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A New Strategy to Estimate Levothyroxine Requirement After Total Thyroidectomy for Benign Thyroid Disease

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Background: The current approach for calculating the starting dose of levothyroxine (LT4) after total thyroidectomy is based on the patient's body weight (BW). The aim of the study was to identify the major predictive factors of LT4 requirement and to elaborate a new method to improve the accuracy of the LT4 starting dose after total thyroidectomy.
Methods: The study consists of two parts. The first part consisted of the retrospective identification of 92 adult patients (retrospective cohort) who had undergone a total thyroidectomy for benign disease and who had begun LT4 treatment at a dose of 1.6 μg/kg/day. Adjustments to optimize the LT4 dose were then performed at the post-surgery follow-up on the basis of serum thyrotropin (TSH) levels. The results of this retrospective analysis were used to formulate a nomogram for a proper calculation of the LT4 starting dose that was then used prospectively in the second part of the study on 31 consecutive patients (prospective cohort).
Results: At the first follow-up, 37 (40%) patients from the retrospective cohort were euthyroid. Univariate analysis indicated significant correlations between the optimal dose of LT4 and BW, body mass index (BMI), age, preoperative mean corpuscular volume, and free triiodothyronine (fT3). The optimal dose of LT4, analyzed for BMI and age, showed an inverse relationship with these two parameters, and ranged from 1.4 to 1.8 μg/kg/day. In the prospective cohort, the use of an age- and BMI-related nomogram improved the prediction of the optimal LT4 starting dose, with 68% of patients being euthyroid at the first follow-up compared to 41% of patients reported to have reached euthyroid state using the best strategy proposed in the literature.
Conclusions: This study confirms that BW is not the only variable for predicting LT4 requirement, as it decreases with the increase in age and BMI, probably due to the relative decrease of lean body mass. A new correlation between optimal dose and presurgical levels of fT3 and mean corpuscular volume was observed. We propose an easy and more efficient method of calculating LT4 starting dose after total thyroidectomy for benign disease.

Introduction

The current approach for calculating the starting dose of levothyroxine (LT4) after total thyroidectomy for benign thyroid disease is mainly based on the patient's body weight (BW) (1). In patients who do not present with cardiac symptoms or malabsorption, the most common recommended starting dose of LT4 ranges from 1.6 to 1.7 μg/kg/day (2,3). Reaching the optimal LT4 replacement dose in the shortest time after thyroidectomy is important but also challenging (4). Indeed, in the literature, this time is highly variable, ranging from 2 to 120 weeks, with a median of 3.6 months (5), and only about 30% reach the euthyroid state at the first post-surgery follow-up (4–7).

This is not surprising, since it is known that BW is not the only factor predicting the optimal dose of LT4 (8). Several authors suggested a correlation between LT4 requirement and other factors, such as body mass index (BMI) or body surface (7,9), sex and menopause (8,10–12), age (6,11,12), and the disease causing the hypothyroidism (3). As suggested by some authors, the role of these variables could be explained by the differences in lean body mass (LBM) (5,7,9,11,13). This may not be surprising considering that most metabolic processes, including thyroxine (T4) and triiodothyronine (T3) deiodination, occur within LBM (14,15). However, from a practical point of view, an accurate calculation of LBM requires the use of formulas (16,17) or techniques that are not cost-effective in the clinical setting, such as the dual Energy X-ray absorptiometry (DEXA) (18). Furthermore, drugs (19–21) and diseases (22–24) that may interfere with the absorption of LT4 and the patient's compliance (25) have to be considered in the management of substitution therapy.

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Table 1. Principal Strategies Proposed in the Literature for the Prediction of LT4 Requirement After Total Thyroidectomy for Benign Disease

Author/location	*Algorithm or formula*	
Olubowale *et al.* 2005/Chesterfield, United Kingdom	Weight (kg)	LT4 dose (μg/day)
	< 53	100
	54–86	125
	87–108	150
	> 108	175
Mistry *et al*. 2011/Hull, United Kingdom	LT4 dose (μg/day) = (0.943 × weight) + (–1.165 × age) + 125.8	
	(simplified) LT4 dose (μg/day) = weight – age + 125	
Ojomo *et al*. 2013/Madison, Wisconsin	LT4 dose (μg/kg/day) = (–0.018 × BMI + 2.13) × weight	

LT4, levothyroxine; BMI, body mass index.

In the literature, few methods are described to calculate the LT4 starting dose after thyroidectomy. These are based on BMI, BW, and age (5–7) (Table 1). However, no formula has been shown to have a better predictive value than the classic method based only on the patient's BW.

