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ORIGINAL CONTRIBUTIONS

Long-term Effect of Bariatric Surgery on the Use of Levothyroxine and Thyroid Levels

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Abstract

Background The aim of this study was to evaluate the effect of bariatric surgery on the defined daily dose of levothyroxine (DDD LT4), thyroid-stimulating hormone (TSH), and free thyroxine (fT4) in female patients with hypothyroidism until 48 months after surgery.

Methods A retrospective observational study of hypothyroid patients who underwent bariatric surgery. Changes in DDD LT4, TSH, and fT4 over a 48 month period after surgery were analyzed.

Results Thirty-seven patients were included: 27 Roux-en-Y gastric bypass (RYGB), 6 sleeve gastrectomy (SG), 3 adjustable gastric band, and 1 one anastomosis gastric bypass. The median DDD LT4 decreased from 125 µg at baseline to 100 µg 12 months after surgery. From 24 to 48 months after surgery, the median DDD LT4 was stable at 125 µg. Most dose adjustments occurred during the first 24 months after surgery. In the time period of 24–48 months after surgery, the dose remained stable in 73.1% of the RYGB patients and in 60.0% of the SG patients. After 48 months in the RYGB group, no significant change in TSH and fT4 levels was observed.

Conclusions Bariatric surgery led to frequent dose adjustments during the first 2 years after surgery. However, 24–48 months after surgery in the majority of patients, the dosage remained stable. No significant change in TSH and fT4 was observed 48 months after RYGB. In the first 2 years after surgery, clinicians should frequently monitor TSH and fT4 for individual dose adjustment of levothyroxine. Thereafter, the frequency of monitoring may be decreased.

Keywords Bariatric surgery · Gastric bypass · Sleeve gastrectomy · Hypothyroidism · Levothyroxine · Thyroid-stimulating hormone

Introduction

Bariatric surgery achieves sustained weight loss and improvement or remission of several weight-related comorbidities [1, 2]. Both weight loss per se and improvement in comorbidities can lead to changes in pharmacotherapy. Moreover, depending on the type of surgical procedure, after bariatric surgery, drug absorption may be altered, leading to changes in pharmacokinetic parameters affecting pharmacotherapy [3]. Changes in thyroid function and use of levothyroxine have been observed after bariatric surgery. The results of previous studies on the use of levothyroxine and thyroid function in the first years after bariatric surgery are not consistent. Most studies demonstrated a decreased levothyroxine dosage after bariatric surgery [4–6]. In a previous study, we found a sustained use of thyroid replacement medication

Key Points \
• Study on the long-term effect of bariatric surgery on the use of levothyroxine.
• Most dose changes of levothyroxine occurred in the first 2 years after surgery.
• Twenty-four to 48 months after surgery, most patients had a stable dosage of levothyroxine.
• Frequent monitoring of TSH and fT4 is advised in the first 2 years after surgery.

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12 months after bariatric surgery with a higher daily dosage per patient [7].

Bariatric surgery is associated with a significant decrease in thyroid-stimulating hormone (TSH) and a non-significant change of free thyroxine (fT4) in the first years after surgery [8, 9]. However, results of TSH and fT4 in hypothyroid patients following bariatric surgery are sparse [5, 6, 10]. Few studies compared the effects of different types of bariatric operations on thyroid function and use of levothyroxine [6, 10, 11]. No results on the effects beyond 2 years after surgery have been reported yet.

The aim of the present study was to evaluate the long-term effect of bariatric surgery on the defined daily dose of levothyroxine (DDD LT4), TSH, and fT4 concentrations in female patients with hypothyroidism until 48 months after surgery.

