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CLINICAL RESEARCH

Levothyroxine Absorption in Morbidly Obese Patients Before and After Roux-En-Y Gastric Bypass (RYGB) Surgery

Ileana Gabriela Sanchez Rubio · Ana Luiza Galrão · Marco Aurelio Santo · Antonio Carlos Zanini · Geraldo Medeiros-Neto

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Abstract
Background Roux-en-Y gastric bypass (RYGB) modifies the anatomical structure of the upper intestine tract, reduces gastric acid secretion, and may impair LT4 absorption. The aim of this study was to evaluate the LT4 absorption in morbidly obese patients before and after RYGB.
Methods Thirty morbidly obese patients were divided in two groups: The NS group included 15 patients before RYGB surgery (BMI=43.1±4 kg/m^2), and the S group included 15 patients after surgery (BMI=37.3±4 kg/m^2). Two baseline samples were collected, and 600 μg of oral LT4 tablets were administered. Blood samples were collected at 30, 60, 120, 180, 240, 300, and 1440 min. Serum-free T4 (FT4), total T4 (TT4), and TSH were measured at each time point. The increase in TT4, FT4, and TSH (ΔTT4, ΔFT4, and ΔTSH) was calculated, subtracting from the baseline mean value.
Results The pharmacokinetics parameters regarding LT4 absorption, maximum ΔTT4, and area under the curve (AUC) of both ΔTT4 and ΔFT4 were significantly higher in the S group compared with the NS group ($p<0.05$). It was observed, however, that there was a significant delay in the absorption of LT4 in the S group. Basal serum TSH and leptin levels were higher in the NS group ($p=0.016$ and 0.026, respectively), whereas basal serum TT4, FT4, ΔTSH, and the AUC of ΔTSH were similar between groups.
Conclusions In this study, we have demonstrated that Roux-en-Y bypass surgery does not diminish LT4 absorption. A small but significant delayed absorption of LT4, however, was observed in patients after surgery.

Keywords L-Thyroxine absorption · Bariatric surgery · Morbid obesity · Roux-en-Y bypass

I. G. S. Rubio
Department of Biological Sciences,
Federal University of São Paulo,
Rua Prof. Artur Riedel 275, Eldorado,
Diadema, São Paulo 09972-270, Brazil

A. L. Galrão
Department of Medicine, Division of Endocrinology,
University of São Paulo Medical School,
Av Dr Arnaldo 455, 4A,
São Paulo, São Paulo 01246903, Brazil

M. A. Santo
Division of Surgery, University of São Paulo Medical School,
Av. Dr. Enéas de Carvalho Aguiar, 255,
São Paulo 05403-000, Brazil

A. C. Zanini
Department of Medicine,
University of São Paulo Medical School,
Av Dr Arnaldo 455,
São Paulo, São Paulo 01246-903, Brazil

G. Medeiros-Neto (✉)
Department of Medicine,
University of São Paulo Medical School,
Artur Ramos 96,
01454-903 São Paulo, Brazil
e-mail: medneto@uol.com.br

Introduction

Levothyroxine sodium (LT4) is an effective drug prescribed as replacement therapy for patients with hypothyroidism, after surgical removal of thyroid cancer and as a controversial suppressive therapy for nodular thyroid disease. Incidence rates of differentiated thyroid cancer of all sizes have increased both in men and women [1], as have the rates of autoimmune thyroiditis [2]. It is estimated that 3.7% of the US population have hypothyroidism, indicating

that a substantial amount of people are in continuous use of LT4 [3]. Papavramidis et al. [4] observed in morbidly obese patients a significant difference in thyroid function tests (FT3, FT4, and TSH) before and after vertical gastroplasty, but these changes were not considered of biological significance. Moreover, Marzullo et al. [5] demonstrated that elevated serum leptin levels are significantly associated with the presence of autoimmune thyroid disease in obese patients. Therefore, LT4 therapy may be prescribed to obese patients if subclinical or clinical hypothyroidism is present. The hypothetical defective absorption of LT4 after bariatric surgery could affect the daily doses of the administered L-T4 therapy.

Absorption of LT4 formulations approximates 80% of the oral dose [6]. It is reduced when LT4 is ingested concomitantly with other drugs, including aluminum hydroxide [7], cholestyramine [8], sucralfate [9], ferrous sulfate [10], calcium carbonate [11], sodium polystyrene sulfonate [12], as well as with coffee [13] and fiber supplements [14].

