TSH normalization in bariatric surgery patients after the switch from L-thyroxine in tablet to an oral liquid formulation.

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Abstract

Objective: Drug malabsorption is one of the potential troubles after bariatric surgery. Evidence for diminished Levothyroxine (L-T4) absorption has been reported in patients after bariatric surgery.

Methods: This study reports 17 cases of hypothyroid patients [who were well replaced with thyroxine tablets (for > 1 year) to euthyroid thyrotropin (TSH) levels before surgery (13 Roux-en-Y gastric bypass (RYGB); 4 biliary pancreatic diversions (BPD)]. From 3 to 8 months after surgery, these patients had elevated TSH levels. Patients were then switched from oral tablets to a liquid L-T4 formulation (with the same dosage, 30 minutes before breakfast).

Results: Two-three months after the switch, TSH was significantly reduced both in patients treated with RYGB, as in those treated with BPD, while FT4 and FT3 levels were not significantly changed (RYGB group, TSH μIU/mL: 7.58 ± 3.07 *vs* 3.808 ± 1.83, $P < 0.001$; BPD group, TSH μIU/mL: 8.82 ± 2.76 *vs* 3.12 ± 1.33, $P < 0.01$).

Conclusions: These results first show that liquid L-T4 could prevent the problem of malabsorption in patients with BPD, and confirm those of previous studies in patients submitted to RYGB, suggesting that the L-T4 oral liquid formulation could circumvent malabsorption after bariatric surgery.

Introduction

In the past decades, demand for bariatric surgery has globally increased, and about 101 000-180 000 surgeries are performed annually in the US alone [1-4].

Surgical procedures include different types of operations: a- purely restrictive (gastric banding, gastroplasty); b- restrictive with limitation of digestive capacity (sleeve gastrectomy); c- restrictive/malabsorptive (gastric bypass); d- purely malabsorptive (biliopancreatic diversion, jejunoileal bypass). Malabsorptive procedures can lead to nutritional deficiencies, [5] or drug malabsorption [6].

People with severe obesity receiving bariatric surgery often have multiple medical comorbidities requiring multidrug treatments. After diversionary procedures drug malabsorption is a potential concern. In fact nearly all oral agents are absorbed mainly in the small intestine, which is bypassed in several bariatric procedures. Other factors that impair drug absorption are: diminished opportunity for mucosal exposure, and changes in drug solubility and dissolution resulting from alterations in intestinal pH [6]. The most consistent evidence for diminished absorption has been found for cyclosporine, phenytoin, rifampin and thyroxine [7].

The prevalence of hypothyroidism in patients with morbid obesity range fro 12 to 25% [8, 9]**.**

Moreover, in obese males, insulin resistance is significantly related with thyroid function impairment [10].

Levothyroxine (L-T4) is the gold standard and effective replacement therapy for patients with hypothyroidism for autoimmune thyroiditis or after radioablative therapies, or suppressive therapy after surgical removal of thyroid cancer [11-13].

To obtain an effective therapy, some requisites are necessary, as L-T4 products are of optimal quality, [14] patients' compliance, [15] dissolution of the hormone in the stomach, [16] adequate

absorption in the intestines, [17, 18] and normal metabolism [19]. Several diseases and drugs affect the absorption and metabolism of L-T4 [20]. Gastritis causes L-T4 malabsorption, by altering the gastric juice pH, thereby affecting L-T4 dissolution [21-23].

Evidence for diminished L-T4 absorption has been reported in patients after bariatric surgery [24, 25].

Recently four cases of hypothyroid patients who were well replaced with thyroxine tablets to euthyroid thyrotropin (TSH) levels prior to Roux-en-Y gastric bypass (RYGB) surgery, and developed elevated TSH levels after the surgery, have been reported [26]. In these patients TSH responded reversibly to switching from L-T4 treatment with oral tablets to a liquid formulation.

Here, we report our experience with the use of liquid L-T4 in patients with bariatric surgery who had developed elevated TSH levels after the surgery.

Methods

We have evaluated 17 out-patients with morbid obesity, recruited from the end of 2013 to first months of 2015 (10 females, 7 males; age 31-59 years), who were diagnosed with hypothyroidism (11 affected by autoimmune thyroiditis, and 6 treated with total thyroidectomy for multinodular goiter) before the bariatric surgery, and were well replaced with thyroxine tablets (for >1 year) to euthyroid TSH, free thyroxine (FT4) and free triiodothyronine (FT3) levels. Thirteen patients were treated with RYGB, [27] while 4 with biliary pancreatic diversions (BPD) [28].

The RYGB group included 9 women and 4 men, mean age of 45 ± 9 years; body mass index (BMI) (before surgery) in this group was ≥ 40 kg/m^2 (mean, 42.9 ± 3.5 kg/m^2). The hypothyroidism in this group was due in 9 cases to autoimmune thyroiditis, and in 4 to total thyroidectomy for multinodular goiter.

