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HEAD AND NECK

Optimal levothyroxine dose in post-total thyroidectomy patients: a prediction model for initial dose titration

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Abstract

Purpose As the lack of consensus in the initial levothyroxine (LT4) dose titration following total thyroidectomy exists, the aim of this study was to identify and quantify predictive factors for LT4 dose replacement.

Methods A retrospective analysis of a prospectively gathered data of 234 patients who underwent total-thyroidectomy at two institutions between November 9, 2009 and January 1, 2016 was conducted. Outcome variable was the clinically observed optimal LT4 dose. Linear and polynomial regression methods were used for prediction. Continuous variables were tested for mean differences using Student's *t*-test and association using Pearson's correlation.

Results We identified Body Surface Area (BSA) as the most significant predictor. We propose a model that titrates LT4 dose based on BSA (1.4 µg /kg/day for BSA > 1.79 m^2 vs. 1.7 µg /kg/day for BSA ≤ 1.79 m^2; $P = 0.00$). Men required higher doses than women and no differences were noted based on DM status or pathological diagnosis.

Conclusions Our analysis shows BSA as an independent predictor of LT4 dose post total thyroidectomy. Despite the possibility of generating different equations for predicting LT4 post total-thyroidectomy, finding a practical and clinically relevant prediction model is yet of limited efficiency.

Keywords Thyroxine · Levothyroxine · Thyroid hormones · Thyroidectomy · Thyroid-stimulating hormone · Thyroid

Introduction

Levothyroxine (LT4) dose replacement has long been the mainstay monotherapy for patients with hypothyroidism and post-total thyroidectomy patients. Although a combination of triiodothyronine (T3) and thyroxine (T4) has been historically proposed in the literature, LT4 still holds a strong and reproducible basis for thyroid hormones replacement with a margin of safety that renders it a superior choice. In addition, and as LT4 is well-studied and vastly prescribed, the challenge in prescribing the proper dose for each patient after total thyroidectomy surgeries is based on patients' individual and general characteristics. Many studies have examined and/or proposed a dosing strategy for LT4 replacement, providing a broad, non-specific ground that merely differs based on different presumed variables such as age, gender, body weight, body surface area (BSA), lean body mass (LBM), body mass index (BMI), drug-drug interactions, absorption, bioavailability, and co-morbidities. Moreover, the nature of the disease may dictate a different treatment strategy (i.e. benign vs. malignant). The substitution dose traditionally follows a general arbitrary approach or uses 1.6 µg/kg/day [1] formula that was mainly designed for hypothyroidism cases. Consequently, the resultant dose may serve as the ideal dose or proves to be over- or under-compensating thyroid function after future assays. The drawback of both approaches, however, can simply be tied to the number of unnecessary future visits for patients and the probability of over- or under-substitution, with the risk that it holds especially in elderly patients. Given that context, providing a

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prediction formula for calculating the proper initial LT4 dose may help decrease the level of uncertainty in LT4 dose replacement and prove to be economically valuable. The aim of this study was to identify and quantify factors that would predict LT4 dose following thyroidectomy. As the lack of consensus in the initial optimal LT4 dose in patients following total thyroidectomy exists, the necessity stands for finding a prediction model for LT4 dose based on primary predictors in the clinical practice.

Methods

We retrospectively reviewed a prospectively gathered data of a cohort of patients who underwent total thyroidectomy between November 9, 2009 and January 1, 2016 at two tertiary academic hospitals in Riyadh, Saudi Arabia. The primary endpoint of the study was patients reaching the optimal dose of LT4 that maintained thyroid stimulating hormone (TSH) levels between (0.26–4.4 mIU/L). LT4 dose was considered optimal after 6 months of therapy monitoring that is receiving the measurements of two normal TSH levels with 3 months apart. The determination of patients' demographic characteristics, past medical history, medications, height, weight, and laboratory results was based on electronic medical records and office-based interviews. BMI was calculated using: [actual body weight (kg)/height^2 (m)], and body surface area (BSA) was calculated using Mosteller's formula [2]. Both were treated as continuous variables in regression models. In addition, BSA was transformed into a dichotomous variable defined by the sample median of 1.79 m^2 for two group comparisons. The study was conducted in accordance with the Helsinki Declaration, as revised in 2013. It was also approved by the Institutional Review Board of King Fahad Medical City (KFMC-IRB #18-245). Patients who were compliant with treatment were included in the study irrespective of age or gender. Patients who underwent total thyroidectomy due to malignant pathology and required suppressive doses of LT4 were excluded.

