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ORIGINAL ARTICLE – OPEN ACCESS

Levothyroxine Dosage Determination According to Body Mass Index (BMI) After Total Thyroidectomy

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ABSTRACT

Objective: Currently, postoperative thyroid hormone replacement dosing is weight-based with adjustments and made following Thyroid Stimulating Hormone (TSH) values, which may lead to delayed achievement of euthyroidism and failure in achieving an accurate estimation of the levothyroxine dose. We aimed to evaluate the relationship between Body Mass Index (BMI) and Lean Body Mass (LBM) with levothyroxine dose.

Materials and Methods: Eighty patients with thyroid disease (benign and malignant) randomly enrolled the study. BMI and LBM were calculated during the pre-operative visit. Thyroid hormone replacement was started five day after surgery for benign and after a month for malignant cases, at a dose of 1.6 mcg/kg/day based on actual body weight. When euthyroidism was achieved, the levothyroxine dose was measured, and efforts were made to analyze its relationship with weight, BMI, and LBM.

Results: In the benign group, levothyroxine dose was obtained at 1.51 mcg/kg per body weight. To determine the levothyroxine dose based on BMI and LBM, Y=–0.013+0.005 BMI and Y=0.048+0.002 LBM formulas were used, respectively. In the malignant group, a levothyroxine dose of 1.56 mcg/kg was obtained based on the weight variable. To determine the levothyroxine dose based on BMI and LBM, Y=0.01+0.004 BMI and Y=0.042+0.002 LBM formulas were used, respectively. In both groups, the levothyroxine dose that was calculated was more accurate using BMI with the obtained formula.

Conclusion: Weight, BMI, and LBM can be used to determine the levothyroxine dose in patients receiving total thyroidectomy, but levothyroxine can be precisely measured using BMI.

Keywords: Levothyroxine, total thyroidectomy, BMI

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INTRODUCTION

Following a total thyroidectomy, an appropriate thyroid hormone replacement is essential, but challenges still exist. Suppressive doses of levothyroxine increase the risk of accelerated bone loss, fractures, arrhythmias, and reduces left ventricular function (1, 2). Long-term treatment with low-dose medicine is associated with clinical symptoms of hypothyroidism, weight gain, dyslipidemia, and cardiovascular dysfunction (3, 4). According to the surgery articles, the time to achieve postoperative euthyroidism is very variable and lasts from 2 weeks to 120 weeks with an average of 14.5 weeks. Many patients require multiple postoperative dose adjustments before achieving euthyroidism (5). The usual method is thyroid replacement therapy, which includes empirical doses of 100–150 mcg/day for women and about 125–200 mcg/day for men. Using this method, less than 50% of patients achieved euthyroidism at the first follow-up (6).

The new generation of Thyroid Stimulating Hormone (TSH) immunoassays allowed the serial titration of levothyroxine based on patient weight (7). Unfortunately, extensive studies of WBD (weight-based dosing) have not been approved for the initial replacement of thyroid hormone to predict the actual euthyroid dose (5, 8). TSH suppression is preferred as adjunctive therapy to reduce thyroid tumor recurrence (9). Many variables affect the required amount of levothyroxine, including age, sex, body weight, lean body mass (LBM), ideal body weight, body surface, menopausal status, hormonal status, and pathology (10, 11). Oral supplementation of calcium, ferrous sulfate, protein pump inhibitors, and sucralfate can also reduce the absorption rate (12, 13).

Few studies suggested LBM to predict postoperative levothyroxine levels in patients with primary hypothyroidism and hypothyroidism (14). However, recent articles are not indicative of a more predictive value of LBM as compared to body weight (6, 15). The accurate calculation of LBM requires complex techniques that are ineffective in the clinical field. Studies show inconsistent results regarding the use of ideal body weight (IBW) (5). Patients who are low-weight require a higher levothyroxine dose by weight than heavier ones (5). Therefore, it is reasonable to assume that BMI, which includes height and weight, may be a stronger predictive factor for the initial thyroid hormone replacement after total thyroidectomy (16).

At present, the postoperative levothyroxine replacement dose is mainly weight-based, which is regulated by the TSH level. This method delays the achievement of the euthyroidism and often does not demonstrate sufficient precision to determine the required dose. However, studies show that there is no correlation between the levothyroxine dose and single factor predicting the initial dose after total thyroidectomy (15, 17, 18). This study was designed to determine the exact dose of levothyroxine based on the BMI of patients.

