



# Changes in Thyroid Replacement Therapy after Bariatric Surgery: Differences between Laparoscopic Roux-en-Y Gastric Bypass and Laparoscopic Sleeve Gastrectomy

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Published online: 25 April 2019  
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## Abstract

**Introduction** Levothyroxine (LT4) requirements can presumably be modified differently after laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG). The present study compared changes in LT4 dose in hypothyroid subjects undergoing LRYGB or LSG 2 years after the procedure.

**Material and Methods** A 2-year follow-up observational study was conducted in a prospective cohort of obese patients who had undergone bariatric surgery and were receiving LT4. Indication for the type of surgical procedure was based on clinical criteria. Repeated measures ANOVA models were used to examine differences within and between groups.

**Results** Thirty-five consecutive patients were included for analysis: 22 LRYGB and 13 LSG. Total daily LT4 dosage decreased in the LSG group ( $133.7 \pm 50.3$  mcg/day at baseline to  $104.3 \pm 43.3$  mcg/day at 2 years;  $p = 0.047$ ) whereas it remained stable in the LRYGB group ( $129.5 \pm 46.1$  mcg/day at baseline to  $125.2 \pm 55.7$  mcg/day at 2 years;  $p = 1.000$ ). Differences between groups became significant at 24 months. Daily weight-based LT4 dose increased in the LRYGB group ( $1.11 \pm 0.38$  mcg/kg day at baseline to  $1.57 \pm 0.74$  mcg/kg day at 2 years;  $p = 0.005$ ) with no significant changes in the LSG group ( $1.15 \pm 0.35$  mcg/kg day at baseline vs  $1.11 \pm 0.49$  mcg/kg day at 2 years;  $p = 1.000$ ).

**Conclusion** LRYGB and LSG showed different changes in LT4 requirements 2 years after surgery. There was an early decrease in daily total LT4 dose requirements after LSG, which suggests an early preventive reduction to be validated in future studies.

**Keywords** Bariatric surgery · Gastric bypass · Sleeve gastrectomy · Hypothyroidism · Thyroxine

## Introduction

Obesity is associated with several hormonal disorders including thyroid dysfunction [1], with the use of levothyroxine (LT4) being more frequent in this population [2–4]. Furthermore, the prevalence of obesity is increasing [5] and, given the lack of effective medical strategies, the demand for bariatric surgery has been rising worldwide in the last decade.

Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) are the two most frequent procedures currently used for bariatric surgery in most countries [6, 7]. LSG is relatively new as a stand-alone procedure for weight loss in patients with morbid obesity; however, its technical simplicity and similar short-term results to those of LRYGB in terms of weight loss and comorbidity improvement render the most widely used bariatric surgery technique since 2013 in the USA [6].

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Both techniques, LSG and LRYGB, along with weight loss can presumably modify LT4 requirements. LT4 is a lipophilic drug absorbed mainly in the upper and lower jejunioileal segments (~53%). Both procedures entail bypass of almost the entire stomach, which results in a reduction in acid contact with oral LT4 that may cause changes in drug solubility and dissolution [8]. Moreover, LRYGB, a technique with a malabsorptive component, involves shortening of the small intestine that might cause a drop in drug absorption and exposure to bile salt. Finally, LT4 pharmacokinetics could be affected by changes in body mass composition after surgery. Despite this, few data regarding changes in LT4 requirements after LRYGB and LSG are available [4, 9–11]. Albeit a frequent scenario in clinical practice, recommendations on thyroid replacement therapy management after bariatric surgery are lacking.

The present study aimed to compare changes in LT4 dosage, in terms of total daily dose and weight-based dosage, in the first 2 years after bariatric surgery with two different techniques, LRYGB and LSG, in patients with morbid obesity and hypothyroidism.

## Material and Methods

This 2-year follow-up observational study was conducted in a prospective cohort of patients with obesity who underwent bariatric surgery between January 2004 and December 2015 at Hospital del Mar, Barcelona. Patients were aged between 18 and 60 years and met the 1991 bariatric surgery criteria of the National Institutes of Health [3]. Patients who were receiving thyroid replacement therapy on preoperative evaluation were included in the study, regardless of the hypothyroidism aetiology which was unknown in many patients. The Ethics Committee of our Institution approved the protocol in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided their written informed consent for the procedure and the study.