Statistical analysis

Statistical analysis was performed using R version 3.3.1 (R Core Team (2016). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). Continuous variables were tested for mean differences using Student's *t*-test and association using Pearson's correlation. To predict a model for the optimal daily LT4 dose, multiple linear and polynomial regression methods were utilized for the combination of categorical and continuous predictors. Values of ($P < 0.05$) were considered significant. Descriptive analysis was interpreted using mean ± SD or counts with percentages.

Table 1 Basic Characteristics of the 234 subjects who matched the inclusion criteria

Characteristic	*N* (%) or mean ± (SD)
Female sex	203 (86.75)
Age (years)	41.36 ± (12.36)
BMI (kg/m^2)	30.98 ± (6.9)
Underweight	4 (1.7)
Normal	40 (17.1)
Overweight	65 (27.8)
Obese	125 (53.42)
Weight (kg)	77.3 ± (17.4)
Height (cm)	158.12 ± (8.47)
BSA (m^2)	1.8 ± (0.22)
History of DM	43 (18.38)
Pathology (benign)	133 (56.84)
Optimal LT4 dose (µg/day)	
Overall	117.24 ± (26.2)
Male	132.66 ± (26.9)
Female	114.89 ± (25.34)

Results

Of the 902 subjects initially enrolled, 234 matched our inclusion criteria. Patients were routinely started on empirical 100 µg of LT4 postoperatively (Day 01). The majority of our subjects were women. Most of the patients had benign thyroid pathology and were not diabetics. Over half of our sample ($n = 125$, 53.42%) were obese (BMI ≥ 30) followed by overweight subjects ($n = 65$, 27.78%) (Table 1). The overall mean dose per body weight required to achieve a normal thyroid function was 1.5 ± 0.5 µg/kg (range 0.93–6.55). Upon further stratification, male patients had a narrower range than female patients (range 0.93 – 2.7). However, when calculated per BSA, the mean dose was 64.5 µg/m^2. The minimum follow-up period was 24 months.

LT4 dose was tested for the mean differences in gender, diabetes mellitus (DM) status, pathological diagnosis (benign vs. malignant), and BSA independently. Men required higher doses than women ($P = 0.0004$) and patients who had larger BSA (> 1.79 m^2) required higher doses than those with lower BSA ($P = 0.00$) (Fig. 1). The optimal LT4 dose was not different when compared based on DM status ($P = 0.32$) or pathological diagnosis ($P = 0.25$) (Table 2). Optimal LT4 dose was weakly but

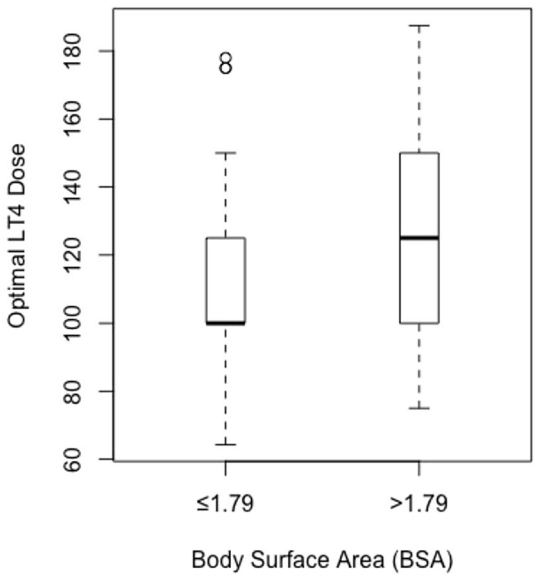

Fig. 1 Final daily LT4 dose by BSA in the 234 patients enrolled in the study. Median (horizontal line), 25th and 75th percentiles (box), and range (whiskers) of optimal LT4 dose by BSA of the subjects enrolled stratified by the median