The aim of this study was to identify major predicting factors for LT4 requirement in order to elaborate a new strategy that could increase the accuracy of the LT4 starting dose after total thyroidectomy for benign disease. A higher performing treatment strategy could allow the optimal LT4 replacement dose after thyroidectomy to be achieved in a shorter period of time with less need for subsequent follow-ups, greater benefits for the patient's health and well-being, and, ultimately, a reduction in healthcare spending. To validate our strategy, we compared it with the different methods currently proposed in the literature.

Methods

The first part of the study was a retrospective review of 92 patients (retrospective cohort) who underwent total thyroidectomy between May 2012 and May 2013 in our Institution. The results obtained by this retrospective analysis were used to formulate a nomogram for the calculation of the LT4 dose. In the second part of the study, this nomogram was prospectively applied in 31 consecutive patients after total thyroidectomy (prospective cohort).

Exclusion criteria for both cohorts were: malignancy at histological examination, presence of symptoms or signs of malabsorption, assumption of drugs interfering with LT4 absorption (such as calcium, iron, or proton pump inhibitor) within four hours following the ingestion of LT4, suspected poor patient compliance, or eating or drinking anything except water within 30 minutes following the intake of LT4, and the switch of generic or brand LT4.

Inclusion criteria for both cohorts were: euthyroid state before thyroidectomy, start of LT4 therapy within three days after thyroidectomy, use of a solid formulation and of the same brand of LT4, determination of serum thyrotropin (TSH) levels at six to eight weeks after thyroidectomy, and subsequent measurements until the achievement of euthyroidism with a serum TSH within the range of 0.4–2.5 μUI/mL.

In the retrospective cohort, we selected only patients who started treatment with LT4 with a starting dose of about 1.6 μg/kg per day approximated to the nearest marketed formulation, that is, the classic method used to estimate the LT4 requirement.

The patients in the prospective cohort began treatment with LT4 with a recommended dose calculated with the nomogram derived from the results of the retrospective cohort. The dose of LT4 calculated using this method was approximated to the nearest marketed formulation. Doses of 75, 87.5, 100, 112.5, 125, 137.5, 150, 175, and 200 μg were prescribed.

Once the proper dose was achieved for each patient from the retrospective cohort, we also calculated the performance of the hypothetical application of the different strategies proposed in the literature (Table 1). Finally, we performed an estimate of healthcare cost savings resulting from the use of the most effective strategy.

Data collection

In both cohorts, the patients' presurgery baseline characteristics were collected for sex, age, menopausal state, BW, height, BMI, thyroid tests (TSH, fT3, fT4, antithyroperoxidase, and antithyroglobulin antibodies), and hematology. Postsurgery data included histological examination, thyroid function tests after six to eight weeks followed by additional thyroid function tests until a euthyroid state was obtained. Thyroid function tests were obtained after every adjustment of the LT4 dose. The LT4 requirement for each patient was calculated as μg/kg of BW per day. The dose at which euthyroidism was obtained was considered as the optimal dose.

Statistical analysis

All data were entered into an electronic database (Microsoft® Excel 2003 for Windows; Microsoft Corporation, Redmond, WA). Descriptive analyses with the use of absolute frequencies and relative percentage for qualitative variables and of mean (M) and standard deviations (*SD*) for quantitative variables were performed. In order to study the possible association between the optimal dose of LT4 and sex, age, height, weight, BMI, hormonal levels at baseline, and the presence of thyroiditis, Mann–Withney and Spearman correlation tests were used respectively for qualitative and quantitative variables. Parameters with a p-value <0.25 in the univariate analysis were included in a multivariate linear model in order to predict the optimal dose of LT4. The backward stepwise method was applied for the identification of the best model, whose effectiveness was analyzed in reference to R^2. The relation between predictive factors and the

optimal dose of LT4 was expressed by a linear equation, which included B coefficients extracted by the model of linear regression. The optimal weight-based LT4 dose was compared in patients based on sex, BMI subgroups (≤ 23, 23–28, and > 28 kg/m^2) and age subgroups (≤ 40, 40–55, and > 55 years). Comparisons of multiple groups were carried out by analysis of variance. The median optimal dose of LT4 in every subgroup based on BMI and age was calculated. Data analyses were performed using SPSS Statistics for Windows® v17.0 (SPSS, Inc., Chicago, IL). *p*-Values <0.05 were considered significant.

