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Change in levothyroxine requirements after bariatric surgery in patients with hypothyroidism

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Objectives. This study aims to evaluate the need to modify the total and weight-adjusted doses of levothyroxine after bariatric surgery, identify predictors, and assess the influence of the weight loss on the levothyroxine requirements.

Methods. A retrospective study in patients with treated hypothyroidism that underwent bariatric surgery. The modification of the levothyroxine dose and its association with the weight loss and other potential predictors were evaluated at 6, 12, and 24 months post-surgery.

Results. Among the 63 patients included, 82.54% needed an adjustment of levothyroxine dose during the follow-up. The total weekly dose of levothyroxine (μg) decreased post-surgery at 6 months (β=-49.1; 95%CI-93.7 to -4.5; p=0.031) and 12 months (β=-54.9; 95%CI-102 to -7.8; p=0.022), but did not significantly change at 24 months (p=0.114). The weekly weight-adjusted dose (μg/k) increased at 6 months (β=1.37; 95%CI 0.91 to 1.83; p<0.001), 12 months (β=2.05; 95%CI 1.43 to 2.67; p<0.001), and 24 months (β=2.52; 95%CI 1.74 to 3.30; p<0.001). The weight loss showed association with the weight-adjusted dose (OR=1.07; 95%CI 1.02 to 1.12; p=0.004), but not the total dose (p=0.320).

Conclusions. This study shows a significant decrease in the total dose of levothyroxine requirements change after bariatric surgery during the first year of the follow-up and an increase in the weight-adjusted dose over the first two years. No predictors of modification of the total dose of levothyroxine were identified.

Key words: bariatric surgery, levothyroxine, hypothyroidism, weight loss

The body weight 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 have an impact on levothyroxine requirements, although results between studies are inconsistent (Jonklaas 2010; Devdhar et al. 2011; Younis et al. 2018). Approximately 68% of oral levothyroxine is absorbed under the normal conditions, with absorption occurring primarily in the duodenum (15%) and the jejunoileal segment (53%) (Hays 1991).

Bariatric surgery is the most effective obesity treatment achieving remarkable quick weight reductions. It has been recommended for patients with a body mass index (BMI) >40 kg/m^2 or BMI >35 kg/m^2 with comorbidities. The bariatric surgery techniques are classified as restrictive, mixed, and malabsorptive. Purely restrictive procedures include 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

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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 the nutrient and drug malabsorptions after the surgery are the alterations of gastric motility, modification of the 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 (Azran et al. 2019).

Due to the high prevalence of hypothyroidism, which affects approximately 3.05% of the European population (Madariaga et al. 2014) and up to 12% of the people with obesity (Michalaki et al. 2006), 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 the 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 or 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.

Table 1
Characteristics of the patients

Variables	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 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 symptom	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.

Material and methods

Study design. This single-center, retrospective and longitudinal study was conducted in patients with hypothyroidism on replacement therapy who underwent bariatric surgery. Patients operated between 1999 and 2019 were included. The 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. The study protocol has been reviewed and approved by the Ethics Committee of La Paz University Hospital.

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

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 measured 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. 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.

Firstly, a descriptive analysis of the data was performed. Afterward, generalized estimating equation (GEE) models were used to carry out the inferential statistics. 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 studied 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. 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/58 women), 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, BMI, thyroid-stimulating hormone (TSH), and free-T4 (FT4) at baseline and 6, 12, and 24 months of follow-up are depicted in Figure 1 and Table 2.

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 modified 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 in 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 weekly dose of levothyroxine (μg) was observed at 6 months post-surgery (β=-49.1; 95%CI -93.7 to -4.5; p=0.031) and also at 12 months post-surgery (β=-54.9; 95%CI -102 to -7.8; p=0.022) compared to the basal dose. However, the change was non-significant at 24 months (β=-38.7; 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 the follow-up (non-significant interactions with different monitoring times).

On the other hand, the weekly weight-adjusted dose of levothyroxine (μg/kg) increased significantly at six months post-surgery (β=1.37; 95%CI 0.91 to 1.83; p<0.001), at 12 months (β=2.05; 95%CI 1.43 to 2.67; p<0.001), and at 24 months (β=2.52; 95%CI 1.74 to 3.30; p<0.001) of follow-up. Likewise, the probability of increasing the weight-adjusted dose