Patients were evaluated preoperatively and at 3, 6, 12, 18 and 24 months post-surgery. Protocol visits included measurements of weight, waist and hip circumferences and blood pressure, daily LT4 dose and laboratory tests for serum thyrotropin (TSH) and free thyroxine (fT4). Thyroid autoimmunity determination was not standardised. Use of omeprazole or ferrous sulphate was recorded.

## Thyroid Function Evaluation

The endocrinologist of the Bariatric Surgery Unit managed the LT4 dosage based on laboratory results and on clinical evaluation during the preoperative and follow-up periods. Weight-based daily dose of LT4 was calculated at each visit.

## Anthropometric and Biochemical Measurements

Body mass index (BMI) was calculated as weight in kilogrammes divided by the square of height in meters, and the percentage of excess weight loss (EWL) was based on excess weight compared to weight corresponding to a BMI of 25 kg/m<sup>2</sup> for each patient [12].

At 8 a.m. after an overnight fast, blood samples were collected before the administration of LT4 tablets. TSH and fT4 were determined by cobas 8000 e801 (Roche Diagnostics, Tokyo, Japan). Normal TSH was defined as 0.3–4.2 mIU/ml, and normal fT4 as 0.8–1.8 ng/dl.

## Surgical Techniques

Indication for the type of surgical procedure (LSG or LRYGB) was based on clinical criteria and the consensus of the Bariatric Surgery Unit.

The LRYGB technique involved a 150-cm antecolic Roux limb with a 25-mm circular pouch-jejunostomy and exclusion of 50 cm of the proximal jejunum. In LSG, the longitudinal resection of the stomach from the angle of His to approximately 5 cm proximal to the pylorus was performed using a 36 French bougie inserted along the lesser curvature. The same team of surgeons performed all the procedures.

## Statistical Analysis

Data were expressed as mean ± standard deviation for continuous variables following a normal distribution, as median with interquartile range for continuous variables with a non-normal distribution and as percentages and frequencies for categorical variables. Normality of the models was evaluated visually and using the Kolmogorov-Smirnov test. For skewed variables (TSH), a logarithmic transformation was used to achieve normality. Student's *t* test was performed to assess differences between two means. Chi-square or Fisher's exact tests were used to evaluate the degree of association between categorical variables. Repeated measures ANOVA models were used to examine differences among changes in LT4 dose during follow-up within and between study groups. A *p* value < 0.05 was considered statistically significant. Statistical analysis was made by SPSS (version 25 for Windows; SPSS Chicago, IL).

## Results

Between January 2004 and December 2015, 463 patients underwent bariatric surgery at our hospital. Thirty-five (35/463, 7.6%) were treated preoperatively for hypothyroidism with LT4 and were included for analysis. Of these, 22 (62.8%) underwent LRYGB and 13 (37.1%) LSG. All

**Table 1** Clinical characteristics of patients undergoing LRYGB or LSG

	LRYGB ( <i>n</i> = 22)	LSG ( <i>n</i> = 13)	<i>p</i>
Age (years) mean ± SD	45.3 ± 9.3	45.0 ± 11.1	0.938
Women, <i>n</i> (%)	20 (90.9)	12 (92.3)	0.678
BMI (kg/m <sup>2</sup> ) mean ± SD	44.7 ± 3.8	40.9 ± 5.0	0.015
Diabetes mellitus, <i>n</i> (%)	6 (27.3)	3 (23.1)	0.557
Hypertension, <i>n</i> (%)	6 (27.3)	6 (46.2)	0.220
Dyslipidaemia, <i>n</i> (%)	7 (31.8)	3 (23.1)	0.440
Daily total LT4 dose (mcg/day) mean ± SD	129.5 ± 45.0	133.7 ± 50.3	0.805
Daily weight-based LT4 dose (mcg/kg day) mean ± SD	1.10 ± 0.37	1.20 ± 0.36	0.438
TSH (mIU/ml), median (interquartile range)	2.82 (1.17–4.76)	3.08 (0.51–4.79)	0.897
fT4 (ng/dl) mean ± SD	1.73 ± 2.10	1.38 ± 0.24	0.551
Omeprazole, <i>n</i> (%)	22 (100)	13 (100)	1.000
Ferrous sulphate, <i>n</i> (%)	6 (27.3)	3 (23.1)	1.000

LRYGB laparoscopic Roux-en-Y gastric bypass, LSG laparoscopic sleeve gastrectomy, BMI body mass index, LT4 levothyroxine, TSH thyrotropin, fT4 free thyroxine

patients included in the present study completed a 2-year follow-up.