Methods

Data Acquisition

For this retrospective observational study, 52 hypothyroid patients were selected from a database of 449 patients who underwent bariatric surgery in the Medical Center Leeuwarden between 2008 and 2011. This database was previously used for a study on the influence of bariatric surgery on the use of medication until 12 months after surgery [7]. A patient was considered hypothyroid if she had been prescribed levothyroxine before surgery. After having obtained written informed consent, demographic data were gathered from the Departments of Surgery and Internal Medicine of the hospital. These data included age, gender, type of surgery (Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), adjustable gastric band (AGB), or one anastomosis gastric bypass (OAGB)), date of surgery, and body mass index (BMI) before and 6, 24, and 48 months after surgery. Dispensing data of levothyroxine, the indication for use of levothyroxine and results for laboratory tests for TSH and fT4, from 12 months before until 48 months after surgery, were collected from the patient's pharmacies, general practitioners, internal medicine specialists, and clinical laboratories. Dispensing data of levothyroxine included dosage form, daily dosage, and total number supplied. Based on dispensing data, the DDD LT4 was determined.

Informed consent was obtained from all individual participants included in the study.

The regional research ethics committee waived this study from ethical review in accordance with Dutch legislation.

Data Analysis

All patient data were anonymized prior to entering in the study database. TSH and fT4 were measured in serum, obtained from blood samples during clinical evaluations. In our hospital, the reference ranges for TSH and fT4 were 0.3–4.0 mU/L and 11–24 pmol/L, respectively. Changes in DDD LT4, TSH, and fT4 over a 48-month period after surgery were analyzed. Patients diagnosed with Hashimoto's thyroiditis were excluded for analysis of the overall DDD LT4, because the progress of this disease may influence the dosing of levothyroxine.

Statistical Analysis

Data were expressed as mean ± standard deviation for continuous variables of patient characteristics with a normal distribution, and as median with Q1–Q3 values with a non-normal distribution. Frequencies and percentages were used for categorical variables.

A paired *t*-test was used to compare levels of TSH and fT4 at baseline and 24 and 48 months postsurgery. The *p* values were two-sided and statistical significance was considered when $p < 0.05$. All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk NY, USA) or SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline Characteristics

With 52 female patients prescribed levothyroxine before surgery from 449 patients undergoing bariatric surgery between 2008 and 2011, the prevalence of hypothyroidism in our population was 11.6%. Of those patients, 15 were excluded: 13 patients of whom no signed informed consent was obtained, and 2 with an incomplete medical history. The mean age of the 37 included patients was 43.7 ± 8.6 years. The patients had a mean preoperative BMI of 46.0 ± 7.9 kg/m^2 (Table 1). Hypothyroidism was the most prevalent indication for levothyroxine suppletion. Twenty-seven patients underwent RYGB, 6 SG, 3 AGB, and 1 OAGB. For some patients, not all data were complete at each time point.

Use of Levothyroxine After Bariatric Surgery

In Fig. 1, the overall changes in DDD LT4 in patients from 6 months before until 48 months after bariatric surgery are shown. The median DDD LT4 decreased from 125 µg at baseline to 100 µg 12 months after surgery. From 24 to 48 months after surgery, the median DDD LT4 was stable at 125 µg, the same as at baseline.

For patients who underwent RYGB and SG, no striking differences were found in median DDD LT4 24 and 48 months after surgery compared to baseline (Table 2).

Table 1 Patient characteristics at baseline

Characteristic	All patients	Roux-en-Y gastric bypass	Sleeve gastrectomy	Adjustable gastric band	One anastomosis gastric bypass
Number of patients (%)	37 (100)	27 (73)	6 (16)	3 (8)	1 (3)
Age (yr)	43.7 ± 8.6	45.1 ± 9.1	41.0 ± 5.7	38.7 ± 8.1	37.0
Indication for LT4 suppletion (*n* (%))					
Hypothyroidism	32 (86.5)	23 (85.2)	5 (83.3)	3 (100)	1 (100)
Hemithyroidectomy	2 (5.4)	1 (3.7)	1 (16.7)	–	–
Hashimoto's thyroiditis	1 (2.7)	1 (3.7)	–	–	–
Extirpation hypophysis adenoma	1 (2.7)	1 (3.7)	–	–	–
Multinodular goiter	1 (2.7)	1 (3.7)	–	–	–
BMI (kg/m^2)					
Presurgery (*n*)	46.0 ± 7.9 (28)	46.7 ± 6.2 (21)	46.6 ± 13.8 (5)	36.8 ± 1.1 (2)	–
6 months postsurgery (*n*)	39.6 ± 6.8 (28)	40.1 ± 5.8 (21)	41.6 ± 11.9 (4)	31.3 ± 0.4 (2)	38.2 (1)
24 months postsurgery (*n*)	29.4 ± 5.1 (11)	30.3 ± 5.1 (9)	–	27.4 (1)	24.3 (1)
48 months postsurgery (*n*)	35.8 ± 5.7 (11)	35.7 ± 6.4 (7)	37.1 ± 7.2 (2)	34.7 ± 5.1 (2)	–