MATERIALS and METHODS

The study was approved by the Tabriz University of Medical Science's ethical committee (8/5/2017–490626/D/5), and all patients who participated in this study signed an informed consent form. In this cross-sectional study, eighty patients who received total thyroidectomy (40 patients with benign causes and 40 patients with malignant papillary carcinoma) in Sina Hospital (Tabriz, Iran) from 2014 to 2016 were enrolled in the study. Patients included those who received total thyroidectomy, had no renal and liver disease, and euthyroidism was achieved and those excluded were <18 years old, pregnant within one year following surgery, those who received gastric bypass, and those who received T3 supplementation. Variables such as age, autoimmune diseases, BMI, LBM, and estrogen consumption were collected. The height and weight of patients were measured to calculate BMI and LBM in the preoperative visit. The oral explanations were given to patients on the levothyroxine administration before surgery. Patients should take levothyroxine with an empty stomach (fasting) and wait for 30 minutes before eating, and there should be a four-hour interval before taking drugs and eating in order to avoid interference with calcium, vitamin, or iron supplements. Also, levothyroxine was taken every day at the specified time. To reduce levothyroxine bias, a specific brand was provided to patients. Total thyroidectomy was performed by a surgeon. Thyroid hormone replacement was started five day after surgery for benign cases and after a month for malignant cases at a dose of 1.6 mcg/kg/day per actual body weight. Given that levothyroxine 0.1 mg is available in the pharmacy, the dose of the intended drug was determined and administered to the patient using the Table 1. Patients were visited 6–8 weeks postoperatively, TSH levels were evaluated, and the dose was adjusted by the surgeon accordingly. Ultimately, the goal is to achieve euthyroidism, which is defined as follows: TSH=0.4–45 mIU/l. Patients were visited every 6–8 weeks, the TSH level was evaluated, and dose titration was performed. The euthyroidism was achieved when the patient reached a normal TSH. All tests are routinely carried out in patients after total thyroidectomy, and no additional costs will be imposed on the patient. The surgery was performed based on the practical indication given by the endocrinologists. The method of prescribing levothyroxine is shown in table No.1. BMI was calculated with the following formula: BMI=Weight (kg)/height^2 (cm). LBM was calculated with the following formula: men: Lean body mass=(0.32810×Weight (kg)+(0.33929×Height (cm) −29.5336; for women: Lean body mass=(0.29569×Weight (kg)+(0.41813×Height (cm) −43.2933.

Statistical Analysis

All data were analyzed using SPSS ver. 18. Statistical analysis was carried out using descriptive statistical methods (frequency, percentage, and mean±standard deviation). A linear regression line has an equation of the form Y=a+bX, where X is the explanatory variable (LBM, BMI, weight) and Y is the dependent variable (predicted dose of levothyroxine). "a" is a constant and "b" is the slope of the line. The correlation coefficient, r, indicates the nature and strength of the relationship between x and y. Values of r range from -1 to +1 (0= no relationship. -1= means a perfect negative coefficient, +1= means a perfect positive coefficient). r^2, is the coefficient of determination that is always a positive number and varies between 0 and 1. The coefficient of determination gives an indication of the contribution of the factor being studied in the regression analysis to the relationship between x and y. A p-value <0.05 was considered as the significant level in this study.

Table 1. The method of prescribing levothyroxine

Prescribed levothyroxine dose (mg)	Calculated levothyroxine dosing interval (mg)
0.025	0-0.0375
0.05	0.0375–0.0625
0.075	0.0625–0.0875
0.1	0.0875–0.1125

RESULTS

Eighty patients receiving total thyroidectomy were enrolled in this study, half of whom received surgery for a benign cause and the other half were malignant causes. Demographic characteristics of the patients in the benign and malignant groups were demonstrated in Table 2.

Gender and age have no effect on the determination of levothyroxine dose in benign and malignant patients (p>0.05).

Patients From the Benign Group

The mean time of achieving euthyroidism was 7.4±0.87 weeks. The researchers found that the postoperative levothyroxine dose was 1.5 mcg/kg/body weight. BMI (OR=0.005, 95% CI=0.003–0.006; p<0.001), LBM (OR=0.002, 95% CI=0.001–0.003; p=0.004) and weight (OR=0.002, 95% CI=0.001–0.002; p<0.001) can predict the levothyroxine dose.

Regression analysis was used to evaluate the relationship between levothyroxine dose with BMI and LBM. As we see from the R value (Pearson correlation between two variables), which is equal to 0.445, there is a moderate correlation between the LBM and the levothyroxine dose variables. Regarding the R^2 value, LBM can account for 19.8% of changes in the levothyroxine dose, which is not significant.

