Change in Levothyroxine Requirements After Bariatric Surgery in Patients With Hypothyroidism.

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Research Article

Keywords: Bariatric surgery, levothyroxine, hypothyroidism, weight loss

Posted Date: May 6th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-467310/v1

Abstract

Purpose

This study aims to evaluate the need to modify the levothyroxine dose after surgery. Additional goals are to estimate the increase or decrease of total dose and weight-adjusted dose, assess the influence of weight loss on the levothyroxine requirements, and identify predictors.

Material and methods

Retrospective study in patients with treated hypothyroidism that underwent bariatric surgery. The required levothyroxine dose was evaluated before the surgery and at 6, 12, and 24 months post-surgery. Dose modification during follow-up and its association with weight loss and other potential predictors were assessed.

Results

Of the 63 patients included, 82.54% needed an adjustment of dose during the follow-up. The total dose of levothyroxine decreased significantly at 6 months post-surgery (-49.1 µg/week; 95%CI= -93.7 to -4.5; p=0.031) and 12 months (-54.9 µg/week; 95%CI= -102 to -7.8; p=0.022), with no significant change at 24 months (p=0.114). The weight-adjusted dose increased at 6 months (1.37 µg/kg/week; 95%CI=0.91 to 1.83; p<0.001), 12 months (2.05 µg/kg/week; 95%CI=1.43 to 2.67; p<0.001), and 24 months (2.52 µg/kg/week; 95%CI=1.74 to 3.30; p<0.001). Weight loss showed significant association with weight-adjusted dose (OR=1.07; 95%CI=1.02 to 1.12; p=0.004) and did not with the total dose (p=0.320).

Conclusions

It is expected that the levothyroxine requirements change in the firsts years after bariatric surgery. This study shows a significant decrease in the total dose during the first year of follow-up and an increase in the weight-adjusted dose over the two first years. No predictors for the modification in the total dose of levothyroxine have been identified.

Introduction

Bodyweight is one of the main factors influencing the dose of levothyroxine required for thyroid hormone replacement therapy in patients with hypothyroidism. Other factors determining the required dose are residual thyroid function and lean mass. Age and gender may also impact levothyroxine requirements, although with inconsistent results between different studies [1–3]. Under normal conditions, 68% of oral levothyroxine is absorbed, 25% in the duodenum, and 53% in the jejunoileal segment [4].

Bariatric surgery is the most effective obesity treatment achieving remarkable weight reductions quickly. It is indicated for patients with a body mass index (BMI) >40 Kg/m^2 or BMI >35 Kg/m^2 with comorbidities. Bariatric surgery techniques are classified as restrictive, mixed, and malabsorptive. Purely restrictive procedures include the laparoscopic adjustable gastric band (LAGB) and sleeve gastrectomy (SG). Mixed techniques involve Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion. The jejunoileal bypass is a purely malabsorptive procedure.

However, bariatric surgery is not without complications, such as a certain degree of nutrient malabsorption due to anatomical and functional changes. It may also affect the adequate absorption of pharmacological treatments. The main factors that may play a role in nutrient and drug malabsorption after the surgery are the alterations of gastric motility, the modification of gastric pH due to the decrease in the number of parietal cells, the impaired secretion of bile acids and biliopancreatic secretions, and the reduction in the intestinal absorption surface [5].

Due to the high prevalence of hypothyroidism that affects approximately 3.05% of the European population [6], and up to 12% of the people with obesity[7], it is a widespread condition in patients undergoing bariatric surgery. Therefore, it is often necessary to adjust the levothyroxine dose to achieve and maintain adequate thyroid replacement therapy in these patients during follow-up.

This research aims to evaluate the dose modifications of levothyroxine required to maintain a state of euthyroidism after bariatric surgery and the importance of close monitoring of thyroid function in these patients. The secondary objectives are to estimate the general trend of increasing o decreasing the total dose of levothyroxine and weight-adjusted dosing, assess whether weight loss influences thyroid hormone requirements, and identify predictors of the need to modify the levothyroxine dose after bariatric surgery.