Results

Retrospective cohort

A total of 92 patients (72 female; median age 53 years, range 26–77 years) were included in the retrospective analysis. All patients were Caucasian except for two Asian individuals. Indications for thyroidectomy were undetermined follicular lesions at preoperative fine needle cytology (63%), symptomatic multinodular goiter (19%), toxic nodular goiter (12%), Graves' disease (5%), and Plummer's disease (1%). The baseline characteristics of the patients are summarized in Table 2.

At the first follow-up after 51 ± 16 ($M \pm SD$) days, only 37 patients were euthyroid (40%), while 55 required a dose adjustment, 31 (34%) because their dose was insufficient and 24 (26%) because their dose was too much. Sixteen patients (17%) required an adjustment of dose of at least 25 μg/day, and 39 (42%) patients of 12.5 μg/day. Of the 55 patients who were not euthyroid at the first follow-up and required a dose adjustment, 23 were euthyroid after 153 ± 49 days after surgery. Of the remaining 32 patients, nine achieved euthyroidism after 241 ± 50 days after surgery, and 23 required a further change in dose. The mean final optimal LT4 dose was 1.61 ± 0.22 μg/kg/day, and the median of the difference between starting and optimal LT4 dose was 0 μg/day (interquartile range –12.5 to 12.5). There were no statistically significant differences in the optimal LT4 dose in μg/kg between males and females ($M \pm SD$: 1.61 ± 0.23 vs. 1.61 ± 0.22 μg/kg/day respectively).

Table 2. Baseline Characteristics of the Retrospective Cohort

Characteristics	n *(%)*
Sex	
Male	20 (21.7)
Female	72 (78.3)
Menopausal state	
Yes	45 (62.5%)
No	27 (37.5%)
Chronic autoimmune thyroiditis	
No	74 (80.4%)
Yes	18 (19.6%)
	$M \pm SD$
Weight, kg	70.4 ± 14.6
Height, cm	167 ± 9
Age, years	51.3 ± 12.7
BMI, kg/m^2	25.2 ± 4.4
TSH (μUI/mL)	1.0 ± 0.8
Reference range: 0.35–2.80	
fT3 (pg/mL)	3.5 ± 1.0
Reference range: 2.3–4.2	
fT4 (pg/mL)	12.1 ± 3.1
Reference range: 8.5–15.5	
fT4/fT3	3.7 ± 0.8
Starting LT4 dose (μg/day)	112.1 ± 22.4

TSH, thyrotropin; fT3, free triiodothyronine; fT4, free thyroxine.

Univariate analysis indicated that the strongest correlation ($r = 076$; $p < 0.01$) with the optimal LT4 starting dose was with BW. The other correlations were with BMI ($r = 0.59$; $p < 0.01$), height ($r = 0.51$; $p < 0.01$), age ($r = –0.24$; $p = 0.02$), preoperative mean corpuscular volume (MCV; $r = –0.29$; $p < 0.01$), and fT3 ($r = 0.23$; $p = 0.04$). A not statistically significant correlation was found between the optimal LT4 starting dose and presurgical TSH ($p = 0.88$), fT4 ($p = 0.83$) and fT4/fT3 ratio ($p = 0.10$). In the multivariate analysis, the best regression model for the prediction of the optimal LT4 starting dose was based on BW and age, and the resulting formula was: LT4 (μg/day) $= 37.421 - 0.299 \times$ age $+ 1.287 \times$ weight ($R^2 = 0.713$; $p < 0.01$).

Based on these observations from the retrospective cohort, an analysis was performed to determine the optimal daily weight-related LT4 dose (expressed as μg/kg/day) in different subgroups based on BMI (≤ 23, > 23–28, and > 28 kg/m^2) and age (≤ 40, > 40–55, and > 55 years). A univariate analysis revealed that the LT4 dose requirement was inversely related to age ($M \pm SD$: 1.69 ± 0.23 μg/kg/day for age ≤ 40 years, 1.64 ± 0.22 μg/kg/day for age > 40 and ≤ 55 years, and 1.52 ± 0.18 μg/kg/day for age > 55 years) and BMI ($M \pm SD$: 1.69 ± 0.26 μg/kg/day for BMI ≤ 23 kg/m^2, 1.59 ± 0.20 μg/kg/day for BMI > 23 and ≤ 28 kg/m^2, and 1.49 ± 0.11 μg/kg/day for BMI > 28 kg/m^2). The comparison between the mean values of the optimal LT4 dose in μg/kg/day in the different age and BMI subgroups revealed that this relationship was statistically significant for both age ($F = 4.749$; $p = 0.01$) and BMI ($F = 5.919$; $p = 0.004$). Finally, the LT4 dose in μg/kg was calculated in the nine subgroups obtained by the combination of previous age and BMI groups. The optimal dose ranged from 1.8 μg/kg/day in patients with lower BMI and younger age to 1.4 μg/kg/day in patients with higher BMI and older age (Table 3). Based on