The BPD group included 1 woman and 3 men, mean age of 42 ± 7 years; BMI (before surgery) in this group was ≥ 40 kg/m^2 (mean, 44.1 ± 4.4 kg/m^2). The hypothyroidism in this group was due in 2 cases to autoimmune thyroiditis, and in 2 to total thyroidectomy for multinodular goiter. From 3 to 8 months after surgery, these patients had elevated TSH levels.

We decided to treat these patients with oral liquid L-T4. Patients were switched from oral tablets to a liquid formulation of L-T4 (Tirosint® fiala monouso, IBSA Farmaceutici Italia) (with the same dosage, 30 minutes before breakfast). Two-three months after the switch, circulating TSH, FT4 and FT3 were re-evaluated. Clinical data and medication information were collected before recruitment from medical records. Patients with other possible causes of altered L-T4 absorption (such as atrophic gastritis, and use of medications associated with impaired L-T4 absorption), were not evaluated.

All patients signed an informed consent. The study was approved by the Ethical Committee.

Serum FT4 (normal range, 0.7 - 1.7 ng/dL), FT3 (normal range, 2.7 - 4.7 pg/ml), and serum TSH (normal range, 0.4 - 4 μIU/mL) were determined in all samples by electrochemiluminescence immunoassay (Roche Corporation, Indianapolis, IN, USA). The concentration of each hormone at baseline, and after the switch, was calculated as a mean of the two samples collected before the L-T4 dose.

Data analysis

Values are given as mean ± SD for normally distributed variables, otherwise as median and [interquartile range]. Mean group values were compared by using one-way analysis of variance (ANOVA) for normally distributed variables (age and BMI). Post-hoc comparisons on normally distributed variables were carried out using the Bonferroni-Dunn test. Proportions were

compared by the χ^2 test. Simple regression was used to evaluate the correlation among changes of TSH (after the switch - baseline), *vs* changes of FT4, or FT3.

Results

After bariatric surgery (at the time of TSH re-evaluation, 3 to 8 months after surgery) in the RYGB group BMI was reduced from 42.9 ± 3.5 kg/m^2 to 37.9 ± 2.7 kg/m^2 ($P < 0.01$), while in the BPD group BMI was reduced from 44.1 ± 4.4 kg/m^2 to 38.6 ± 3.7 kg/m^2 ($P < 0.01$).

Although the reduction of body weight, with the same L-T4 dosage (mean 192 ± 32 μg/day) in tablets, 30 minutes before breakfast, after bariatric surgery TSH was increased in both groups (**Table 1**), while FT4 and FT3 levels were not significantly changed. The only symptom observed in patients with high TSH was fatigue in 11/17 (65%) of patients**.** Then patients were switched from oral tablets to a liquid formulation of L-T4 (Tirosint® fiala monouso, IBSA Farmaceutici Italia) (with the same dosage, 30 minutes before breakfast). Two-three months after the switch, when circulating TSH, FT4 and FT3 were re-evaluated, in the RYGB BMI was reduced from 37.9 ± 2.7 kg/m^2 to 36.3 ± 2.5 kg/m^2 ($P < 0.01$), while in the BPD group BMI was reduced from 38.6 ± 3.7 kg/m^2 to 37.9 ± 3.4 kg/m^2 ($P > 0.05$).

After the switch from oral tablets to a liquid formulation of L-T4, circulating TSH levels were significantly reduced in both groups, while FT4 and FT3 levels were not significantly changed (RYGB group, TSH μIU/mL: 7.58 ± 3.07 *vs* 3.808 ± 1.83, $P < 0.001$; BPD group, TSH μIU/mL: 8.82 ± 2.76 *vs* 3.12 ± 1.33, $P < 0.01$) (**Fig. 1**).

The comparison of TSH values before surgery, 3 to 8 months after surgery, and 2-3 months after the switch are shown in **Fig. 2**, and data show that the TSH values after the switch are higher, even if not significantly ($P = 0.064$), with respect to the TSH values before surgery.

A negative correlation between decrease of TSH (after the switch - baseline), *vs* the increase of FT4 (after the switch - baseline) was observed by simple regression (r = 0.754, *P* = 0.007) (Fig. 3). While no significant association was observed between changes of TSH (after the switch - baseline) and changes of FT3 (after the switch - baseline).

There was no significant difference between gender in changes of TSH values after surgery, or in the response to the switch to the liquid L-T4 formulation.

No patient before and after bariatric surgery, or after the switch had euthyroid sick syndrome [29].

Albumin levels were in the normal range (3.5 to 5.5 g/dL) in all patients before and after bariatric surgery, or after the switch.