Materials And Methods

Study design

This single-center, retrospective, longitudinal study was conducted in patients with hypothyroidism on replacement therapy who underwent bariatric surgery. Patients operated between 1999 and 2019 were included, and data from the last visit before surgery to the two years of subsequent follow-up were collected. The data collection period was from May to December 2020.

Participants

Participants were selected from the Obesity Unit of our hospital. The inclusion criteria were: adult patients with grade II or III obesity who had undergone bariatric surgery; compliance with follow-up after surgery in our Obesity Unit; hypothyroidism diagnosed before surgery and on replacement therapy; good adherence to levothyroxine treatment. Exclusion criteria were: hypothyroidism diagnosed after surgery; untreated hypothyroidism or poor compliance of treatment; and loss of follow-up after bariatric surgery.

Variables

Response variables were weekly total levothyroxine dose and weekly weight-adjusted dose. The possible predictor variables studied were: age, gender, the etiology of hypothyroidism, the surgical technique, the weight loss after surgery, the presence of symptoms of malabsorption, poor food tolerance, deficiency or need of supplementation of fat-soluble vitamin and B12 vitamin.

For the statistical analysis, the etiology of hypothyroidism was classified according to whether there was functioning thyroid tissue (including primary autoimmune hypothyroidism, secondary hypothyroidism, and postsurgical hypothyroidism after hemithyroidectomy) or there was no functioning thyroid (total thyroidectomy). Likewise, the variable bariatric surgery technique was classified as restrictive or mixed.

Data collection

Data compilation was carried out by reviewing the clinical records of the included patients. Data were collected from the last visit before the surgery and the follow-up at 6, 12, and 24 months post-surgery.

The total weekly levothyroxine dose was measured in micrograms (µg), and the weight-adjusted dose was measure in µg/kg. It was decided to collect the weekly dose instead of the daily dose because many patients had different dosage regimens each day of the week.

Statistical analysis:

Firstly, a descriptive analysis of the data was performed, and afterward, generalized estimating equation (GEE) models were used to carry out the inferential statistics. An analysis of the missing data and imputation of missing values using a linear regression method was performed. Multivariate predictive models to evaluate the effect of potential predictors on modifying the total dose of levothyroxine and the weight-adjusted dose over time were built using a forward stepwise selection strategy. For this purpose, we study the interactions between each potential predictor and the assessment time. Regarding the quantitative variables, the total levothyroxine dose, the weight-adjusted dose, and the weight loss were included as continuous variables, and the month of follow-up was treated as a categorical variable. P-value <0.05 was considered statistically significant. We used the statistical software R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and the statistical package “geepack.”

Results

A total of 63 patients (5 men/58women), with an average of age 48.78+/- 10.80-year-old at the time of surgery, were included. The characteristics of the patients about the etiology of hypothyroidism, surgical technique, post-surgery symptoms, or deficiency of vitamins are described in table 1. The results of the total dose of levothyroxine, weight-adjusted dose, weight, body mass index (BMI), TSH, and free-T4 (FT4) at baseline and 6, 12, and 24 months of follow-up are detailed in table 2 and figure 1.

An adjustment of the total levothyroxine dose at six months post-surgery was necessary for 35 patients (55.56%), with a decrease in 25 (39.68%) and an increase in 10 patients (15.87%). At 12 months post-surgery, 34 patients (53.97%) had to modify the levothyroxine dose, decreasing in 19 (30.16%) and increasing in 15 (23.81%). Finally, 36 patients (57.14%) needed to readjust the dose at 24 months post-surgery, with a decrease in 25 (23.81%) and an increase in 21 patients (33.33%). Therefore, 25 patients (82.54%) required some adjustment of the total levothyroxine dose during the first two years of follow-up.

A multivariate model adjusted for the etiology of hypothyroidism was the best model to explain the change in levothyroxine dose. A significant decrease in the total dose of levothyroxine was observed at 6 months post-surgery (-49.1 μg/week; 95%CI= -93.7 to -4.5; p=0.031), and also at 12 months post-surgery (-54.9 μg/week; 95%CI= -102 to -7.8; p=0.022) compared to the basal dose. However, at 24 months, the change was non-significant (-38.7 μg/week; 95% CI = -86.6 to 9.27; p=0.114). Age, gender, type of surgical technique, etiology of hypothyroidism, vitamin B12 deficiency, fat-soluble vitamins deficiency, and poor food tolerance did not significantly affect the change in the total dose of levothyroxine during follow-up (non-significant interactions with different monitoring times).

