



Levothyroxine Dosing after Total Thyroidectomy and Radioactive Iodine Treatment: Development and Validation of a Unified Predictive Formula

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Background and Objectives: Levothyroxine (LT4) replacement is required following total thyroidectomy (TT) for differentiated thyroid cancer (DTC), with the need and degree of thyroid-stimulating hormone (TSH) suppression determined by recurrence risk. Excessive or insufficient suppression increases cardiovascular, skeletal, and recurrence risks. Nonetheless, optimal LT4 dosing to achieve target TSH remains uncertain. This study aimed to develop and validate a formula to predict individualized LT4 requirements after thyroidectomy. **Materials and Methods:** Using data from 444 DTC patients who underwent TT and radioactive iodine therapy at Seoul National University Hospital, multiple linear regression identified body weight, height, age, sex, and TSH as predictors of daily LT4 dose ($\mu\text{g/day}$). A unified model ("Formula 1") was compared with the American Thyroid Association (ATA) weight-based recommendation ($2.1\text{--}2.7 \mu\text{g/kg}$). **Results:** The mean LT4 dose was $126\pm 38 \mu\text{g/day}$ ($1.9 \mu\text{g/kg}$). Body surface area demonstrated the strongest correlation with LT4 dose ($r=0.481$). In multivariable analysis, body weight and height positively associated with LT4 requirements, whereas age, female sex, and TSH associated inversely. The proposed formula exhibited a higher correlation with actual LT4 dose compared to the ATA method ($r=0.574$ vs. 0.462), as well as a lower prediction error (17.7 ± 15.0 vs. $23.6\pm 19.9 \mu\text{g/day}$). **Conclusion:** The new multivariable formula reduced prediction error compared with conventional weight-based dosing, particularly among patients requiring stronger TSH suppression. By incorporating demographic and biochemical factors, this approach enables more precise LT4 adjustment and demonstrates clinical utility for model-informed individualized therapy.

Key Words: Differentiated thyroid cancer, Levothyroxine, Thyroid-stimulating hormone suppression, Dose prediction model, Total thyroidectomy

Introduction

Patients with differentiated thyroid cancer (DTC) routinely require lifelong levothyroxine (LT4) therapy

following total thyroidectomy, with the degree of thyroid-stimulating hormone (TSH) suppression adjusted according to their recurrence risk. Contemporary guidelines recommend risk-stratified TSH targets: the 2025

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American Thyroid Association (ATA) guideline recommends individualized TSH suppression initiation, considering subnormal TSH levels for patients at high risk or with persistent disease, while maintaining TSH within the normal range for low- and intermediate-risk patients.¹⁾ The UK's National Institute for Health and Care Excellence guideline NG230 recommends initial suppression to <0.1 mIU/L following thyroidectomy and radioactive iodine ablation, followed by TSH titration at 9–12 months based on dynamic response assessment.²⁾ Similarly, the 2019 European Society for Medical Oncology advises serum TSH suppression (<0.1 mIU/L) for all patients with thyroid cancer with persistent structural disease; milder suppression (0.1–0.5 mIU/L) or low-normal levels (0.5–2 mIU/L) are recommended for intermediate- and low-risk patients, respectively.³⁾ The Japan Association of Endocrine Surgeons recommends maintaining TSH in the low-normal range for low-risk patients, suppressing TSH moderately in high-risk cases to prevent recurrence, avoiding excessive suppression, and individualizing intermediate-risk disease therapy.⁴⁾ The 2024 Korean Thyroid Association recommends a risk-adapted strategy following initial therapy—no routine suppression in low-risk disease (target TSH ~ 0.5 –2.0 mIU/L), individualized 0.1–2.0 mIU/L in intermediate-risk, and <0.1 mIU/L for high-risk—with subsequent relaxation based on ongoing response and patient comorbidity to avoid over-suppression.⁵⁾

Despite broad consensus on risk-based target TSH levels, optimal LT4 dosing to achieve these targets remains less standardized.^{1–5)} The 2014 ATA guideline proposed a simplified weight-based method, calculating daily LT4 requirements for patients with thyroid cancer requiring TSH suppression by multiplying 2.1–2.7 $\mu\text{g}/\text{kg}$ by actual body weight, as a practical reference.⁶⁾ Nevertheless, such fixed-dose formulas may not adequately capture interindividual variation arising from demographic and clinical factors, causing biochemical response heterogeneity. Therefore, this study aimed to develop a real-world data-based LT4 dosing formula to more precisely achieve individualized TSH suppression targets in post-thyroidectomy DTC patients, facilitating initial therapy and recurrence risk alignment.