At baseline, 91.4% of hypothyroid patients were women, with mean age  $45.2 \pm 9.9$  years and BMI  $42 \pm 4.4$  kg/m<sup>2</sup>. Except for BMI, which was higher in the LRYGB group, no statistically significant differences existed in baseline characteristics between subjects on LRYGB and those on LSG (Table 1).

During follow-up, no significant differences in percentage of excess weight loss were detected between groups ( $p = 0.76$ ) (Fig. 1).

### Total Daily LT4 Dose

Evolution of total daily LT4 dosage differed between the two surgical techniques ( $p = 0.046$ ): it decreased significantly in the LSG group ( $133.7 \pm 50.3$  mcg/day at baseline to  $104.3 \pm 43.3$  mcg/day at 2 years;  $p = 0.047$ ) whereas it remained stable in the LRYGB group ( $129.5 \pm 46.1$  mcg/day at baseline to  $125.2 \pm 55.7$  mcg/day at 2 years;  $p = 1.000$ ). Differences

became significant between groups at 24 months of follow-up (Fig. 2).

The percentage of patients with reduction, increase or no change in total LT4 dose requirements was not statistically significant between groups (Table 2).

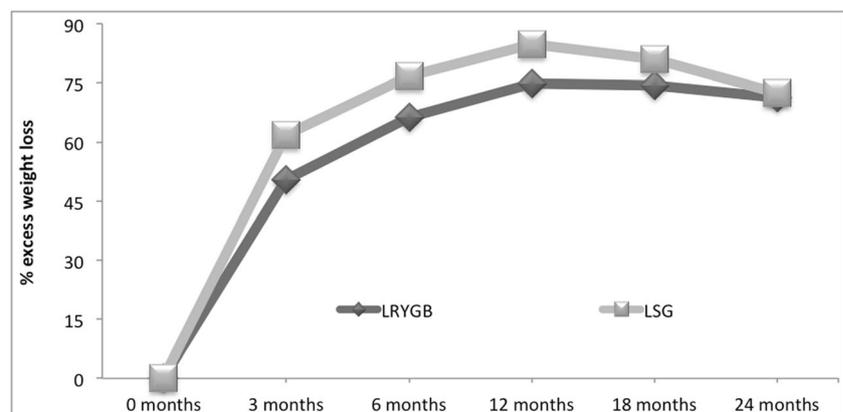
### Daily Weight-Based LT4 Dose

Changes in daily weight-based LT4 dose also differed between groups during follow-up ( $p = 0.005$ ), increasing in the LRYGB group ( $1.11 \pm 0.38$  mcg/kg d at baseline to  $1.57 \pm 0.74$  mcg/kg d at 2 years;  $p = 0.005$ ) with no significant changes in the LSG group ( $1.15 \pm 0.35$  mcg/kg d at baseline to  $1.11 \pm 0.49$  mcg/kg d at 2 years;  $p = 1.000$ ). Differences between groups became significant at 18 months of follow-up (Fig. 3).