On the other hand, the weight-adjusted levothyroxine dose had a significant increase at all times of follow-up. In a multivariate model adjusted for the etiology of hypothyroidism and its interaction with follow-up time, the estimated increase at six months post-surgery was 1.37 μg/kg/week; 95%CI(0.91 to 1.83); p<0.001. The estimation of change at 12 months was 2.05 μg/kg/week; 95%CI (1.43 to 2.67); p<0.001, and at 24 months, it was 2.52 μg/kg/week; 95%CI (1.74 to 3.30); p<0.001. Likewise, the probability of the need to increase the weight-adjusted dose in the patients with total thyroidectomy was higher than in those with functioning thyroid tissue at 6 months (OR=6.04; 95%CI=1.05 to 34.80; p=0.044) and 12 months after surgery (OR=9.75; 95%CI=1.73 to 55.0; p=0.010) compared to baseline, although at 24 months there were no significant differences (OR= 5.75; 95%CI= 0.705 to 46.9; p=0.102). The other possible predictors studied did not significantly affect the change in the weight-adjusted levothyroxine dose.

Weight loss after surgery was not significantly associated with the change in total dose (OR= 0.28; 95%CI=0.024 to 3.33; p=0.320) but was with the variation in weight-adjusted dose (OR=1.07; 95%CI= 1.02 to 1.12; p=0.004).

Discussion

In our cohort, a high percentage of patients required at least one dose adjustment in the first two years of follow-up. The total dose of levothyroxine decreased significantly throughout the first year after surgery. However, the need for adjustment was highly variable between patients. The reduction in the total dose was not significantly associated with weight loss after surgery. The etiology of hypothyroidism, or rather the total thyroidectomy, was a predictor of a higher increase of weight-adjusted levothyroxine. No other predictors were found.

The relation between bariatric surgery and the variation in thyroid hormone requirements for replacement therapy after this procedure has been studied previously. The results of previous research are consistent with what we have observed in our study. In a retrospective study in 93 patients, the total levothyroxine dose was significantly lower after surgery. Still, only 50% of these patients required a reduction in the total dosing while remaining stable or increased in the other patients [8]. A review about the variation of levothyroxine requirements after bariatric surgery found that most of the studies showed a decrease in the total dose. However, in several other studies, it did not change, and, on the other hand, there were some case reports of patients requiring a marked increase in levothyroxine dose [9].

A possible explanation for the lack of association between the variation in the total dose of levothyroxine during the follow-up period and weight loss may be that levothyroxine requirements are not closely related to the entire body weight but rather to lean mass or, more specifically, to muscle mass, as Santini et al. reported [10]. After bariatric surgery, the loss of fat mass accounts for most weight loss, while the changes in lean mass are more variable and mainly related to physical activity. In our Obesity Unit, patients who undergo bariatric surgery are included in a therapeutic education program and receive nutritional advice and a physical exercise plan during the follow-up. Hence, they tend to increase their physical activity compared to before surgery. Because of this, we believe that most of our patients maintain their muscle mass or even improve it. However, unfortunately, the body composition data of patients included in our study were not available, so we could not corroborate this hypothesis.

The higher increase of the weight-adjusted dose in patients with total thyroidectomy than other causes of hypothyroidism could be justifed by the residual hormone production when there is thyroid tissue, which would partially compensate for the change in thyroid hormone requirements without the need to increase the exogenous hormone supply as much. However, the type of hypothyroidism did not influence the adjustment in the total weekly dose. Therefore, it seems to be more a predictor of weight loss after surgery and, consequently, weight-adjusted dosing than of total levothyroxine dose.

A retrospective study comparing the effect of different bariatric techniques on the dose of levothyroxine found no significant differences between restrictive and malabsorptive procedures [11]. This is consistent with our results, supporting that the bariatric technique does not influence modifying the levothyroxine dose.