Materials and Methods

Data Source and Participant Selection

This retrospective cohort comprised patients diagnosed with thyroid cancer at Seoul National University from 2011 to 2015. Only those who provided written informed consent were included; overall, 1,175 datasets were collected from 964 patients, and those meeting all of the following inclusion criteria were selected for analysis: (1) previous total thyroidectomy; (2) radioactive iodine therapy with a dose ≥ 30 mCi at least once; (3) body weight and height recorded within 1 month of thyroid function test (TFT); (4) free T3, free T4, and TSH measured between 2011 and 2015; (5) consistent daily dose of LT4 for at least 2 months before TFT measurement; and (6) TSH level <2.0 mIU/L. Patients under 20 years of age were excluded. Overall, 444 eligible datasets from 431 patients were included in the final analysis. Each data set consisted of a patient's demographic and clinical information along with a corresponding LT4 dose and TSH value (Fig. 1).

LT4 Dose Prediction Formula Development

We developed a multiple linear regression model to predict the required LT4 dose ($\mu\text{g}/\text{day}$) based on clinically relevant variables. Candidate predictors were selected according to prior literature and included actual body weight (kg), age (years), sex, height (cm), and

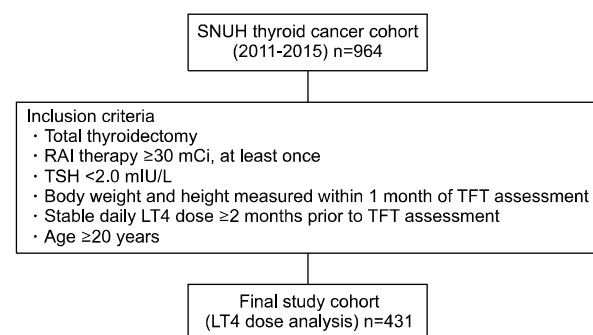


Fig. 1. Flowchart of patient selection for levothyroxine dose analysis in the SNUH thyroid cancer cohort (2011–2015). LT4: levothyroxine, RAI: radioactive iodine, SNUH: Seoul National University Hospital, TFT: thyroid function test, TSH: thyroid-stimulating hormone

serum TSH level (mIU/L).⁷⁻¹⁰⁾

Additionally, each patient's lean body mass (LBM) and body surface area (BSA) were estimated to assess potential correlations between LT4 requirements and body composition. LBM was calculated using the Hume equation, and BSA was derived using the DuBois formula.

$$\text{Hume LBM (men)} = 0.32810 \times \text{BWt} + 0.33929 \times \text{Ht} - 29.5336$$

$$\text{Hume LBM (women)} = 0.29569 \times \text{BWt} + 0.41813 \times \text{Ht} - 43.2933$$

$$\text{DuBois BSA} = 0.007184 \times (\text{BWt}^{0.425}) \times (\text{Ht}^{0.725})$$

These derived indices were not directly incorporated into the regression model to avoid multicollinearity with weight and height. Nonetheless, they were examined in univariate correlation analyses of LT4 dose versus body composition parameters.

Subsequently, separate multiple linear regression models were developed for each TSH subgroup to derive subgroup-specific predictive formulas. These subgroup models aimed to explore the potential benefit of tailoring LT4 dose estimation to different TSH target ranges. However, the primary focus for clinical applicability remained on a single unified model ("Formula 1") encompassing the entire suppressed range ($0 \leq \text{TSH} < 2.0$ mIU/L).

For comparison, the 2015 ATA weight-based dosing recommendations were applied, assuming 2.1–2.7 $\mu\text{g/kg}$ for patients requiring TSH suppression.