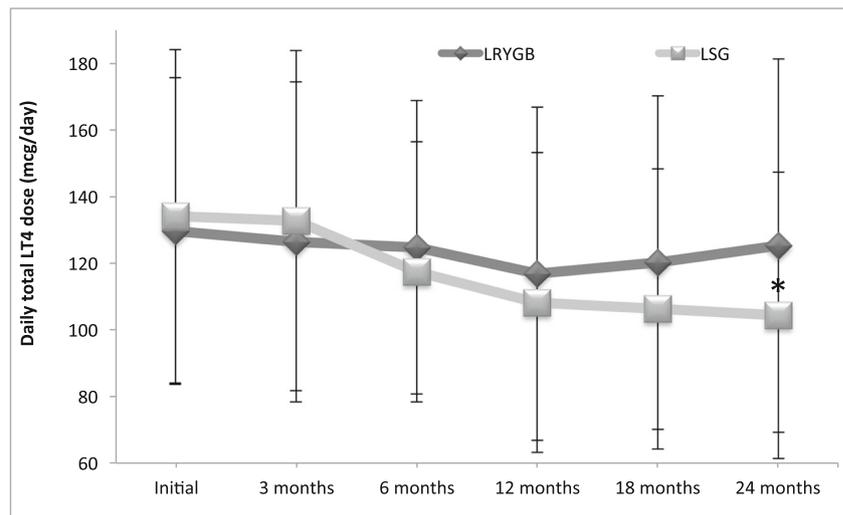
### TSH Levels

No differences in median TSH values were observed during follow-up between groups. The median TSH value at 3 months

**Fig. 1** Percentage of excess weight loss after LRYGB and LSG. \*Differences between groups from initial value ( $p < 0.05$ ).  $p = 0.76$  when comparing the evolution of the %EWL during follow-up. %EWL: percentage of excess weight loss; LRYGB: laparoscopic Roux-en-Y gastric bypass; LSG: laparoscopic sleeve gastrectomy



**Fig. 2** Postoperative changes in total LT4 requirements after LRYGB and LSG. \*Differences in the evolution of total LT4 dose between groups ( $p < 0.05$ ).  $p = 0.046$  when comparing the evolution of the total LT4 dose between groups. LT4: levothyroxine; LRYGB: laparoscopic Roux-en-Y gastric bypass; LSG: laparoscopic sleeve gastrectomy



in the LSG group was below our laboratory reference value (Fig. 4).

## Discussion

The present study showed variations in LT4 requirements after two bariatric surgery procedures, LSG and LRYGB, in a 2-year follow-up. A decrease in daily total LT4 dose after LSG was found with no changes in weight-based LT4 dose. In contrast, an increase was observed in daily weight-based LT4 dose after LRYGB with no changes in daily total LT4 dose.

To date, only four studies have reported the evolution of thyroid replacement therapy after bariatric surgery in patients who underwent LSG or LRYGB [4, 9–11]. Comparisons with the present study are difficult owing to the heterogeneous clinical follow-up and the low number of LSG procedures included. Moreover, only two studies [4, 11] compared both procedures directly. Sundaram et al. [4] included 74 patients, most of them operated on with LRYGB (73%) and a low proportion of LSG procedures (11%). The proportion of patients who required a reduction in total LT4 dose was higher in the LSG group (50% in the LSG group vs 22% in the LRYGB group) whereas the ratio of patients requiring an increase in weight-based LT4 dose was higher in the LRYGB group (85 and 66% in LRYGB and LSG groups, respectively),

**Table 2** Postoperative changes in total LT4 requirements after bariatric surgery

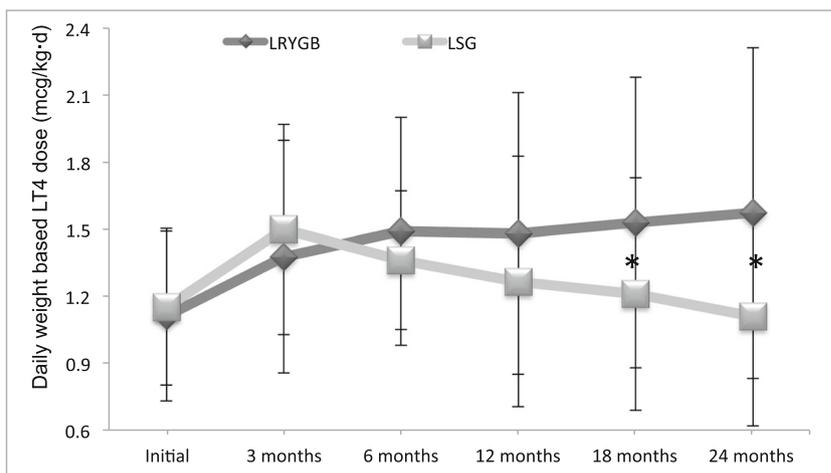
	LRYGB (n = 22)	LSG (n = 13)	
Reduced, n (%)	9 (40.9)	8 (61.5)	$p = 0.213$
No change, n (%)	9 (40.9)	5 (38.5)	
Increased, n (%)	4 (18.2)	0 (0.0)	