Just as the previous factors do not fully explain the levothyroxine dose change, it seems malabsorption after surgery does not either. We found that indirect markers of malabsorption, such as malabsorptive symptoms, poor food tolerance, and fat-soluble or B12 vitamin deficiencies, did not significantly affect dose modification. Since most levothyroxine absorption occurs in the jejunoileal segment [4], it makes sense that relevant malabsorption should not happen in those techniques that do not affect this segment. Gkotsina et al. observed that the bioavailability of oral levothyroxine following bariatric surgery not only did not worsen but even improved in the subgroups of SG and biliopancreatic diversion [12]. A possible reason might be that lower exposure of levothyroxine to biliopancreatic secretions, especially to glucuronide-conjugated bilirubin, improves its absorption. Glucuronide is water-soluble, and when levothyroxine binds to it, the molecule cannot cross the membrane of the intestinal mucosa cells [12]. Other explanations would be the cell proliferation in the jejunum mucosa observed after the RYGB, the changes in the intestinal microbiota, and the decrease in levothyroxine binding to proteins present in the stomach and the duodenum [12–15]. In the same line, another study also showed better absorption of levothyroxine in patients with RYGB than the control group without bariatric surgery, although several patients had some delay in absorption [16]. On the contrary, there are reported cases of severe levothyroxine malabsorption after bariatric surgery [17,18].

Finally, another potential predictor factor has been evaluated in some studies, but its role has not yet been elucidated. Leptin level is usually elevated in obese patients and tends to decrease after bariatric surgery. It is believed to play a relevant role in the hypothalamic-pituitary-thyroid (HPT) axis by regulating the TRH gene expression. A positive correlation between the decrease in leptin levels after bariatric surgery and the reduction in TSH has been observed in euthyroid patients [19]. However, a retrospective study did not found a significant association between the decrease in plasma leptin level and the decrease in levothyroxine dose [8]. It would have been interesting to include this variable in our research if we had data available.

Our study has the limitations of a retrospective study, such as missing data in some patients or the lack of data on some variables that would have been interesting to include to better understand the factors involved in adjusting the levothyroxine dose after surgery. Consequently, it does not allow definitive conclusions about the influence of the change in body composition or the malabsorption on the modification in the levothyroxine requirements after surgery since they were not directly evaluated, so we can only make hypotheses about it. Likewise, the sample size is small, which reduces statistical power and makes it difficult to draw conclusions about dose adjustment possible predictors. However, in our opinion, the results of this study reflect the need to delve deeper into this topic with more researches that directly assess the influence of these factors on the change of levothyroxine requirements after bariatric surgery.

Conclusion

Close monitoring of thyroid function is necessary to adjust the levothyroxine, avoiding iatrogenic states of hypothyroidism and hyperthyroidism after bariatric surgery. Our results suggest that the total dose decreases significantly during the first year of follow-up, while the weight-adjusted dose increases over the two first years. However, the need for adjustment is highly variable among patients. No predictors of total dose modification have been identified. Regarding the weight-adjusted dose variation, the only predictors of its increase are the total thyroidectomy and, logically, weight loss. In contrast, weight loss does not seem to be associated with the change of total levothyroxine dose. Surgical technique and indirect malabsorption markers have also not shown a correlation with levothyroxine requirements. All this suggests the presence of other factors involved in the need for dose adjustment after surgery. More studies are needed to understand the factors that play a role in levothyroxine requirements after bariatric surgery.

Declarations

Funding sources

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Availability of data and material

All data used in this review are available upon request to the corresponding author.

Code availabilitly:

Code is available upon request to the corresponding author.

Authors´s contributions

A.C. and R.G. designed the study. A.C. selected the participants. R.G. collected the data, preformed the statistical analysis and drafted the manuscript. I.C., M.Z. and L.H. provided additional information for data collection and the preparation of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study protocol was reviewed and approved by the Ethics Committee of La Paz University Hospital

Consent to participate

Informed consent was obtained from all the participants.