Outcomes

The primary outcome was the development of a formula to determine the daily LT4 dose ($\mu\text{g/day}$) required to achieve and maintain TSH levels of 0–0.1, 0.1–0.5, or 0.5–2.0 mIU/L after total thyroidectomy (TT) and radioactive iodine therapy. LT4 dose and corresponding thyroid function tests were included only when patients had maintained a stable LT4 regimen for at least 2 months before measurement. Secondary analyses assessed associations between the actual LT4 dose and clinical parameters, including body weight, height, age, sex, and serum TSH level. Derived

indices—LBM (Hume equation) and BSA (DuBois formula)—were further examined to evaluate the influence of body composition on LT4 requirements. Predicted LT4 doses from the regression model were compared with estimates derived from the 2015 ATA weight-based recommendation (2.1–2.7 $\mu\text{g/kg}$ for TSH suppression).

Statistical Analyses

Continuous variables are summarized as means with standard deviations and compared using one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Categorical variables are described using counts and percentages and compared using the chi-square test. Simple correlation analyses were performed with daily LT4 dose as the dependent variable and body weight, age, sex, height, and TSH as independent variables. Subsequently, multiple linear regression analyses identified independent predictors of LT4 dose requirements. The initial model included all candidate variables (actual body weight, age, sex, height, and TSH), and stepwise selection was applied to retain only statistically significant predictors. Moreover, separate regression models were fitted within each TSH subgroup (0–0.1, 0.1–0.5, and 0.5–2.0 mIU/L) to generate subgroup-specific dose prediction formulas, while a unified model ("Formula 1") was derived for the overall cohort ($0 \leq \text{TSH} < 2.0$ mIU/L). Sex was coded as a binary variable (0=female, 1=male). A two-sided p -value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (version 22; IBM Corporation, Armonk, NY, USA).

Results

Baseline Characteristics

Of the 444 datasets analyzed, 87% were female, and the mean age was 53 years (range, 22–82). The overall mean TSH was 0.38 mIU/L. Table 1 presents the baseline characteristics across TSH levels. Except for the LT4 dose, there were no significant differences among baseline anthropometric and demographic

Table 1. Baseline characteristics of patients with thyroid cancer according to TSH levels

	Total (n=444)	TSH levels (mIU/L)			p value
		0≤TSH<0.1 (n=233)	0.1≤TSH<0.5 (n=153)	0.5≤TSH<2.0 (n=58)	
Age (years)	53.3±11.6	53.1±11.8	53.9±11.1	52.7±12.0	0.747
Female	386 (86.9)	202 (86.7)	133 (86.9)	51 (87.9)	0.969
Weight (kg)	60.5±10.1	60.2±10.0	60.3±10.0	61.9±10.9	0.549
Body mass index (kg/m ²)	23.5±3.2	23.3±3.1	23.6±3.1	23.7±3.8	0.778
Hume lean body mass (kg)	42.0±5.9	42.0±5.9	41.6±5.8	42.9±5.8	0.134
DuBois body surface area (m ²)	1.6±0.1	1.6±0.1	1.6±0.1	1.7±0.2	0.298
Levothyroxine dose (μg)	126.0±28.3	132.0±28.7	121.7±25.5	113.8±28.4	0.000

Data are presented as mean±SD or number (%).

TSH: thyroid-stimulating hormone

characteristics. The mean daily LT4 dose in the cohort was 126 μg (approximately 1.9 μg/kg), with wide inter-individual variability (standard deviation, 38.3 μg).

Association between Clinical Parameters and LT4 Dose

In univariate analyses, the actual daily LT4 dose significantly correlated with several anthropometric and clinical parameters (Table 2). The strongest positive correlations were observed with BSA, LBM, and body weight ($r=0.481$, 0.477 , and 0.462 , respectively; all $p<0.001$), indicating that larger body size and higher lean mass were major determinants of LT4 requirement. Moderate correlations were found with height ($r=0.384$) and body mass index (BMI) ($r=0.305$). Contrastingly, the LT4 dose demonstrated inverse correlations with age ($r=-0.262$, $p<0.001$), sex ($r=-0.349$, $p<0.001$), and serum TSH level ($r=-0.154$, $p<0.001$), indicating that older and female patients generally required lower doses for equivalent TSH suppression.