Table 2 Mean differences in LT4 dose based on different variables using Student's *t* test ($n = 234$)

Characteristic	Mean difference	95% CI	*t* value	*P* value
Gender	17.76	[8.05, 27.47]	3.61	0.0004*
DM	− 4.44	[− 13.15, 4.27]	− 1.00	0.32
Pathology[a]	− 3.9	[− 10.7, 2.89]	− 4.95	0.25
BSA[b]	− 16.16	[− 22.59, − 9.73]	5.24	< 0.0001*

CI confidence interval

[a]Pathology, benign vs. malignant

[b]BSA > 1.79 vs. ≤ 1.79 m^2

positively correlated with BMI ($r = 0.236$, $P = 0.0003$), BSA ($r = 0.33$, $P < 0.0001$), and weight ($r = 0.32$, $P < 0.0001$) and inversely correlated with age ($r = -0.132$, $P = 0.04$).

Multi-predictor regression models

To predict the continuous numerical outcome that is, optimal LT4 dose, we initially considered 2 models to enter the selection criteria for the best fit model based on 4 and 6 predictors. The first model's independent predictors were age and BMI as continuous variables, and gender and DM as nominal variables. We added two more predictors to the second model which were BSA and actual body weight.

The highest R^2 values that were obtained from the multiple linear regression models of the 4 and 6 predictors were 0.194 and 0.21, respectively. Moreover, and by using polynomial regression for 14 predictors (Gender, DM, Age, Age^2, Age^3, BMI, BMI^2, BMI^3, Weight, $Weight^2$, $Weight^3$, BSA, BSA^2, BSA^3), the maximum R^2 was 0.24.

The presence of small R^2 values generally indicates that the initial generated models did not fully explain the variability in the outcome, creating a notable difference between the observed and predicted values, which would more or less hinder the clinical application of such models. We attributed that to the presence of many repetitive values (i.e. 100 µg) in the observed outcome, which affected the prediction model and in turn created a low R^2.

As all the above methods resulted in relatively small R^2, and using all subset regression method, an updated sample of 63 observations was found to be the most useful for modelling. The best linear model was the 7-predictor linear regression model of height (m), weight (kg), BMI, age, gender, DM, and BSA with an R^2 that was equal to 0.47.

For the polynomial model, the best model with the largest R^2 value was an initial polynomial model with 22 predictors with an R^2 of 0.53. Considering that too many predictors were introduced to the model, another polynomial model with only 12 predictors was derived, but with an almost equal R^2 value that was equal to 0.50 ($P = 0.00015$).

The resultant equation of the cubic polynomial multi-predictor model was:

$$\begin{aligned}\text{Predicted LT4 Dose} = {} & -533.5 + (760.1 \times \text{Height}) \\ & + (32 \times \text{BMI}) - (0.445 \times \text{Age}) \\ & - (680.2 \times \text{BSA}) - (51.36 \times \text{Height}^2) \\ & + (0.0919 \times \text{Weight}^2) - (0.00039 \times \text{Weight}^3) \\ & - (0.676 \times \text{BMI}^2) + (0.00496 \times \text{BMI}^3) \\ & - (1.203 \times \text{Gender}^3) + (33.99 \times \text{DM}^2) \\ & - (14.63 \times \text{DM}^3)\end{aligned}$$

The 7-predictor linear model equation was:

$$\begin{aligned}\text{Predicted LT4 Dose} = {} & 148.569 - (63.4 \times \text{Height}) \\ & - (0.618 \times \text{Weight}) - (0.385 \times \text{BMI}) \\ & - (0.48 \times \text{Age}) - (25.41 \times \text{Gender}) \\ & + (1.13 \times \text{DM}) + (118 \times \text{BSA})\end{aligned}$$

Based on the analytical observations from our cohort, bivariate analysis between the mean values of optimal LT4 dose (expressed in µg/kg/day) and BSA was performed showing a statistical significance ($P = 0.00$). A proposed algorithm for this model is shown in (Fig. 2).