Consent for publication

Informed consent was obtained from all the participants.

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Tables

Table 1. Characteristics of the patients

	N(%)
Bariatric surgery technique	Restrictive: - Sleeve gastrectomy: 14 (22.2%) - Laparoscopic adjustable gastric band: 1 (1.6%)
	Mixed: - Roux-en-Y gastric bypass: 48(76.2%)
Etiology of hypothyroidism	Autoimmune primary hypothyroidism: 48(76.2%)
	Central hypothyroidism: 1(1.6%)
	Postsurgical after hemithyroidectomy: 2 (3.2%)
	Total thyroidectomy for multinodular goiter: 4 (6.3%)
	Total thyroidectomy for Graves disease: 3(4.8%)
	Total thyroidectomy for thyroid cancer: 5(7.9%)*
Post-surgery gastrointestinal symptoms	13(20.6%)
Post-surgery poor food tolerance	16 (25.4%)
Post-surgery deficiency and/or need of supplementation of vitamin	Fat-soluble vitamin: 48(76.2%)
	B12 vitamin: 14 (22.2%)

*None of them under levothyroxine suppressive therapy.

Table 2. Descriptive analysis of quantitative variables

	Baseline	6 months post-surgery	12 months post-surgery	24 months post-surgery
Weekly total dose (µg)	801.78±378.91	752.70±379.95	746.84±357.44	763.12±345.68
Weekly dose adjusted to weight (µg/kg)	6.85±3.44	8.56±4.71	9.33±4.98	9.70±5.12
Weight (kg)	120.22±20.36	90.04±13.18	83.07±14.01	82.91±15.37
BMI (kg/m2)	44.63±6.30	33.50±4.52	31.00±5.73	31.40±5.28
TSH µUI/ml	2.42±1.79	2.48±3.29	3.99±7.20	2.32±1.95
FT4 ng/dl	1.25±0.25	1.25±0.37	1.20±0.31	1.29±0.33

*Results expressed in mean and standard deviation.

Figures

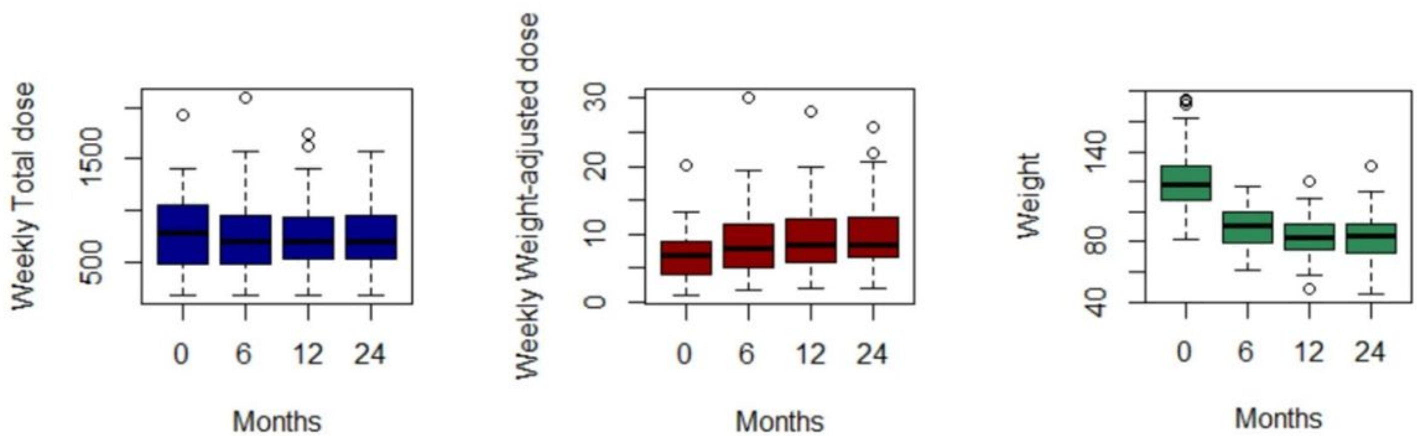

Figure 1

Change in levothyroxine doses and weight over time.