Multivariable Dose Prediction Formula

Using 444 datasets with TSH<2.0 mIU/L, we developed multivariable linear regression models to predict daily LT4 dose. Based on significant univariate correlations with LT4 dose, five variables, namely body weight, height, age, sex, and TSH, were included as predictors. The overall model explained approximately 33% of the variance in LT4 dose ($R^2=0.329$) (Formula 1) (Table 3). Sex was coded as 0=female and 1=male, indicating that men required approximately 10 μg

Table 2. Correlation between daily levothyroxine dose and clinical parameters (n=444)

Parameter	r	p value
Body weight (kg)	0.462	<0.001
Age (years)	-0.262	<0.001
Sex (0=female, 1=male)	-0.349	<0.001
Height (cm)	0.384	<0.001
TSH (mIU/L)	-0.154	<0.001
Body mass index (kg/m ²)	0.305	<0.001
Lean body mass (kg, Hume)	0.477	<0.001
Body surface area (m ² , DuBois)	0.481	<0.001

TSH:thyroid stimulating hormone

r: Pearson correlation coefficient, p values were derived from Pearson's correlation analyses between daily levothyroxine dose and each clinical parameter.

higher LT4 doses on average than did females. LT4 dose decreased with increasing age (-0.62 μg/day per year) and increased with greater body weight and height (Formula 1) (Table 3). To explore potential differences across TSH ranges, separate regression models were constructed for each subgroup (Formulas 2–4) (Table 3).

Across all models, body weight and height positively associated with LT4 dose; age and female sex inversely associated. In the deeply suppressed group (TSH<0.1), the TSH coefficient was negative, indicating greater LT4 requirements under stronger suppression. Conversely, the TSH coefficient was small or positive in higher TSH ranges, suggesting limited biochemical influence on dose determination near the low-normal range. The predictive performance ($R^2=0.29-0.39$) was comparable among all models.

Table 3. Predictive equations for daily levothyroxine dose in different TSH subgroups

TSH (mIU/L)	Formula No.	LT4 dose prediction formula (ug/day)
0≤TSH<2.0	1	LT4 dose=105.304−13.547×TSH+1.112×BWt+0.064×Ht−10.712×Sex−0.623×Age (R ² =0.329, p<0.001)
0≤TSH<0.1	2	LT4 dose=157.567−362.531×TSH+1.014×BWt−0.054×Ht−16.056×Sex−0.543×Age (R ² =0.291, p<0.001)
0.1≤TSH<0.5	3	LT4 dose=81.856+8.528×TSH+1.108×BWt+0.157×Ht−6.754×Sex−0.766×Age (R ² =0.387, p<0.001)
0.5≤TSH<2.0	4	LT4 dose=31.439+3.494×TSH+1.237×BWt+0.220×Ht−4.533×Sex−0.482×Age (R ² =0.365, p<0.001)

LT4: levothyroxine, TSH: thyroid stimulating hormone

BWt: body weight (kg), Ht: height (cm), Sex coded as 0=female, 1=male, Age in years.

Body weight, height, age, sex, and TSH were included as predictors in multivariable linear regression analyses and all were statistically significant (p<0.001). R² values represent the proportion of variance in LT4 dose explained by each model.

Comparison with ATA Weight-Based Dosing

The predictive performance of the newly developed multivariable formula (Formula 1) was compared with the conventional ATA weight-based method. In the overall cohort, Formula 1 demonstrated a higher correlation with the actual LT4 dose than did the ATA recommendation¹⁾ (r=0.574 vs. 0.462) (Supplementary Table 1). Stratified analyses demonstrated that, across TSH ranges, Formula 1 generally exhibited numerically higher correlations than the ATA method, with r=0.528 and 0.448 for 0≤TSH<0.1 mIU/L and 0.610 and 0.525 for 0.1≤TSH<0.5 mIU/L for Formula 1 and the ATA method, respectively, whereas in the 0.5≤TSH<2.0 mIU/L subgroup the ATA method was numerically higher (r=0.533 vs. 0.550) (Supplementary Table 2). All correlations were statistically significant (p<0.001), confirming that both models captured meaningful dose-response relationships.

Accuracy assessed by the mean absolute error likewise tended to favor Formula 1. The mean±standard deviation (SD) absolute difference between predicted and actual doses was numerically lower with Formula 1 (17.7±15.0 μg/day) than with the ATA upper-limit dose (23.6±19.9 μg/day) and the ATA lower-limit dose (31.3±22.7 μg/day) (Supplementary Table 3).