Intestinal absorption of LT4 depends primarily on its dissolution in gastric acid secretion. Therefore, absorption may be affected by *Helicobacter pylori* infection [15] and autoimmune gastritis [16]. There are substantial interindividual variations in LT4 requirements. These requirements are dependent on patient's age, gender and body size, lean body mass, body mass index (BMI), and body surface area [17–20].

The prevalence of obesity has increased to epidemic proportions [21]. Effective treatment may be achieved by bariatric surgeries, but these procedures are associated with several morbidities, such as gastrointestinal and nutritional complications [22]. It is possible that Roux-en-Y gastric bypass (RYGB), which bypasses almost the entire stomach, minimizes acid contact with oral LT4 and could impair absorption. The aim of this study was to evaluate the absorption of LT4 tablets in morbidly obese patients before and after RYGB in order to determine the need for adjustment of LT4 doses.

Subjects and Methods

Subjects

Patients were recruited from the Gastric Surgery Division of Hospital das Clínicas. Thirty morbidly obese patients (age range, 18–64 years) agreed to participate into the study. The patients were divided in two groups: the NS group (before surgery) included 15 patients (12 women and three men, mean age of 36±13 years) for whom RYGB surgery was planned. Body mass index (BMI) in this group was ≥40 kg/m^2 (mean, 43.1±4 kg/m^2). The S group (after surgery) included 15 patients (13 women and two men, mean age of 44.9±12 years, mean BMI of 37.3±4 kg/m^2) who had undergone RYGB 2–3 months before inclusion in the study.

Clinical data and medication information were collected before recruitment. Exclusion criteria included a previous diagnosis of thyroid cancer, diabetes mellitus using insulin, chronic or atrophic gastritis, and use of medications associated with impaired LT4 absorption.

Patients in the NS group used LT4 for thyroid nodular disease (n=11) or Hashimoto's thyroiditis with subclinical hypothyroidism (n=4), but the drug was suspended 2 months before the patients were referred for RYGB surgery. All 15 patients from the S group had a previous prescription for LT4 from their respective clinicians (all patients had thyroid nodular disease). The decision to introduce LT4 for the S patients was left for the attending physician after the RYGB surgery.

All patients signed an informed consent. The study was approved by the Ethical Committee of Hospital das Clínicas, University of São Paulo Medical School (CAPPesq no. 1039/07; ClinicalTrials ID no. NCT01189344).

Methods

Absorption of LT4 was measured using a previously described nonisotopic method [6]. After an overnight fast, a forearm intravenous catheter was inserted, and two blood samples were collected with a 30-min interval before administration of 600 μg of oral LT4. Blood samples were collected 30, 60, 120, 180, 240, 300, and 1,440 min (24 h) after administration of LT4. Patients fasted for 5 h after receiving the drug. They were then instructed to have a light meal in the evening and to return the next morning in a fasting state to collect the 24 h sample.

Serum-free T4 (FT4 normal range, 9–21.9 pmol/L), total T4 (TT4 normal range, 51.5–154.4 nmol/L), and serum TSH (normal range, 0.5–4 mU/L) were determined in all samples by electrochemiluminescence immunoassay (Roche Corporation, Indianapolis, IN, USA). The concentration of each hormone at baseline was calculated as a mean of the two samples collected before the LT4 dose. To correct for endogenous hormone synthesis, the incremental rise of each hormone concentration (ΔTT4, ΔFT4, and ΔTSH) was calculated by subtracting the basal value from the subsequent time intervals samples. To evaluate LT4 absorption, the area under the curve of ΔTT4 and ΔFT4 from baseline to 240 min and to 300 min (AUC_{240} and AUC_{300}) as well as the peaks of ΔTT4 and ΔFT4 concentrations were determined [13].

Serum leptin (lean individuals; BMI, 18–25 kg/m^2; normal range, men 3.8±1.8 ng/mL and women 7.4±3.7 ng/mL) was measured by Human Leptin Elisa Kit (Millipore, Billerica, MA, USA) in all patients before and after weight loss following the surgery.

Chronic autoimmune gastritis was ruled out by absence of clinical signs and negative antiparietal autoantibodies [16].

Statistical Analysis

Results are expressed as mean±standard deviation (SD). Analysis of variance and Tukey multiple comparison tests were performed to compare both groups at all time points. Results were also analyzed with Student's *t* test and Spearman correlation analysis. All tests were performed with a significance level of 5%.

Results

The weight of the patients in the NS group (113.5±17.6 kg) was significantly higher compared with the S group (96.2±15.5 kg, $p=0.008$). Similarly, BMI in the NS group was significantly higher (43.14±4.5 kg/m^2) versus the S group (37.34±4.61.2 kg/m^2, $p=0.0017$).

