg of LBM/day was suggested to shorten the time required to attain a stable LT4 dose. Our present study is aligned with this earlier one, but we provide more accurate dosing in GD patients with post-ablative hypothyroidism. Our study showed that a daily LT4 dose of 2.0 µg/kg of LBM/day achieved euthyroidism in patients with BMI of 18.5-29.9 kg/m<sup>2</sup>. This dosage corresponded to a daily LT4 dose of 1.4 µg/kg of ABW, differing from the results of a previous study from Singapore (1.1 µg/kg of ABW)<sup>9</sup> and a previous European study (1.6 µg/kg of ABW).<sup>7</sup>

In many countries including Thailand, the limited available LT4 preparations pose a challenge to meticulous LT4 titration. Sophisticated regimens (alternate dosage or segmented weekend method) could be used in some patients but exercise caution with elderly patients or in those with polypharmacy. Moreover, both intrinsic and extrinsic factors which could affect LT4 dosage should be thoroughly reviewed before dose adjustment.

When prescribing initial LT4 replacement therapy, calculate BMI and LBM to guide the dose. In patients with BMI ≥ 25 kg/m<sup>2</sup>, LBM is a better gauge to calculate daily LT4 dose than ABW or IBW. In patients requiring unusually high LT4 doses, investigate other factors apart from compliance and concomitant medications, including gastrointestinal tract malabsorption, concomitant food and drink, and *Helicobacter pylori* infection.<sup>26-28</sup>

LT4 dose requirements decrease with age due to decreased LBM, thus, elderly patients are specially vulnerable to adverse events from over-treatment.<sup>29</sup> Periodic monitoring is recommended in this particular age group with the aim of maintaining the serum TSH levels at the upper end of the reference range.

Our study had several limitations. First, the retrospective nature of data collection has inherent weaknesses. Several relevant data were missing from the medical records, including concomitant food and drink, over-the-counter medications, menstrual status and undocumented chronic illnesses. Second, self-reported compliance could not be ascertained by more objective medication adherence assessment such as electronic pill counter or validated questionnaire. Third, only the latest serum TSH levels were used as a marker for euthyroidism. This might not reflect the dynamic process of clinical practices to adjust LT4 dose based on serum TSH levels. However, our study selected the patients who received LT4 for at least 6 months after the initiation of LT4 replacement therapy and the duration of LT4 treatment was over 2 years. Also, our hospital provides only branded LT4 drugs to avoid the variable bioavailability of generic LT4 drugs.<sup>30</sup> Finally, estimated LBM was calculated using the Hume formula, which was introduced over 50 years before sophisticated imaging was available to analyze body composition.<sup>24</sup>

In conclusion, suboptimum LT4 replacement therapy was common in GD patients with post-ablative hypothyroidism. Our study showed that over-treatment of LT4 was more common than under-treatment. Estimated LBM was a better gauge to calculate doses compared with ABW and IBW. The complexity of maintaining biochemical and clinical euthyroidism in LT4-treated hypothyroid patients warrants more attention to dose adjustments, especially in populations at-risk for optimum therapy.

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### Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

### Author Disclosure

The authors declared no conflict of interest.