BMI body mass index

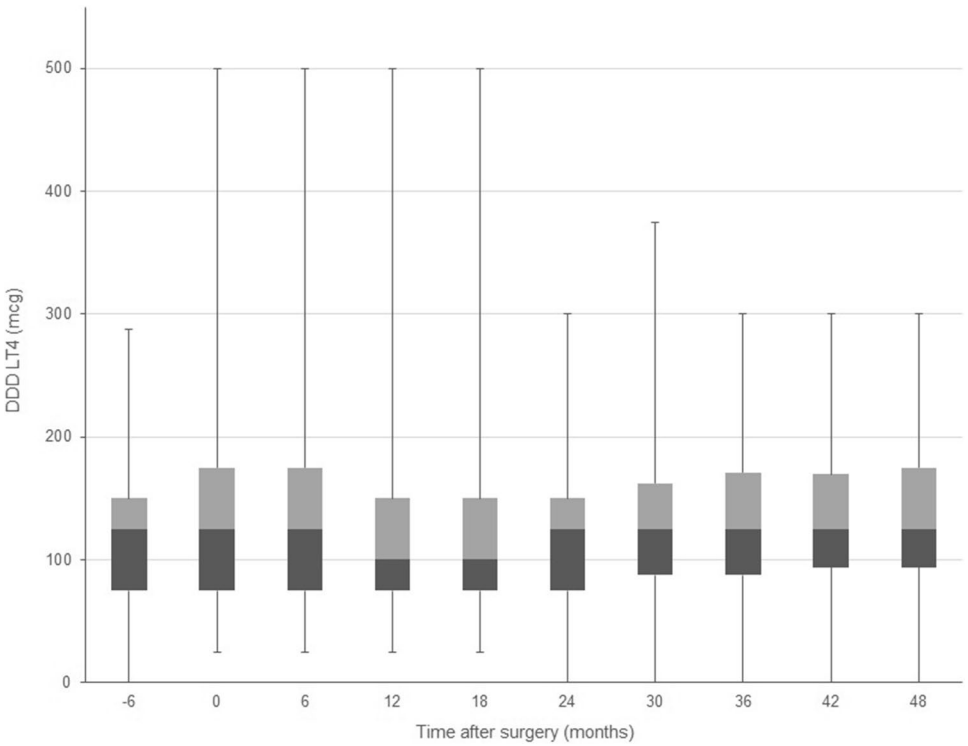

Fig. 1 Changes in DDD LT4 in patients after bariatric surgery

Table 2 Median DDD LT4 in patients at baseline, 12, 24, and 48 months after Roux-en-Y gastric bypass and sleeve gastrectomy

Median [Q1–Q3] DDD LT4 (μg)	Baseline	After 12 months	After 24 months	After 48 months
RYGB	125 [75–175] (*n* = 26)	100 [75–175] (*n* = 26)	125 [100–150] (*n* = 25)	125 [100–175] (*n* = 26)
SG	75 [75–100] (*n* = 6)	87.5 [75–100] (*n* = 6)	100 [75–100] (*n* = 5)	100 [75–100] (*n* = 5)