LRYGB laparoscopic Roux-en-Y gastric bypass, LSG laparoscopic sleeve gastrectomy

concurring with the results of the present study. Contrasting with our results, two-thirds of patients who underwent LSG had their weight-based LT4 dose increased. This could be explained by the variable follow-up period that ranged from 3 to 108 months, including patients with a very short follow-up. In this respect, we found an increase in daily weight-based LT4 dose in the first 3–6 months post-LSG, probably due to a lack of early dose adjustment considering the new weight. A recent study also compared both surgical techniques without showing differences in total and weight-based LT4 dose at 1 year of follow-up [11]. These results are similar to those of the present study at 1 year of follow-up, since differences between surgical procedures were only achieved at 18 and 24 months post-surgery, when the LT4 dose was adjusted and stable. Moreover, those authors compared LRYGB with LSG and lap banding, grouping patients who underwent the two last procedures. Nevertheless, LT4 requirements could presumably differ between LSG and lap banding taking into account that LSG seems to accelerate stomach and small bowel motility [12] while, in contrast, lap banding delays gastric emptying [13].

Other studies on thyroid replacement therapy did not make any comparisons between LSG and LRYGB or included patients operated on with only one of the procedures. Fierabacci et al. [9], in a study that included 60% of LRYGB procedures, described an increase in weight-based LT4 dose from 1.1 to 1.4 mcg/kg d; the results are similar to those observed in our study in the LRYGB group. Two studies that exclusively included patients undergoing LRYGB [14, 15] reported no absolute changes in total LT4 dosage but did observe a reduction in total LT4 dose in 35 and 43% of subjects, similar to the 40.9% observed in patients operated on with LRYGB in the present study. Finally, studies carried out mostly or exclusively in patients undergoing LSG [10, 16] reported results consistent with those observed in our LSG group: a daily total LT4 dose reduction. Aggarwal et al. [16] referred a drop in

**Fig. 3** Changes in daily weight-based LT4 dose evolution after LRYGB and LSG. \*Differences in the evolution of weight-based LT4 dose between groups ( $p < 0.05$ ).  $p = 0.005$  when the evolution of the weight-based LT4 dose was compared between groups. LT4: levothyroxine; mcg: microgram; kg: kilogramme; LRYGB: laparoscopic Roux-en-Y gastric bypass; LSG: laparoscopic sleeve gastrectomy



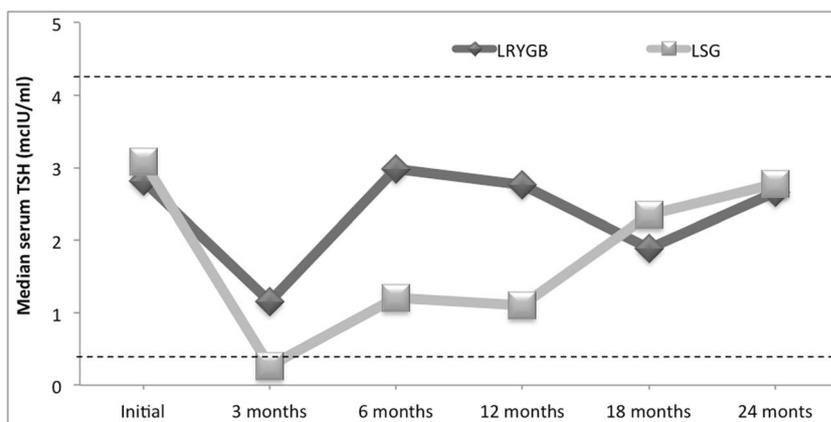
LT4 requirements with a mean reduction of 36.15 mcg/day (–28.78%) at the 18-month follow-up. These results are similar to the decrease in total LT4 dose of 29.6 mcg/day (–22.11%) following LSG observed in the present study.