Discussion

In this single-center retrospective study of patients with DTC who underwent TT and radioactive iodine therapy, we developed a multivariable regression model to predict individualized LT4 requirements according to TSH suppression targets. The predictive model, which incorporated anthropometric and clinical variables associated with LT4 requirements, had clinical utility in that it reduced prediction error by approximately 25%–30% compared with the conventional ATA weight-based method. Additionally, compared with the conventional ATA weight-based method, it demonstrated a numerically higher correlation with actual LT4 dose and a tendency toward lower prediction error across most TSH suppression ranges. In high-risk patients requiring intensive suppression (TSH<0.5 mIU/L), the model tended to provide more precise dose estimates, potentially reducing the risks of both over- and under-suppression.

TSH suppression with LT4 supraphysiological doses is employed in patients with DTC to decrease recurrence risk or slow disease progression^{11,12)} moreover, major clinical guidelines recommend this approach.^{1–5)} LT4 overtreatment is associated with increased risks to the cardiovascular and skeletal systems, including atrial fibrillation and osteoporosis.^{13–15)} Conversely, in high-risk patients who have undergone radioactive iodine therapy and require TSH sup-

pression, undertreatment may be closely linked to a higher thyroid cancer recurrence.^{12,13)} Thus, careful thyroid hormone replacement adjustment remains an important aspect of post-thyroidectomy management.

Previous studies have proposed various empirical or formula-based approaches to estimate LT4 requirements after total thyroidectomy; nonetheless, none have fully accounted for interindividual variability. Jin et al.¹⁶⁾ and Ojomo et al.¹⁷⁾ suggested fixed initial doses of approximately 1.5 $\mu\text{g/kg}$ after TT and 1.3 $\mu\text{g/kg}$ after lobectomy, or BMI-adjusted corrections to improve accuracy. Zaborek et al.¹⁸⁾ later developed a BMI-based algorithm that enhanced initial prescription precision, while Papoian et al.¹⁹⁾ demonstrated that conventional weight-based dosing tends to overdose patients with obesity and recommended formulas incorporating both weight and BMI. More recently, Dawn Paul et al.²⁰⁾ demonstrated that LBM is a better predictor of LT4 requirements than total body weight. In contrast, Al-Dhahri et al.²¹⁾ found that BSA is superior and proposed a BSA-based dosing model. Although these studies established important frameworks, none provided a unified, clinically practical equation applicable across different TSH suppression targets, thereby limiting their relevance for DTC, where individualized hormone suppression is essential.

The regression-based model developed here was designed to address this gap by integrating key anthropometric and biochemical variables, namely body weight, height, age, sex, and serum TSH, to estimate patient-specific LT4 requirements more accurately. By quantifying the relative contribution of each factor, the model demonstrates clinical usefulness, reducing prediction error by approximately 25%–30% compared with the weight-based approach. The remaining unexplained variance may be attributable to unmeasured factors, including intestinal absorption, treatment adherence, formulation variability, radioactive iodine dose, and residual thyroid tissue. These factors should be acknowledged as limitations, and future studies incorporating them are warranted to enhance the model's explanatory power.

The key strengths of this study include the development of a multivariable regression-based LT4 dosing

model using real-world clinical data from patients with DTC who underwent TT and radioactive iodine therapy. By integrating routinely available parameters such as thyroid function indices, body weight, height, age, sex, and TSH, the model reflects physiologic variability and is associated with more precise and personalized LT4 dose estimation than conventional weight-based methods. Finally, the model was derived from a large tertiary care database with systematically collected clinical and laboratory data under standardized treatment protocols, ensuring data integrity and supporting its use as a practical tool for precision LT4 dosing in thyroid cancer management.

This study has some limitations. First, it was a retrospective analysis conducted among patients treated at tertiary care centers within a single country, potentially limiting the generalizability of the findings. All participants were Korean, and body size distribution differences—including the higher average BMI observed in Western populations—may cause regression coefficient variations. Moreover, even within Korean cohorts, prediction accuracy may decline in patients with obesity ($\text{BMI} > 30 \text{ kg/m}^2$) or older adults (> 70 years), in whom the contribution of the weight coefficient may be overestimated. To improve predictive precision in these subgroups, future extended models incorporating interaction terms based on BMI or LBM should be developed. Second, although the model demonstrated good internal validity, external validation using an independent cohort was not performed, and future multicenter studies involving ethnically diverse populations are warranted to validate the reproducibility and generalizability of the proposed formula. Third, while the sample size was adequate for a single-center analysis, it does not represent a large-scale population-based study. In real-world practice, factors such as medication adherence, comorbidities, and formulation variability may influence LT4 requirements, and thus model performance may differ across clinical settings. Lastly, the clinical utility of the formula has not yet been prospectively evaluated. Further multicenter, prospective studies are needed to determine whether LT4 dosing guided by this model can improve thyroid cancer follow-up therapy safety and efficiency.

compared with conventional empiric titration.