We tested the resultant predicted values from the three above-mentioned models on the existing observed optimal LT4 dose, in addition to the weight-based (1.6 µg/kg) model for comparison purposes and assessment of models' performance. Given that 25 µg is the smallest incremental dose in LT4 drug forms, and for consistency and practicality, we

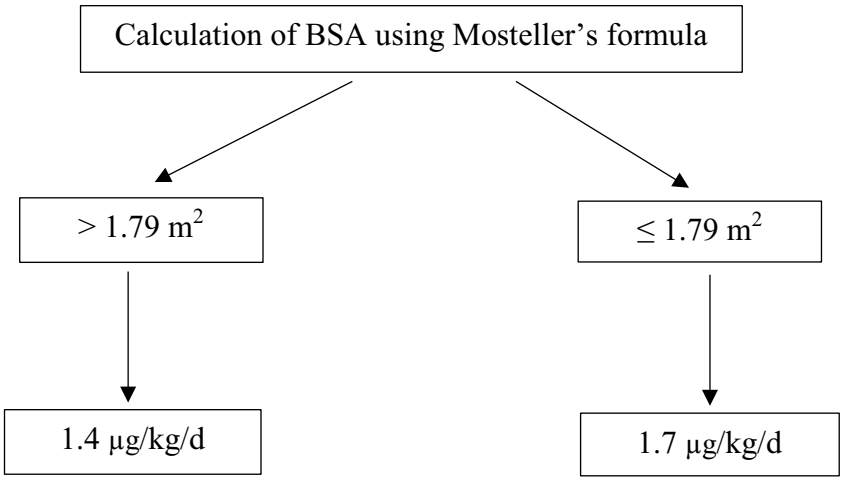

Fig. 2 Proposed algorithm of LT4 dose titration based on BSA from a cohort of 234 subjects

Table 3 Models performance compared to the final LT4 dose achieved in the 234 subjects

LT4 dose estimation	Model performance, *n* (%)			
	Polynomial	Linear	BSA (overall)	Weight-based (1.6 µg /kg/ day)
Correct estimation	154 (65.8)	120 (51.3)	151 (64.5)	137 (58.5)
Underestimation	38 (16.24)	11 (4.7)	41 (17.52)	36 (15.4)
Overestimation	42 (17.95)	103 (44)	42 (17.95)	61 (26)

Table 4 Detailed performance of BSA algorithm in the 234 subjects

LT4 dose estimation	Model performance, *n* (%)		
	BSA		
	Overall	> 1.79 m^2 1.4 µg/kg/day	≤ 1.79 m^2 1.7 µg/kg/day
Correct estimation	151 (64.5)	72 (61.5)	79 (67.5)
Underestimation	41 (17.52)	20 (17)	21 (18)
Overestimation	42 (17.95)	25 (21)	17 (14.5)

considered any prediction values (from all models including the weight-based model) that fell within (+/–25 µg) of the predicted dose as a correct estimation of the clinical optimal dose. Consequently, the polynomial model had the best performance in our sample (65.8%) followed by the BSA algorithm (64.5%), then the weight-based model (58.5%), and finally the linear model (51.3%) (Tables 3, 4).

Discussion

Prediction models that aim at finding an accurate initial dose of LT4 post-total thyroidectomy have been published in the literature. With their diversity in introducing different predictors to account for in their formulas, it is easy to deduce that there is a need for a universal formula that is characteristically simple and at the same time highly accurate for dose adjustment. The literature is abundant in identifying dose adjustments in patients with hypothyroidism, with the conventional dose of 1.6 µg/kg/day being the average LT4 replacement dose required to normalize elevated TSH values [1]. Yet still, patients who undergo total thyroidectomy surgeries are certainly in dire need for replacement, but with formulas that identify with the ensuing deficiency or the lack thereof of thyroid hormones. Moreover, and as is the case with those who have hypothyroidism, it is acknowledged that such adjustments may be demographically and anthropometrically influenced. Using multiple regression methods, we were able to generate two formulas: one that is linear with 7 predictors and the second, which was more fitting, is polynomial with 12 predictors. Our interpretation relied mainly on the latter model as it explained 50% of the variability in the model; a percentage that parallels other fitting models in the literature [3].