RYGB Roux-en-Y gastric bypass, *SG* sleeve gastrectomy, *μg* microgram

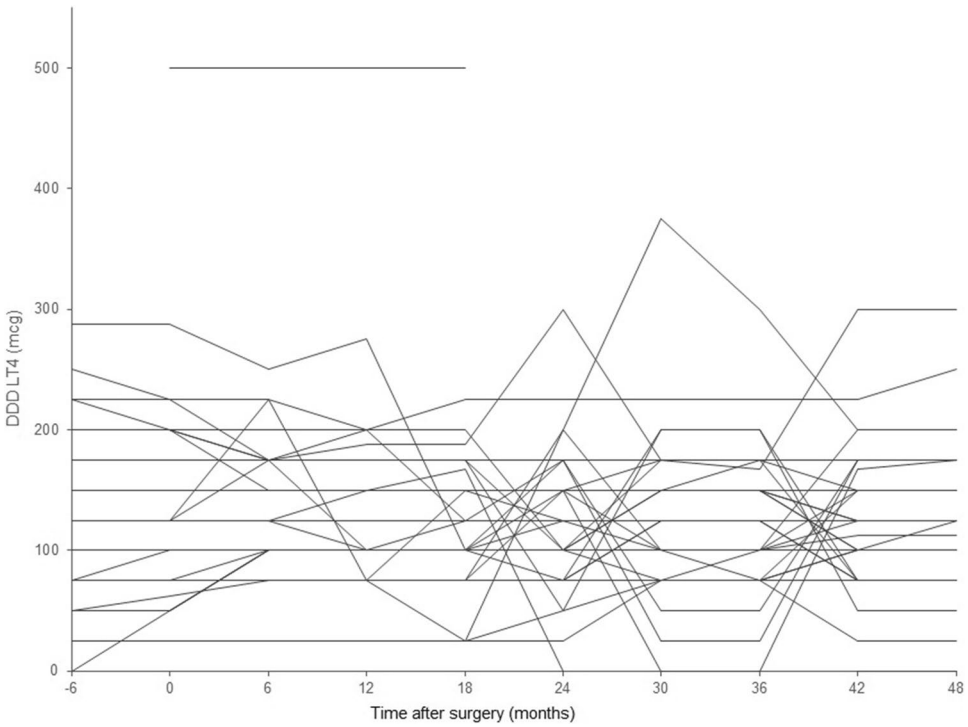

Fig. 2 Individual changes in DDD LT4 in patients after bariatric surgery

Table 3 Changes in DDD LT4 after bariatric surgery

Type of surgery	Dose adjustment	0–48 months *n* (%)	0–12 months *n* (%)	12–24 months *n* (%)	24–48 months *n* (%)
RYGB[1]	Adjusted	20[2] (74.1)	13[2] (48.1)	9 (34.6)	7 (26.9)
	Reduction	6[1] (22.2)	6 (22.2)	2 (7.7)	2 (7.7)
	Increase	13[2] (48.1)	7[2] (25.9)	7 (26.9)	4 (15.4)
	Same at endpoint	1 (3.8)			1 (3.8)
	Same dose throughout	7 (25.9)	14 (51.9)	17[2] (65.4)	19[2] (73.1)
SG	Adjusted	4 (66.7)	2 (33.3)	1 (16.7)	2 (40.0)
	Reduction	2 (33.3)	1 (16.7)	1 (16.7)	1 (20.0)
	Increase	2 (33.3)	1 (16.7)		1 (20.0)
	Same dose throughout	2[3] (33.3)	4 (66.7)	5[3] (83.3)	3 (60.0)
AGB	Adjusted	2 (66.7)	1 (33.3)	2 (66.7)	2 (66.7)
	Reduction	1 (33.3)	1 (33.3)	1 (33.3)	
	Increase	1 (33.3)			2 (66.7)
	Same at endpoint			1 (33.3)	
	Same dose throughout	1[4] (33.3)	2 (66.7)	1[4] (33.3)	1[4] (33.3)
OAGB	Same dose throughout	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)