The regression model can significantly (and appropriately) predict levothyroxine dose changes (p=0.004). We used the non-standardized regression coefficient to generate the regression equation. The regression equation is used to accurately predict the values of the levothyroxine dose variable, and its formula is as follows:

Y=0.048+0.002 LBM

As we see from the R value (Pearson correlation between two vari-

Table 2. Demographic characteristics of the patients in benign and malignant group

	Benign group patients	Malignant group patients
Age	53±11.39 years (23–73 yrs)	49.95±11.01 years (21–65 yrs)
Sex		
Male	7 patients (17.5%)	7 patients (17.5%)
Female	33 patients (82.5%)	33 patients (82.5%)
Height	164.57±5.16 cm (151–174 cm)	165.9±6.4 cm (150–176 cm)
Weight	74.57±10.31 kg (59–98 kg)	79.92±13.39 kg (63–110 kg)
BMI	27.44±3.17 (22.18–33.17)	28.99±4.47 (22.3–40.85)
LBM	46.08±6.04 (34–60.2)	48.68±6.19 (40–65.1)
Initial dose of levothyroxine	0.09±0.015 mg (0.075–0.125 mg)	0.098±0.027 mg (0.075–0.15 mg)
Final dose of levothyroxine	0.117±0.02 mg (0.1–0.15 mg)	0.121±0.023 mg (0.1–0.175 mg)
TSH level		
Before surgery	8.7±1.32 mIU/l	2.21±1.31 mIU /l
2nd week	5.31±1.52 mIU/l	1.36±0.45 mIU /l
4th week	3.36±1.03 mIU/l	0.84±0.38 mIU /l
6th week	1.75±0.84 mIU/l	0.51±0.21 mIU /l
Final	1.21±0.47 mIU/l	0.27±0.09 mIU /l

BMI: Body mass index; LBM: Lean body mass; TSH: Thyroid Stimulating Hormone

ables) of 0.735, there is a significant correlation between BMI and levothyroxine dose. Considering the R^2 value, BMI can account for 54% of the levothyroxine dose changes, which is moderate. The regression model could significantly (and appropriately) predict levothyroxine dose changes (p<0.001). We used the non-standardized regression coefficient to generate the regression equation. The regression equation is used to accurately predict the values of the levothyroxine dose variable, and its formula is as follows:

Y=(−0.013)+0.005 BMI

In benign group

Y=0.048+0.002 LBM (r=0.445, r^2=19.8%)

Y=(-0.013)+0.005 BMI (r=0.735, r^2=54%)

Y=0.002+0.002 Weight (r=0.774, r^2=59.8%)

In malignant group:

Y=0.042+0.002 LBM (r=0.435, r^2=19%)

Y=0.01+0.004 BMI (r=0.746, r^2=55.7%)

Y=0.008+0.001 Weight (r=0.822, r^2=67.5%)

As we see from the R value (Pearson correlation between two variables), which was found to be 0.774, there is a significant correlation between the two variables of weight and levothyroxine dose. Considering the R^2 value, the weight could explain 59.8% of changes in the levothyroxine e dose, which is moderate.

The regression model could significantly (and appropriately) predict levothyroxine dose changes (p<0.001). The non-standardized regression coefficient was used to generate the regression equation. The regression equation is used to accurately predict the values of the levothyroxine dose variable, and its formula is as follows:

Y=0.002+0.002 Weight

Patients From the Malignant Group

The mean time to achieve euthyroidism was 8.3±2.1 weeks. The researchers found that the post-thyroidectomy levothyroxine dose was 1.5 mcg/kg/body weight. BMI (OR=0.004, 95% CI=0.003–0.005; p<0.001), LBM (OR=0.002, 95% CI=0.001–0.003; p=0.005), and weight (OR=0.001, 95% CI=0.001–0.002; p<0.001) can predict the levothyroxine dose.

Regression analysis was used to evaluate the relationship between the levothyroxine dose with BMI and LBM. As we see from the R value (Pearson correlation between two variables), which was obtained as 0.435, there is a moderate correlation between the LBM and the levothyroxine dose variables. Regarding the R^2 value, LBM can account for 19% of the changes in the levothyroxine dose, which is not significant. The regression model could significantly (and appropriately) predict levothyroxine dose changes (p=0.005). We used the non-standardized regression coefficient to generate the regression equation. The regression equation is used to accurately predict the values of the levothyroxine dose variable, and its formula is as follows:

Y=0.042+0.002 LBM

As we see from the R value (Pearson correlation between two variables), which was obtained as 0.746, there is a significant correlation between BMI and levothyroxine dose. Regarding the R^2 value, BMI can explain 55.7% of the levothyroxine dose changes, which is moderate. The regression model could significantly (and appropriately) predict levothyroxine dose changes (p<0.001). We used the non-standardized regression coefficient to generate the regression equation. The regression equation is used to accurately predict the values of the levothyroxinedose variable, and its formula is as follows:

Y=0.01+0.004 BMI

As we see from the R value (Pearson correlation between two variables), which was obtained as 0.822, there is a significant correlation between the two variables of weight and levothyroxine dose. Considering the R^2 value, weight could explain 67.5% of the changes in the levothyroxine dose, which is statistically significant. The regression model could significantly (and appropriately) predict levothyroxine dose changes (p<0.001). We used the non-standardized regression coefficient to generate the regression equation. The regression equation is used to accurately predict the values of the levothyroxine dose variable, and its equation is as follows:

Y=0.008+0.001 Weight

DISCUSSION

The hormone replacement therapy in patients receiving thyroidectomy for benign diseases is traditionally calculated based on the actual body weight (mcg/kg), a method that was initially taken from patients who were treated for primary hypothyroidism (19). After the postoperative initial replacement therapy, TSH levels were measured and the levothyroxine dose was titrated until normal serum levels of TSH were achieved (20). In primary hypothyroidism, the remaining thyroid tissue may produce endogenous thyroid hormone, which complicates the precise need for exogenous thyroxine (5). To this end, initial dosing of levothyroxine (1.6 mcg/kg/day) starts after thyroidectomy, which is a standard dose for the hypothyroidism treatment. Although this dose may be a simple initial estimate, the efficacy of this method has not yet been approved for achieving euthyroidism in patients receiving total thyroidectomy. The results of previous studies suggest that BMI, IBW, and Body Surface Area are more accurate in predicting levothyroxine doses compared to body weight. Other factors include the age and gender of patients that can be effective in determining the initial dose of thyroid hormone (16).

The results of the present study are as follows: in this case of using weight to determine the dose of levothyroxine in patients who received surgery for benign causes, the dose is 1.51 mcg/kg, and for malignant cases, the dose is 1.56 mcg/kg.

After dosage adjustment, Jin et al. reported the mean postoperative levothyroxine doses of 1.5 and 1.3 mcg/kg for total thyroidectomy and lobectomy, respectively (20). In their study, Meinke Baehr et al. determined that the post-thyroidectomy levothyroxine dose was 1.4–2.2 mcg/kg using the actual body weight, which was dependent on diagnosis (benign or malignant), TSH target, gender, and menopausal status of women (10). Mistry et al. achieved a predicted levothyroxine dose of 1.6 mcg/kg after total thyroidectomy (5). Also, Fallahi et al. reported the mean postoperative levothyroxine dose of 1.5 for total thyroidectomy (21).

According to the results of this study, LBM can significantly (and appropriately) predict changes in levothyroxine dose using the (Y=0.048+0.002 LBM) formula in patients with benign tumors ($p=0.004$). LBM can also significantly (and appropriately) predict levothyroxine dose changes using the (Y=0.042+0.002 LBM) formula in patients with malignant tumors ($p<0.001$). The results of the Mistry et al. study showed a significant relationship between the levothyroxine dose and LBM, which can accurately adjust the levothyroxine dose (5). Di Donna et al. also showed a strong and significant correlation between the levothyroxine dose and LBM (14). According to the results of this study, BMI can significantly (and appropriately) predict levothyroxine dose changes using the (Y=−0.013+0.005 BMI) formula in patients with benign tumors ($p<0.001$). Also, BMI can significantly (and appropriately) predict levothyroxine dose changes using the (Y=0.01+0.004 BMI) formula in patients with malignant tumors ($p<0.001$). Ojomo et al. used BMI to predict the appropriate levothyroxine dose after total thyroidectomy, and the simple formula can determine the levothyroxine dose (Mcg/kg/day=−0.018 * BMI+2.13) (16). In another study, Jin et al. used BMI to determine the levothyroxine dose. Accordingly, the levothyroxine dose was 1.4 and 1.5 mcg/kg in BMI >30 and BMI <30, respectively (20). In other study, Zaborek et al. used the below formula to determine the daily LT4 dose (22).

Daily LT4 Dose $(\mu g)=e^{x}$,

$$X=2.02+0.01\,(W)-0.0037\,(A)-0.098\,(F)-0.01\,(B)+0.007\,(T)+0.108\,(I)-0.014\,(M)$$

CONCLUSION

The results of the current study showed that weights, BMI, and LBM can be used to determine the levothyroxine dose in patients who received total thyroidectomy, but BMI is more accurate in estimating levothyroxine dose.

Ethics Committee Approval: The study was approved by the Tabriz University of Medical Science's ethical committee (8/5/2017–490626/D/5).

Informed Consent: All patients who participated in this study signed an informed consent form.

Peer-review: Externally peer-reviewed.

Author Contributions: Designed the study: MH, TSEM, MNA, PN, GA. Collected the data: TSEM, SSA, TSBM. Analyzed the data: TSEM. Wrote the paper: TSEM, SSA. All authors have read and approved the final manuscript.

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