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## References

- Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and Management of Hyperthyroidism and Other Causes of thyrotoxicosis. *Thyroid*. 2016;26(10): 1343–421. PMID: 27521067. <https://doi.org/10.1089/thy.2016.0229>
- Thewjitcharoen Y, Karndumri K, Chatchomchuan W, et al. Practice patterns and outcomes in the management of Thai patients with Graves' disease. *Thyroid Res*. 2021;14(1):5. PMID: 33658045. PMID: PMC7927256. <https://doi.org/10.1186/s13044-021-00097-y>
- Biondi B, Cooper DS. Thyroid hormone therapy for hypothyroidism. *Endocrine*. 2019;66(1):18-26. PMID: 31372822. <https://doi.org/10.1007/s12020-019-02023-7>
- Garber J, Cobin R, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*. 2012;22(12):1200-35. PMID: 22954017. <https://doi.org/10.1089/thy.2012.0205>
- Jonklaas J. Optimal thyroid hormone replacement. *Endocr Rev*. 2020;43(2):366-404. PMID: 34543420. PMID: PMC8905334 (available on 2022-09-20). <https://doi.org/10.1210/edrv/bnab031>
- Gordon MB, Gordon MS. Variations in adequate levothyroxine replacement therapy in patients with different causes of hypothyroidism. *Endocr Pract*. 1999;5(5):233-8. PMID: 15251659. <https://doi.org/10.4158/ep.5.5.233>
- Roos A, Linn-Rasker SP, van Domburg RT, Tijssen JP, Berghout A. The starting dose of levothyroxine in primary hypothyroidism treatment: A prospective, randomized, double-blind trial. *Arch Intern Med*. 2005;165(15):1714-20. PMID: 16087818. <https://doi.org/10.1001/archinte.165.15.1714>
- Rajatanavin R, Chailurkit L, Kongsuksai A, Chalayondeja W, Sirisriro R, Choksuwatanasakul P. Optimum replacement, suppressive doses and bioavailability of levothyroxine therapy in Thai patients. *Intern Med*. 1990;6:128-34.
- Tan NC, Chew RQ, Koh YLE, et al. Primary hypothyroidism in the community: Lower daily dosages of levothyroxine replacement therapy for Asian patients. *Medicine (Baltimore)*. 2017;96(7):e6145. PMID: 28207545. PMID: PMC5319534. <https://doi.org/10.1097/md.00000000000006145>
- Ratanapornsompong G, Sriphrapradang C. Appropriate dose of levothyroxine replacement therapy for hypothyroid obese patients. *J Clin Transl Endocrinol*. 2021;25:100264. PMID: 34401353. PMID: PMC8350177. <https://doi.org/10.1016/j.jcte.2021.100264>
- Vaidya B, Pearce SH. Management of hypothyroidism in adults. *BMJ*. 2008;337:a801. PMID: 18662921. <https://doi.org/10.1136/bmj.a801>
- Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: Statement by the British Thyroid Association Executive Committee. *Clin Endocrinol (Oxf)*. 2016;84(6):799-808. PMID: 26010808. <https://doi.org/10.1111/cen.12824>
- Somwaru LL, Arnold AM, Joshi N, Fried LP, Cappola AR. High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. *J Clin Endocrinol Metab*. 2009;94(4):1342-5. PMID: 19126628. PMID: PMC2682480. <https://doi.org/10.1210/jc.2008-1696>
- Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrinol Metab*. 2010;95(1):186-93. PMID: 19906785. <https://doi.org/10.1210/jc.2009-1625>
- Thayakaran R, Adderley NJ, Sainsbury C, et al. Thyroid replacement therapy, thyroid stimulating hormone concentrations, and long-term health outcomes in patients with hypothyroidism: Longitudinal study. *BMJ*. 2019;366:l4892. PMID: 31481394. PMID: PMC6719286. <https://doi.org/10.1136/bmj.l4892>
- Scargill JJ, Livingston M, Holland D, Duff CJ, Fryer AA, Heald AH. Monitoring thyroid function in patients on levothyroxine. Assessment of conformity to national guidance and variability in practice. *Exp Clin Endocrinol Diabetes*. 2017;125(9):625-33. PMID: 28407667. <https://doi.org/10.1055/s-0043-103018>
- Yavuz DG, Yazıcı D, Keskin L, et al. Out-of-reference range thyroid-stimulating hormone levels in levothyroxine-treated primary hypothyroid patients: A multicenter observational study. *Front Endocrinol (Lausanne)*. 2017;8:215. PMID: 28955301. PMID: PMC5600911. <https://doi.org/10.3389/fendo.2017.00215>
- Shim J, Lin T, Dashiell-Earp C, Nechrebecki M, Leung AM. Endocrinology practice patterns of hypothyroidism and osteoporosis management in a U.S. tertiary academic medical center. *Clin Diabetes Endocrinol*. 2019;5:10. PMID: 31360539. <https://doi.org/10.1186/s40842-019-0085-8>
- Cunningham JJ, Barzel US. Lean body mass is a predictor of the daily requirement for thyroid hormone in older men and women. *J Am Geriatr Soc*. 1984;32(3):204-7. PMID: 6699335. <https://doi.org/10.1111/j.1532-5415.1984.tb02003.x>
- Santini F, Pinchera A, Marsili A, et al. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. *J Clin Endocrinol Metab*. 2005;90(1):124-7. PMID: 15483074. <https://doi.org/10.1210/jc.2004-1306>
- Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage. Implications for drug therapy. *Clin Pharmacokinet*. 1994;26(4):292-307. PMID: 8013162. <https://doi.org/10.2165/00003088-199426040-00005>
- Papoian V, Ylli D, Felger EA, Wartofsky L, Rosen JE. Evaluation of thyroid hormone replacement dosing in overweight and obese patients after a thyroidectomy. *Thyroid*. 2019;29(11):1558-1562. PMID: 31573413. <https://doi.org/10.1089/thy.2019.0251>
- Jin J, Allemang MT, McHenry CR. Levothyroxine replacement dosage determination after thyroidectomy. *Am J Surg*. 2013;205(3):360-3. PMID: 23369308. <https://doi.org/10.1016/j.amjsurg.2012.10.015>
- Hume R. Prediction of lean body mass from height and weight. *J Clin Pathol*. 1966;19(4):389-91. PMID: 5929341. <https://doi.org/10.1136/jcp.19.4.389>
- Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. *Ann Pharmacother*. 2000;34(9):1066-9. PMID: 10981254. <https://doi.org/10.1345/aph.19381>
- Centanni M, Gargano L, Canettieri G, et al. Thyroxine in goiter, *Helicobacter pylori* infection, and chronic gastritis. *N Engl J Med*. 2006;354(17):1787-95. PMID: 16641395. <https://doi.org/10.1056/nejmoa043903>
- Devdhar M, Drooger R, Pehlivanova M, Singh G, Jonklaas J. Levothyroxine replacement doses are affected by gender and weight, but not age. *Thyroid*. 2011;21(8):821-7. PMID: 21751885. PMID: PMC3148125. <https://doi.org/10.1089/thy.2011.0029>
- Caron P, Grunenwald S, Persani L, Borson-Chazot F, Leroy R, Duntas L. Factors influencing the levothyroxine dose in the hormone replacement therapy of primary hypothyroidism in adults. *Rev Endocr Metab Disord*. 2021;1-21. PMID: 34671932. PMID: PMC8528480. <https://doi.org/10.1007/s11154-021-09691-9>
- Effraimidis G, Watt T, Feldt-Rasmussen U. Levothyroxine therapy in elderly patients with hypothyroidism. *Front Endocrinol (Lausanne)*. 2021;12:641560. PMID: 33790867. PMID: PMC8006441. <https://doi.org/10.3389/fendo.2021.641560>
- Benvenega S, Carlé A. Levothyroxine formulations: Pharmacological and clinical implications of generic substitution. *Adv Ther*. 2019;36 (Suppl 2):59-71. PMID: 31485974. PMID: PMC6822816. <https://doi.org/10.1007/s12325-019-01079-1>