Different factors may play a role in LT4 dose requirements after bariatric surgery. Firstly, LT4 absorption can be altered or improved by different mechanisms owing to the new anatomic gastrointestinal configuration. In this respect, some case reports demonstrated diminished absorption of the LT4 tablet after jejunoileal bypass [8] and LRYGB [17, 18]; however, larger studies [19, 20] evaluating changes in LT4 absorption after bariatric surgery reported an improvement in LT4 absorption following LSG and no change after LRYGB. Those authors hypothesised that LT4 is absorbed mainly in the distal jejunum and ileum given that absorption is not affected after LRYGB or biliopancreatic diversion. They also suggest that the enhanced absorption after LSG might be due to absence of stomach acids that do not neutralise the administered basic LT4 solution, absence of bile salts and changes in intestinal microbiota [19, 20]. Nevertheless, Nakatani et al. demonstrated that bile salts increase after LRYGB and LSG [21]. Secondly, weight loss after bariatric surgery [9] is expected to reduce post-operative LT4

requirements [22]. It has been postulated that lean body mass, which is involved in thyroxine degradation, is the best correlate of LT4 requirements [23]. A recent study [9] that assessed body composition in 20 hypothyroid patients with obesity after bariatric surgery showed that LT4 dose relative to lean body mass remained unchanged while LT4 dose relative to fat body mass increased by 63%. It must be taken into account that, after bariatric surgery, weight loss is associated with a drop in fat mass, accompanied by a loss of lean body mass to a lesser extent at a 3:1 ratio [24]. Therefore, since there is a reduction in total lean body mass after surgery, a reduction in total LT4 dose would be expected, and as proportionally more fat mass than muscle is lost, an increase in weight-based LT4 dose should be expected.

It is conceivable that the decrease in total LT4 dose after LSG can be ascribed to the increased absorption and modest reduction in lean body mass after surgery and that this reduction in total LT4 dose combined with the higher proportion of fat mass loss results in a weight-based dose after LSG similar to the dose before the surgery. Moreover, the absorption mechanism seems to be predominant. This interpretation is supported by the finding that a drop in total LT4 dose is evident at 3 months post-procedure when there has not yet been major

**Fig. 4** Changes in TSH values after LRYGB and LSG. \*Differences in median serum TSH between groups ( $p < 0.05$ ). Normal serum TSH values in our laboratory: 0.3–4.2 mIU/ml. TSH: thyrotropin; LRYGB: laparoscopic Roux-en-Y gastric bypass; LSG: laparoscopic sleeve gastrectomy



weight loss. In contrast, after LRYGB the increased weight-based LT4 dose could be explained by unaltered absorption and predominant fat mass reduction. After LRYGB, total LT4 dose was not stable in all patients and 40.9% of them showed a drop in their requirements. This heterogeneity in total LT4 dose after LRYGB could be attributed to different rates of lean body mass loss due to physical activity after bariatric surgery [25, 26].

Another interesting finding of the present study was the drop in TSH levels 3 months after surgery in half of the LSG patients, indicating that these patients were overdosed owing to a delay in LT4 adjustment. These results suggest that LT4 dose adjustment should be started just before LSG, with close monitoring of thyroid function.

The present study had some limitations. Firstly, it was a retrospective analysis with a small number of patients. Secondly, a moderate heterogeneity in LT4 requirements has been detected. A source of heterogeneity might be the aetiology of hypothyroidism, which was not available in most patients. Patients with autoimmune hypothyroidism are known to have different baseline LT4 requirements depending on the thyroid functionality. Moreover, a progressive decline in thyroid function that causes an increase in total LT4 requirements have been described in patients with autoimmune hypothyroidism operated on bariatric surgery [9, 15]. Nevertheless, the sample size and variability in hormone replacement therapy requirements are similar to previous studies. Another limitation was that the contribution of lean body mass loss after bariatric surgery to the change in LT4 dose could not be evaluated since body mass composition was not assessed.

## Conclusion

In patients with morbid obesity and hypothyroidism under replacement therapy, different bariatric surgery techniques are associated with different changes in LT4 requirements in the first 2 years after surgery: an early decrease in daily total LT4 dose requirements after LSG and an unpredictable response after LRYGB. These findings suggest an early preventive reduction in total LT4 dose only after LSG that should be validated in future studies. Above all, it is advisable to closely monitor thyroid function in these patients in the first 2 years after bariatric surgery.

**Acknowledgements** We thank Miss Christine O'Hara for the review of the English version of the manuscript. CIBEROBN and CIBERESP are an initiative of the Instituto de Salud Carlos III (ISCIII).

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical 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 Declaration of Helsinki and its later amendments or comparable ethical standards.

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

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