Our results put BSA at the centre of LT4 dose modelling, as opposed to other studies that used BMI [4–6] and actual body weight [3, 7–10] as primary predictors of LT4 dose adjustment. A finding that supports Sukumar and colleagues [11] in which they found that BSA was more correlated than body weight in their analysis.

BSA is thought to fare better in distinguishing body fat from muscle mass, as muscle mass takes up less surface area

than fat, providing a better estimate of obesity [12], unlike BMI that lacks that distinction [13]. Furthermore, BSA was found to be positively associated with thyroid nodules [14, 15], providing what seems to be an established association between thyroid diseases and BSA. Consequently, we indicate that it is favourable to consider BSA in LT4 dose calculation as is the case with chemotherapy dose titrations [16].

In conjunction with that, we found that men would require higher doses than women. However, that difference seems to be of a lesser important effect as the mean difference was around 17 µg (Table 2). The similarity in LT4 dose in the benign and malignant groups reaffirms that our sample was homogenous and that those who had malignant pathology were low risk patients who did not require dose suppression.

Baehr et al. used actual body weight as the main predictor of LT4 replacement and factored in the status of malignancy, gender, menopause, and TSH goals [9]. Our sample was different in that we excluded patients who required suppressive doses due to malignancy and accordingly, we achieved a homogenous group that shared the same treatment goal. Interestingly, and among the many models they generated, Jin et al. came up with two prediction models that distinguished LT4 dosing of total- from hemi-thyroidectomy patients (1.5 µg/kg and 1.3 µg/kg respectively) [3]. Although interesting in that a minute difference between the two models was demonstrated, we never felt that such distinction would matter as thyroid lobectomy patients are fundamentally subject to physiological compensation that plays a role in dose replacement.

The fact that the most fitting model was polynomial in our study turns our attention to the imperfect nature of prediction models with LT4 titration. Hence, this may be attributed to one of the two reasons. Firstly, that the titration of Levothyroxine is inherently too complex with the coexistence of different factors (e.g., physiological, pharmacological, demographic, and anthropometric) that the use of empirical dosage seems a pragmatic first-hand choice, or secondly; the identification of the right set of predictors has not been established yet. Moreover, the challenge of proper dose initiation has been steadily addressed in the literature.

The collective scholarly work shows tangible efforts towards trials of dose estimation. Although few in number, they provide ample insight into LT4 dosing using various variables and cofactors. While insightful, the discordance between statistical results and models performance in the clinical practice is apparent and raises many questions at the heart of methodology: Why is it that the performance of these models has mediocre clinical application despite the inclusion of logical and common predictors of LT4 in the practice? In order for us to overcome the statistical constraints and come up with high performance models, we must ask the right questions before moving into more sophisticated methods. Another viewpoint is the schematic statistical methods employed in predicting the optimal LT4 dose; statistical modelling no matter how robust or novel, will still have limitations if the data itself is statistically flawed. In conducting this study, we realize the need to re-examine our conceptual understanding of LT4 dosing. We argue that the nuanced LT4 titration is principally a conditional outcome with different trajectories, which may in turn reflect a reductionist and too simplistic approach in modelling that masks a deeper analysis. We are also inclined to stress on interindividual variability and its weight in changing the model. This assessment is one with the aim of aiding our quest to find a reproducible model.

Compliance with ethical standards

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (KFMC-IRB approval #18–245) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Waived.