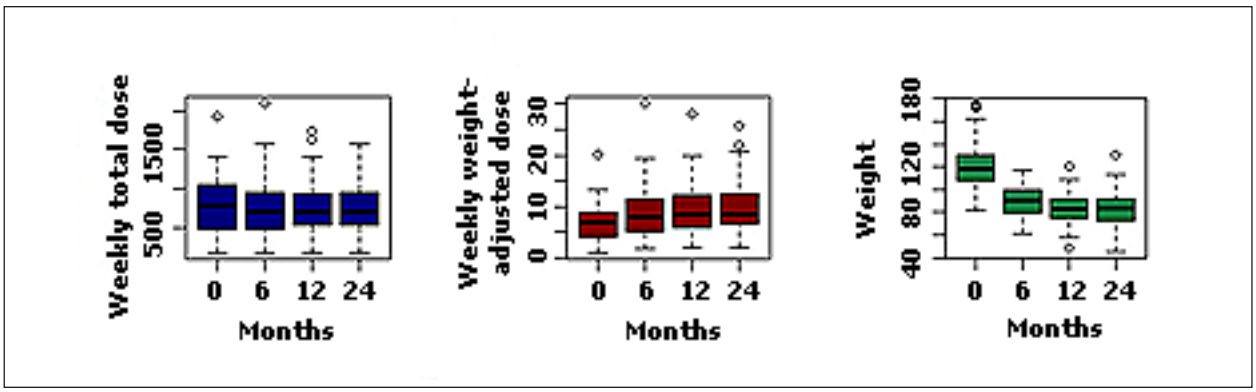


Figure 1. Change in levothyroxine doses and weight over time.

Table 2
Descriptive analysis of the quantitative variables

Parameter	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/m^2)	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 are expressed as mean ± standard deviation.

requirements 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 the surgery (OR=9.75; 95%CI 1.73 to 55.0; p=0.010) compared to the baseline, whereas, there were no differences at 24 months (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 dose of levothyroxine.

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 it was associated 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 the 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. Reduction of the total dose of levothyroxine was not significantly associated with weight loss after surgery. The etiology of hypothyroidism, or rather total thyroidectomy, was a predictor of a higher increase in the weight-adjusted levothyroxine dose. 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 our observation in the present 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 (Fierabracci et al. 2016). A review of the variation of levothyroxine requirements after bariatric surgery found that most of the studies showed a decrease in the total dose. In several other studies, however, it did not change. On the other hand, there were some case reports of patients requiring a marked increase in levothyroxine dose (Gadiraju et al. 2016).

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. (2005) have reported. After bariatric surgery, the loss of fat mass accounts for the most weight loss, while the changes in lean mass are more variable, mainly related to physical activity. In our Obesity Unit, patients who undergo bariatric surgery are included in a therapeutic education program receiving 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 a total thyroidectomy than other causes of hypothyroidism could be justified 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 etiology 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 has not found significant differences between restrictive and malabsorptive procedures (Pedro et al. 2018). This study is consistent with our results, supporting that the bariatric technique does not influence levothyroxine dose modification.

Just as the previous factors do not fully explain the levothyroxine dose change, it seems that malabsorption after surgery does not explain 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 the dose modification. Since most levothyroxine absorption occurs in the jejunoileal segment (Hays 1991), it makes sense that those techniques that do not affect this segment do not lead to significant malabsorption of this medication. Gkotsina et al. (2013) have observed that the bioavailability of oral levothyroxine has not only not worsened after bariatric surgery, but even improved in the subgroups of SG and biliopancreatic diversion. 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 (Gkotsina et al. 2013). 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 (Herz et al. 1961; Zhang et al. 2009; Spak et al. 2010; Gkotsina et al. 2013). In the same line, another study also has shown better absorption of levothyroxine in patients with RYGB than the control group without bariatric surgery, although several patients had some delay in the absorption (Rubio et al. 2012). On the contrary, there are reported cases of severe levothyroxine malabsorption after bariatric surgery (Azizi et al. 1979; Bevan and Munro 1986).

Finally, another potential predictor 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. This hormone is believed to play a relevant role in the hypothalamic-pituitary-thyroid (HPT) axis by regulating the thyrotropin-releasing hormone (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 (Yu et al. 2019). However, a retrospective study found no significant association between the decrease in plasma leptin level and the decrease in levothyroxine dose (Fierabracci et al. 2016). It would have been interesting to include this variable in our research if we had the data available.

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

Conclusion

Close monitoring of the thyroid function is necessary to adjust the levothyroxine dose avoiding iatrogenic states of hypothyroidism and hyperthyroidism after the bariatric surgery. Our results suggest that the total levothyroxine dose decreases significantly during the first year of the follow-up, while the weight-adjusted dose increases over the first two years. However, the need for the adjustment is highly variable among patients. No predictors of the total dose modification were identified. Regarding the weight-adjusted dose variation, the only predictors of its increase are the total thyroidectomy and, logically, the weight loss.

On the contrary, the weight loss does not seem to be associated with the total levothyroxine dose change. Surgical technique and indirect malabsorption markers also did not show a correlation with levothyroxine requirements. All this may suggest that there are other factors involved in the need for dose adjustment after surgery. Actually, more studies are needed to understand the factors that play a role in the levothyroxine requirements after bariatric surgery.

Conflict of interest: *The authors report no conflict of interest.*

A.C. and R.G. designed the study. A.C. selected the participants. R.G. collected the data, performed 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.

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