Table 3. Median and Interquartile Range of Optimal LT4 Dose in Nine Subgroups of Retrospective Cohort Based on Age and BMI

Age and BMI	*Median (interquartile range) of optimal LT4 dose (μg/kg/day)*	n
≤ 40 years; BMI ≤ 23 kg/m^2	1.82 (1.50–1.87)	11
≤ 40 years; BMI 23–28 kg/m^2	1.71 (1.63–1.78)	6
≤ 40 years; BMI > 28 kg/m^2	1.60 (1.54–1.60)	5
> 40–55 years; BMI ≤ 23 kg/m^2	1.75 (1.68–1.82)	9
> 40–55 years; BMI 23–28 kg/m^2	1.60 (1.54–1.61)	14
> 40–55 years; BMI > 28 kg/m^2	1.49 (1.46–1.52)	7
> 55 years; BMI ≤ 23 kg/m^2	1.60 (1.41–1.68)	13
> 55 years; BMI 23–28 kg/m^2	1.56 (1.41–1.67)	17
> 55 years; BMI > 28 kg/m^2	1.45 (1.41–1.46)	10

Table 4. Nomogram for the Prediction of LT4 pro Kilogram Starting Dose Based on the Findings in the Retrospective Cohort

	BMI		
	≤23	*23–28*	*>28*
Age			
≤40	1.8	1.7	1.6
>40–55	1.7	1.6	1.5
>55	1.6	1.5	1.4

BMI in kg/m^2; age in years; LT4 dose in μg/kg/day.

these findings, a user-friendly nomogram was developed (Table 4).

Prospective cohort

Thirty-one patients were included in the prospective cohort (26 female; median age 49 years, range 20–73 years). All patients were Caucasian except for one Asian and one Hispanic individual. Their baseline characteristics were well matched with the 92 patients of the retrospective cohort (*M* ± *SD*: weight: 66.1 ± 11.9 kg; age: 47.4 ± 12.2 years; BMI: 24.44 ± 5.3 kg/m^2). Using the nomogram presented in Table 4, the mean LT4 starting dose was 107 ± 15.3 μg/day. At the first post-thyroidectomy follow-up (*M* ± *SD*: 50 ± 19 days), 21 (68%) patients were euthyroid (*M* ± *SD*: TSH 1.10 ± 0.98 μUI/mL), while six (20%) were under-dosed (*M* ± *SD*: TSH 6.49 ± 6.33 μUI/mL) and four (12%) were overdosed (*M* ± *SD*: TSH 0.15 ± 0.14 μUI/mL). The median difference between optimal and starting prescribed LT4 dose was 0 (interquartile range: 0 to 0). Of the 10 patients who were not euthyroid at first follow-up (*M* ± *SD*: 45 ± 11 days after thyroidectomy) and required a dose adjustment, eight were euthyroid by 121 ± 23 days after surgery. The remaining two patients required a further change in dose.

In the retrospective cohort, 37% of elderly patients (age >65 years; *M* ± *SD*: TSH 0.75 ± 0.66 μUI/mL) were overtreated at the first post-thyroidectomy follow-up. However, in the prospective cohort, no elderly patients were overtreated at the first post-thyroidectomy follow-up (*M* ± *SD*: TSH 1.83 ± 0.81 μUI/mL).

An analysis of how the different strategies proposed in the literature would have performed in the retrospective cohort showed that the formula proposed by Ojomo *et al*. (7) would have predicted the correct LT4 starting dose in 38 of our patients (41%), over-replacing in 40 (43.5%), and under-replacing in 14 (15.5%). The comparison between the classic method and other methods proposed in the literature is shown in Table 5.

Considering the high number of thyroidectomies in Italy (about 40,000 per year), we estimated a saving resulting from the application of our nomogram of about €600,000 per year (about US$800,000).