RYGB Roux-en-Y gastric bypass, *SG* sleeve gastrectomy, *AGB* adjustable gastric band, *OAGB* one anastomosis gastric bypass

[1]Including one patient with no data on $T = 24$ months

[2]Including one patient with Hashimoto's thyroiditis

[3]Including one patient with follow-up until 18 months after surgery (no change in dose)

[4]Including one patient who stopped using levothyroxine after 18 months

When focusing on individual patients, after bariatric surgery, the DDD LT4 may fluctuate over time (Fig. 2). Results show differences in dose adjustment of levothyroxine after different types of surgery (Table 3). Most dose adjustments took place during the first 24 months after surgery. In contrast, in the time period of 24 to 48 months after surgery, the

dose remained stable in 73.1% of the RYGB patients and in 60.0% of the SG patients.

TSH and fT4 Levels After RYGB

Only for patients who underwent RYGB sufficient data of TSH and fT4 levels were available for analysis. No significant changes in TSH and fT4 were observed in patients 48 months after RYGB compared to baseline (Table 4). The mean change in TSH was 0.2 ± 2.2 mU/L ($p = 0.78$) and the average decrease in fT4 level was -0.9 ± 3.5 pmol/L ($p = 0.49$).

Discussion

We examined the long-term effect of bariatric surgery on the levothyroxine requirement and thyroid function in female patients. In this retrospective observational study, we found a prevalence of hypothyroidism of 11.6% in patients undergoing bariatric surgery. The prevalence of hypothyroidism in this study was comparable to earlier reported prevalences of 7.3–11.8% in bariatric surgery patients [10–14].

Overall we observed no effect of bariatric surgery on the dosage of levothyroxine 4 years after surgery. The median DDD LT4 remained the same the first 4 years after surgery except for a small decline in the period of 6–24 months after surgery. Yet, on patient level, bariatric surgery may have different effects on the dosage of levothyroxine. In the individual patient, the dosage may decrease, increase, or remain stable in comparison to presurgery. Most changes in the dosage of levothyroxine occurred in the first 24 months after surgery. In the majority of patients between 24 and 48 months after surgery, the dose of levothyroxine remained stable. In the first years after bariatric surgery, patients should be frequently monitored for individual dose adjustment of levothyroxine. After this time period, the frequency of monitoring may be reduced. Compared to presurgery, no significant changes in TSH and ft4 were observed in patients 24 and 48 months after RYGB.

Levothyroxine is a compound with low solubility at pH higher than 1 and low permeability [15]. It is absorbed mostly from the jejunum and the upper ileum. Gastric bypass surgery reduces functional gastrointestinal length, so drug absorption may be reduced. Gastric pH is increased after gastric bypass surgery and SG, hampering dissolution of levothyroxine. Postsurgical use of proton pump inhibitors may further contribute to the elevated gastric pH. By all of these mechanisms, the absorption of levothyroxine might be decreased, implying that an increased dose of levothyroxine may be necessary [15]. Weight loss after surgery and an altered set point of thyroid hormone homeostasis might still result in a decreased dose requirement of levothyroxine [4]. Using a solution of levothyroxine, dissolution and low solubility problems may be avoided. In a pharmacokinetic study on levothyroxine administered as oral solution in euthyroid patients before and 35 days after surgery, absorption of levothyroxine was improved following SG and biliopancreatic diversion and no change in absorption was observed after RYGB [16]. In a pharmacokinetic study with levothyroxine administered as a tablet, Rubio et al. showed that on a population level RYGB does not reduce mean levothyroxine absorption parameters. In some patients, however, a small delayed absorption of levothyroxine was observed [17].