The proposed dosing formula represents a step toward model-informed precision dosing in thyroid-cancer follow-up care. By enabling patients to reach their target TSH levels more rapidly and consistently, this approach may enhance both the safety and efficiency of post-thyroidectomy management. Specifically, patients requiring TSH suppression could achieve target TSH levels more promptly, thereby minimizing suboptimally elevated TSH exposure that may promote tumor growth while avoiding overtreatment and unnecessary suppression. Such optimization can reduce dose adjustment frequency, improving treatment satisfaction, quality of life, and healthcare efficiency. In the future, integrating this formula into electronic medical record systems or clinical calculator tools could support endocrinologists in making evidence-based decisions when prescribing the initial LT4 dose after thyroidectomy.

In conclusion, in this single-center retrospective study, we developed a multivariable regression-based formula to predict the optimal daily LT4 dose required to achieve individualized TSH suppression targets in patients with DTC who underwent TT and radioactive iodine therapy. Incorporating body weight, height, age, sex, and TSH, the new formula exhibited a numerical trend toward higher predictive accuracy and lower mean absolute error than the ATA weight-based method, indicating improved predictive performance, particularly in patients requiring moderate to strong TSH suppression (<0.5 mIU/L). These findings indicate that considering demographic and biochemical factors beyond body weight allows more precise LT4 dose estimation, potentially reducing both over- and under-suppression. Further large-scale, multicenter studies are warranted to validate its generalizability and clinical applicability.

Author Contributions

Conception or design: Y.J.P. Acquisition, analysis, or interpretation of data: S.M.S, K.Y.J, H.S.C, J.H.M, S.W.C, K.H.Y, Y.J.P. Drafting the work or revising: S.M.S, K.Y.J, H.S.C, J.H.M, S.W.C, K.H.Y, Y.J.P. Final

approval of the manuscript: S.M.S, K.Y.J, H.S.C, J.H.M, S.W.C, K.H.Y, Y.J.P.

Ethics Approval and Consent to Participate

This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved and informed consent was waived by the Institutional Review Board of Seoul National University Hospital (IRB number: 1510-092-712).

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Correlation between actual levothyroxine dose and predicted dose by method (n=444)

Methods	r	p value
ATA (2015)	0.462	<0.001
Formula 1	0.574	<0.001

ATA: American Thyroid Association

r: Pearson correlation coefficient, p values were obtained from Pearson correlation analyses between the actual daily levothyroxine dose and the predicted dose.

Supplementary Table 2. Correlation between actual levothyroxine dose and predicted dose by TSH range (n=444)

TSH (mIU/L)	ATA (r)	p value	Formula 1 (r)	p value
0≤TSH<0.1 (n=233)	0.448	<0.001	0.528	<0.001
0.1≤TSH<0.5 (n=153)	0.525	<0.001	0.61	<0.001
0.5≤TSH<2.0 (n=58)	0.55	<0.001	0.533	<0.001

ATA: American Thyroid Association, TSH: thyroid-stimulating hormone

r: Pearson correlation coefficient, p values were obtained from Pearson's correlation analyses between the actual daily levothyroxine dose and the predicted dose in each TSH subgroups.

Supplementary Table 3. Mean absolute error between actual levothyroxine dose and predicted dose (n=444)

Methods	Mean±SD (min, max) (μg/day)
ATA low limit	31.3±22.7 (0.20, 134.8)
ATA high limit	23.6±19.9 (0.6, 120.6)
Formula 1	17.7±15.0 (0.11, 100.4)

SD: standard deviation

Mean absolute error was calculated as the absolute difference between predicted and actual daily LT4 doses and is presented as mean±SD and range. ATA low-limit and high-limit estimates refer to weight-based doses of 2.1 μg/kg and 2.7 μg/kg, respectively, according to the 2015 American Thyroid Association (ATA) guideline.