References

1. Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH (1987) Replacement dose, metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism. Role of triiodothyronine in pituitary feedback in humans. N Engl J Med 316(13):764-770. doi:10.1056/nejm198703263161302
2. Mosteller RD (1987) Simplified calculation of body-surface area. N Engl J Med 317(17):1098. https://doi.org/10.1056/nejm198710223171717
3. Jin J, Allemang MT, McHenry CR (2013) Levothyroxine replacement dosage determination after thyroidectomy. Am J Surg 205(3):360–364. https://doi.org/10.1016/j.amjsurg.2012.10.015
4. Elfenbein DM, Schaefer S, Shumway C, Chen H, Sippel RS, Schneider DF (2016) Prospective Intervention of a Novel Levothyroxine Dosing Protocol Based on Body Mass Index after Thyroidectomy. J Am Coll Surg 222(1):83–88. https://doi.org/10.1016/j.jamcollsurg.2015.10.005
5. Ojomo KA, Schneider DF, Reiher AE, Lai N, Schaefer S, Chen H, Sippel RS (2013) Using Body Mass Index to Predict Optimal Thyroid Dosing after Thyroidectomy. J Am Coll Surg 216(3):454–460. https://doi.org/10.1016/j.jamcollsurg.2012.12.002
6. Di Donna V, Santoro MG, de Waure C, Ricciato MP, Paragliola RM, Pontecorvi A, Corsello SM (2014) A new strategy to estimate levothyroxine requirement after total thyroidectomy for benign thyroid disease. Thyroid 24(12):1759–1764. https://doi.org/10.1089/thy.2014.0111
7. Olubowale O, Chadwick DR (2006) Optimization of thyroxine replacement therapy after total or near-total thyroidectomy for benign thyroid disease. Br J Surg 93(1):57–60. https://doi.org/10.1002/bjs.5157

8. Mistry D, Atkin S, Atkinson H, Gunasekaran S, Sylvester D, Rigby AS, England RJ (2011) Predicting thyroxine requirements following total thyroidectomy. Clin endocrinol (Oxf) 74(3):384–387. https://doi.org/10.1111/j.1365-2265.2010.03940.x
9. Baehr KM, Lyden E, Treude K, Erickson J, Goldner W (2012) Levothyroxine dose following thyroidectomy is affected by more than just body weight. Laryngoscope 122(4):834–838. https://doi.org/10.1002/lary.23186
10. Glymph K, Gosmanov AR (2016) Levothyroxine replacement in obese hypothyroid females after total thyroidectomy. Endocr Pract 22(1):22–29. https://doi.org/10.4158/ep15836.or
11. Sukumar R, Agarwal A, Gupta S, Mishra A, Agarwal G, Verma AK, Mishra SK (2010) Prediction of LT4 replacement dose to achieve euthyroidism in subjects undergoing total thyroidectomy for benign thyroid disorders. World J Surg 34(3):527–531. https://doi.org/10.1007/s00268-009-0345-3
12. Roy SK, Zeb I, Kadakia J, Li D, Budoff MJ (2012) Body surface area is a predictor of coronary artery calcium, whereas body mass index is not. Coron Artery Dis 23(2):113–117. https://doi.org/10.1097/MCA.0b013e32834f1b72
13. Rothman KJ (2008) BMI-related errors in the measurement of obesity. Int J Obes 32(S3):S56–S59. https://doi.org/10.1038/ijo.2008.87
14. Xu W, Chen Z, Li N, Liu H, Huo L, Huang Y, Jin X, Deng J, Zhu S, Zhang S, Yu Y (2015) Relationship of anthropometric measurements to thyroid nodules in a Chinese population. BMJ Open 5(12):e008452. https://doi.org/10.1136/bmjopen-2015-008452
15. Wang N, Fang H, Fu C, Huang P, Su M, Jiang F, Zhao Q, Chen Y, Jiang Q (2017) Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficient areas: an observational study. BMJ Open 7(10):e016706. https://doi.org/10.1136/bmjopen-2017-016706
16. Punke AP, Waddell J (2019) Creation and evaluation of a cancer chemotherapy order review guide for use at a community hospital. J Oncol Pharm Pract 25(1):25–43. https://doi.org/10.1177/1078155217726162