A recent review of the literature by Azran et al. showed a lack of high-quality large prospective studies on the effects of bariatric surgery on levothyroxine dosing and hypothyroidism [15]. From the available literature, they concluded that there is contradicting evidence regarding postoperative oral levothyroxine dose requirement and that most studies show a trend toward a decrease in TSH [15]. Nonetheless, so far only results are available from the first years after bariatric surgery. Although several studies showed a decrease in levothyroxine dosage requirement in many patients, in other

Table 4 Changes in levels of TSH and free T4 after Roux-en-Y gastric bypass

RYGB ($n = 26$[1])	Baseline	After 24 months	After 48 months	Change baseline – 24 months	Change baseline – 48 months
TSH	$n = 19$	$n = 17$	$n = 13$	$n = 14$	$n = 11$
Median [Q1–Q3] (mU/L)	1.4 [0.4–3.0]	2.1 [0.1–3.3]	0.6 [0.3–2.7]		
Mean ± SD (mU/L)				-0.3 ± 2.0 $p = 0.573$[2]	0.2 ± 2.2 $p = 0.782$[2]
fT4	$n = 16$	$n = 14$	$n = 10$	$n = 10$	$n = 8$
Mean ± SD (pmol/L)	17.4 ± 4.1	18.6 ± 4.6	17.4 ± 7.1	-1.2 ± 3.8 $p = 0.338$[2]	-0.9 ± 3.5 $p = 0.489$[2]

RYGB Roux-en-Y gastric bypass, *TSH* thyroid-stimulating hormone, *fT4* free thyroxine, *SD* standard deviation

[1]Excluding one patient with extirpation hypophysis adenoma

[2]Paired *t*-test

patients no change or an increase in dosage was necessary [6, 11, 12, 18, 19]. Julià et al. showed a difference in use of levothyroxine in the first 2 years after surgery: an early decrease in daily levothyroxine dose requirement after SG and an unpredictable response after RYGB [10]. Yet, other studies did not find significant differences in the postsurgical variation of levothyroxine dosage among SG and RYGB [6, 11, 18]. Although in our study the number of patients after SG was small, we found a higher median DDD LT4 from 12 months after SG compared to baseline. Median values of DDD LT4 in patients after SG were lower than after RYGB.

In our study, we did not find significant changes in TSH and fT4 levels 24 and 48 months after RYGB, indicating proper adjustment of levothyroxine dosing. Two years after SG and RYGB, Julià et al. also observed no change in TSH in hypothyroid patients [10]. However, in short-term studies in patients with hypothyroidism, TSH levels significantly decreased in the first year following SG and RYGB [5, 6], whereas fT4 remained stable [5].

Based on the results of our study, we advise frequent monitoring of TSH and fT4 in the first 2 years after bariatric surgery. The dose of levothyroxine should be adjusted accordingly. After this time period, the frequency of monitoring may be reduced, for instance, to once a year.

This study has some limitations. It was a retrospective analysis in a small number of patients. In this study, data on BMI, TSH, and fT4 were not always available at all time points. For that reason, the dose of levothyroxine could not be related to bodyweight and it was not possible to assess a correlation between TSH and BMI. The sample size, however, is similar to previous studies. To explore the use of levothyroxine, dispensing data from patient's pharmacies has been utilized. Yet, there may be a discrepancy between the patient's actual use of medication and the use assessed by dispensing information. Nevertheless, to determine the change in levothyroxine use over time, dispensing data should be an adequate substitute for the actual use of medication.

Conclusion

Four years after bariatric surgery, no change in the median DDD LT4 was observed compared to presurgery. However, the influence of bariatric surgery on the use of levothyroxine can be different in the individual patient. Dosages of levothyroxine may decrease, increase, or stay the same. Bariatric surgery led to frequent dose adjustments during the first 2 years after surgery. Nevertheless, 24–48 months after surgery in the majority of patients, the dosage remained stable. Compared to presurgical levels, there was no significant change in TSH and fT4 48 months after RYGB. In the first 2 years after surgery, clinicians should frequently monitor TSH and fT4 for individual dose adjustment of LT4. Thereafter, the frequency of monitoring may be decreased.

Author Contribution All authors approved the final version of the manuscript.

Declarations

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest The authors declare no competing interests.

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