Discussion

The abovementioned data suggest that the L-T4 oral liquid formulation could avoid the problem of the malabsorption after bariatric surgery. The obtained results first show that liquid L-T4 could prevent the problem of the malabsorption in patients with BPD, and confirm those obtained in a previous study in patients submitted to RYGB. The serum TSH levels in our patients (according to the selection criteria) was increased after bypass surgery, suggesting a malabsorption of L-T4, [24-26] in agreement with Azizi *et al.*, Bevan *et al.* and Pirola *et al.*

RYGB reduces the size of the stomach to a small pouch – about the size of an egg. It does this by stapling off a section of it. This reduces the amount of food patients can take in at meals. This pouch is then attached directly to the small intestine, by-passing most of the rest of the stomach and the upper part of the small intestine, and reducing the amount of fat and calories that are absorbed from the foods [30]. A recent review demonstrated that RYGB is associated with

diminished absorption of lypophilic drugs such as cyclosporine, phenytoin, rifampin and thyroxine [7].

BPD is a bariatric surgery for patients with severe obesity. The primary mechanism of weight loss with the BPD is malabsorption. BPD removes approximately 3/4 of the stomach to produce both restriction of food intake and reduction of acid output. Leaving enough upper stomach is important to maintain proper nutrition. The small intestine is then divided with one end attached to the stomach pouch to create what is called an "alimentary limb." All the food moves through this segment, however, not much is absorbed. The bile and pancreatic juices move through the "biliopancreatic limb," which is connected to the side of the intestine close to the end. This supplies digestive juice in the section of the intestine now called the "common limb." The surgeon varies the length of the common limb to regulate the amount of absorption of protein, fat and fat-soluble vitamins [31, 32]. A recent review demonstrated that also BPD is associated with diminished absorption of lypophilic drugs and thyroxine [31].

The mechanisms by which liquid L-T4 circumvent malabsorption in bariatric surgery remain to be studied. It has been suggested that absorption of thyroxine is greater with oral liquid formulations in patients after bariatric surgery [26]. In fact, normal gastric acid secretion is necessary for effective absorption of L-T4 [18] by dissolution of tablets, and drug dissolution and solubility may be altered by restrictive procedures that increase gastric pH in the newly created stomach pouch; this may occur in gastric bypass [7]. Since it has been shown that the liquid formulation of L-T4 is extremely effective to circumvent the problem of incomplete absorption of L-T4 caused by proton pump inhibitor-induced, [33] this formulation could also circumvent the pH alteration resulting from gastric bypass [34].

Furthermore the presence of alcohol in the L-T4 liquid formulation could also play a key role in thyroxine absorption. Indeed, oral mucosal is highly vascularised, and drugs that are absorbed

through the oral mucosal directly enter the systemic circulation, bypassing the gastrointestinal tract [35]. Further studies are needed to clarify these intriguing points.

The comparison of TSH values before surgery, after surgery, and 2-3 months after the switch show that the TSH values after the switch are higher (near to the statistical significance, $P = 0.064$), with respect to the TSH values before surgery. These results suggest that in patients with bariatric surgery a slight malabsorption persits even when the liquid L-T4 formulation is given. However, there was no significant difference in the decrease of TSH in RYGB group *vs* the BPD group, nor in females *vs* males.

In conclusion, the abovementioned data suggest that the L-T4 oral liquid formulation could circumvent L-T4 malabsorption both in patients submitted to BPD, as in those submitted to RYGB; further studies are needed to enlarge the number of participants and to clarify the implicated mechanisms .

Conflict of Interest Statement: PF: no conflict of interest; SMF: no conflict of interest; SC: no conflict of interest; UP: no conflict of interest; IR: no conflict of interest; RV: no conflict of interest; GN: no conflict of interest; SB: no conflict of interest; AA: 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 Helsinki declaration 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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Figure Legends

Figure 1. Change of TSH levels in RYGB group (**A**), or in the BPD group (**B**), after surgery, and 2-3 months after the switch from oral tablets to a liquid formulation of Levothyroxine (with the same dosage, 30 minutes before breakfast). There was no significant difference in the decrease of TSH in RYGB group, *vs* the BPD group.

Figure 2. Comparison of TSH values before surgery, 3 to 8 months after surgery, and 2-3 months after the switch in all bariatric patients, are shown. The TSH values (box-plot) after the switch are higher, even if not significantly ($P = 0.064$), with respect to the TSH values before surgery.