**SUPPLEMENT TABLE 1**

Lean body mass (LBM) was calculated based on actual body weight (ABW), height, and gender using the Hume formula<sup>1</sup>:

**Hume formula**

Lean body mass (male) =  $( (0.32810 \times \text{BW,kg}) + (0.33929 \times \text{height,cm}) ) - 29.5336$

Lean body mass (female) =  $( (0.29569 \times \text{BW,kg}) + (0.41813 \times \text{height,cm}) ) - 43.2933$

Ideal body weight (IBW) was calculated based on height using the Devine formula<sup>2</sup>:

**Devine formula**

Ideal BW (male) =  $50.0\text{kg} + 0.9(\text{height,cm} - 152)\text{kg}$

Ideal BW (female) =  $45.5\text{kg} + 0.9(\text{height,cm} - 152)\text{kg}$

**Sample cases**

Female 40 yrs, height 160 cm, actual body weight 55 kg

Female 40 yrs, height 160 cm, actual body weight 65 kg

Female 40 yrs, height 160 cm, actual body weight 75 kg

No. of Subject	Actual body weight (ABW)	Ideal body weight (IBW)	Lean body mass (LBM)
1.	55.0	52.7	39.9
2.	65.0	52.7	42.8
3.	75.0	52.7	45.8

**References**

- Hume R. Prediction of lean body mass from height and weight. *J Clin Pathol.* 1966;19(4):389-91.
- Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. *Ann Pharmacother.* 2000;34(9):1066-9. PMID: 10981254.

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