Discussion

Several authors have shown the limited efficiency of the classic formula based only on BW for the calculation of LT4 requirement in patients who have undergone thyroidectomy, with only 25–32% of patients being reported as being euthyroid at their first post-surgery laboratory follow-up (5,6). The retrospective portion of our study generally confirms these data. Using the classic method, the starting dose of LT4 was predicted correctly in only 40% of patients. Only Jin *et al*. reported a better efficiency of this weight-based strategy (59%), but the data compare poorly with other studies due to the large proportion of patients with partial thyroidectomy and lobectomy included in the study (12). The reason of the poor accuracy of this method is based on the presence of additional factors influencing the LT4 requirement. Santini *et al*. demonstrated the role of LBM in the prediction of LT4 requirement (13), probably due to the role of striated muscle in the conversion of T4 to T3 or to rT3. Moreover, several authors noted that LBM correlates with thyroid (26) and liver size, another important site of T4 conversion (27). Methods for the assessment of this parameter are expensive and not used in the current clinical setting. Weaker evidence supports the independent role of sex, age, and BMI (6,10–12) that seem to be more likely related to the differences in LBM associated with these variables. However, there are no comparisons between the methods reported in the literature to calculate the LT4 starting dose after thyroidectomy, which are based on BMI, BW, and age (Table 1) (5–7).

Our study confirms that BW is a relevant but not the only variable in the prediction of LT4 requirement. Our data confirm the findings by Ojomo *et al.*, showing an inverse correlation between BMI and the optimal LT4 dose per kilogram of BW per day, probably caused by the decrease of LBM in patients with a higher BMI (7). Also, the inverse correlation between age and LT4 pro kilogram requirement (6,28,29) that we have found confirms the data of several other authors. This aspect could be explained by the reduction in LBM observed with aging (30), in addition to the increased prevalence of obesity in elderly patients as suggested by Devdhar *et al*. (11). Indeed, in our analysis, the correlation with age also remains significant in the subgroup analysis by

Table 5. Efficacy of the Different Strategies for the Prediction of LT4 Starting Dose After Total Thyroidectomy in Retrospective Cohort

	Patients euthyroid at first control after surgery	*Patients with an error >25 μg of starting dose*	*Difference between optimal and predicted LT4 dose*
Weight × 1.6	37 (40%)	16 (17%)	0 (−12.5 to 12.5)
Ojomo *et al.*	38 (41%)	17 (18%)	0 (−12.5 to 0)
Olubowale *et al.*	21 (23%)	44 (48%)	−12.5 (−28.5 to 0)
Mistry *et al.*	12 (13%)	55 (60%)	−25 (−25 to −12.5)
Mistry *et al.* simplified	7 (8%)	76 (83%)	−37.5 (−37.5 to 25.0)

Difference between optimal and predicted LT4 dose is expressed as median and interquartile range (μg/kg/day).

BMI. Perhaps this correlation could also be explained by a possible reduction of thyroxine metabolism in older patients. Concerning a possible impact of sex, we did not find a statistical difference between females and males, in contrast to Jin *et al.* and Devdhar *et al.* who reported a higher LT4 pro kilogram dose in premenopausal women (11,12). Moreover, differently from Sukumar *et al*. (9), we found a correlation between height, but not body surface area, and the optimal LT4 dose.

The interesting direct correlation between the optimal LT4 dose and the presurgical level of fT3 could be explained by the correlation between the level of the T3 thyroidal production and the rate of conversion of T4 to T3 due to type 1 deiodinase. Moreover, a variable sensitivity of thyroid hormone receptor could be involved. More studies to investigate this matter are required. The inverse correlation between MCV and the optimal LT4 dose has never reported in the literature. Although it is not easy to explain this correlation, one can speculate that it may reflect the similarity between iron and LT4 absorption (31) and the presence of factors interfering with the absorption of both molecules, such as a subclinical reduced gastric acidity (24).

Although the analysis of the variables determining the LT4 requirement in post-surgical hypothyroidism does not contradict the results reported by Mistry *et al.*, Ojomo *et al.*, and Olubowale *et al.* (5–7), the hypothetical application of their strategies to our patients would have given a different and more unsatisfying efficiency, with a correct prediction of the optimal LT4 dose in only 13%, 41%, and 23% of patients respectively. These discordant results could partially be due to the differences in anthropometric or genetic characteristics of different ethnic groups, targets of TSH ranges, or different formulations of LT4 (32) considered by these authors. However, the use of our nomogram based on BMI and age predicted the correct starting dose of LT4 in 68% of patients compared to 40% of patients in whom the classic formula based on only BW was used. This performance could allow a more cost-effective management of postsurgical hypothyroidism.

Author Disclosure Statement

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