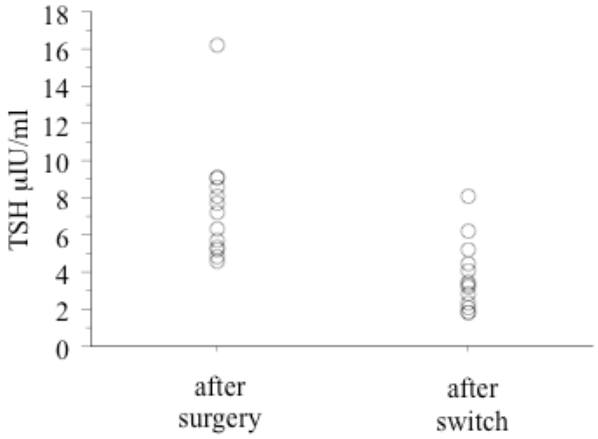
Figure 3. A negative correlation between decrease of TSH (after the switch - baseline) (TSH final – TSH basal), *vs* the increase of FT4 (after the switch - baseline) (FT4 final – FT4 basal), was observed by simple regression ($r = 0.754$, $P = 0.007$).

Table 1. TSH, FT4, FT3 levels before and after bariatric surgery.

	RYGB (before surgery)	RYGB (after surgery)	*P* value (by ANOVA)
TSH	2.21 ± 0.91	7.58 ± 3.07	< 0.001
FT4	1.27 ± 0.31	1.18 ± 0.37	ns
FT3	3.12 ± 0.91	2.98 ± 0.98	ns
	BPD (before surgery)	BPD (after surgery)	
TSH	2.65 ± 0.86	8.82 ± 2.76	0.005
FT4	1.31 ± 0.28	1.20 ± 0.36	ns
FT3	2.99 ± 0.92	2.87 ± 0.96	ns

Roux-en-Y gastric bypass (RYGB); Biliary pancreatic diversions (BPD). Serum TSH, normal range 0.4 – 4 μIU/mL; serum FT4, normal range 0.7 – 1.7 ng/dL; serum FT3, normal range 2.7 – 4.7 pg/mL.

a


18
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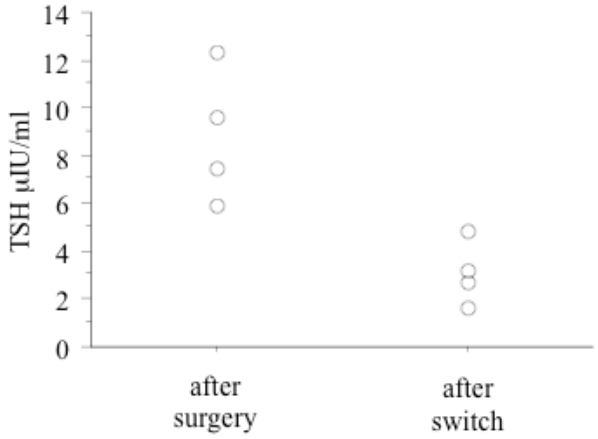
TSH µIU/ml
after surgery
after switch

b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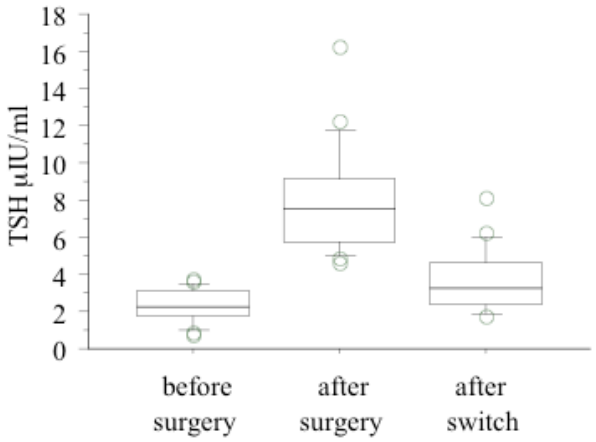
TSH µIU/ml
after surgery
after switch

Figure 1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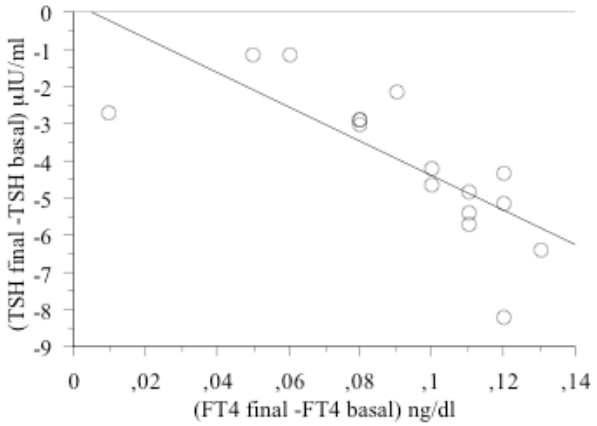
TSH µIU/ml
before surgery
after surgery
after switch

Figure 2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-4
-5
-6
-7
-8
-9
(TSH final -TSH basal) µIU/ml
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,02
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,08
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(FT4 final -FT4 basal) ng/dl

Figure 3