Serum TT4, FT4, and TSH data are summarized in Table 1. Levels of TT4 and FT4 started increasing within 30 min of LT4 ingestion and were not significantly different between the groups at any moment ($p=0.1$ and $p=0.46$, respectively). There was a significant delay in TT4 maximum value in the S group (294±18 min) when compared with the NS group (226±74 min, $p=0.015$). FT4 peaked at 218.6±89 min in the NS group and at 248±54 min in the S group ($p=0.28$). Both hormone concentrations decayed at 1,440 min. Levels of TSH were higher in the NS group when compared with the S group at all moments ($p=0.016$). In both groups, it declined 1,440 min after LT4 administration. Basal Serum leptin was significantly higher in the NS group (55.4±29.7 ng/mL) as compared with S group (29.7±15.28 ng/mL) ($p=0.026$) and positively correlates with BMI and TSH when all the patients (NS and S groups) were included.

Pharmacokinetic parameters evaluating LT4 absorption are presented in Table 2. Increases in TT4 (ΔTT4) and FT4 (ΔFT4) were higher in the S group when compared with the NS group ($p=0.018$ and $p=0.007$, respectively) (Fig. 1). ΔTT4 maximum value was higher in the S group ($p=0.04$ versus the NS group). No difference was observed in ΔFT4 peak between groups. The S group showed a tendency for a delay to reach maximum levels of ΔTT4 and ΔFT4 ($p=0.33$ and $p=0.12$, respectively), whereas ΔTSH values were similar in both groups at all moments ($p=0.66$; Fig. 2).

The ΔTT4-AUC$_{300}$ in the S group was higher as compared with the NS group ($p=0.027$). A tendency of this difference was also observed for the ΔTT4-AUC$_{240}$ ($p=0.059$; Table 2). The ΔFT4-AUC$_{240}$ and ΔFT4-AUC$_{300}$ were significantly higher in the S group when compared with the NS group ($p=0.033$ and $p=0.036$ respectively).

A significant and negative correlation between the ΔTT4 peak and BMI ($p=0.021$, $r=-0.47$) as well as ΔTT4-AUC$_{300}$ and BMI ($p=0.037$, $r=-0.435$) was observed. These results were obtained only when the whole group of 30 patients was analyzed.

Discussion

Intestinal absorption of LT4 is affected by reduced gastric secretion, concomitant ingestion of other medications, and also coffee. In this study, we evaluated the effect of RYGB surgery for weight reduction on the absorption of LT4 in two groups of individuals: the NS group (severe obese patients waiting for RYGB) and the S group (severely obese patients who had undergone RYGBwithin 3 months of surgery). We detected that the LT4 absorption was similar in both groups of patients.

A thorough review on intestinal absorption of LT4 has been published by Hays [23] and Hennemann et al. [24]. Studies with ^{131}I-LT4 have shown that intestinal absorption of LT4 takes place in part in the duodenum (~15%), but mostly in the upper and lower jejunoileal segments (~53%) [23]. It is maximal during the fasting state [25] but with some interindividual delay [17]. Cellular uptake of native lipophilic thyroxine is conducted by both passive diffusion

Table 1 Thyroid function tests at baseline and after 600 μg of oral LT4 in the NS and S groups

Parameter	Groups		*P* value
	Non-surgery (NS)	Surgery (S)	
Basal TT4 (nmol/L)	108.23±19.5	95.62±15.5	NS
Basal FT4 (pmol/L)	12.99±2.5	13.25±4.1	NS
Basal TSH (mU/L)	3.56±1.66	2.52±1.21	0.016[a]
Maximum TT4 (nmol/L)	170.9±23	182.11±49	NS
Time to maximum TT4 (minutes)	226±74	294±18	0.015[a]
Maximum FT4 (pmol/L)	26.22±7.1	29.91±10.1	NS
Time to maximum FT4 (minutes)	218.6±89	248±54	NS
ΔTSH (mIU/L)	−1.83	−1.78	NS
Basal serum leptin (ng/mL)	55.4±29.7	29.7±15.28	0.026[a]

TT4 total T4, *FT4* free T4, *ΔTSH* serum TSH levels at 24 h minus baseline levels

[a] Significant difference between groups

Table 2 Pharmacokinetics parameters of LT4 (600 μg) absorption in the NS and S groups

Parameter	Groups		*P* value
	Non-surgery (NS)	Surgery (S)	
Maximum ΔTT4 (nmol/L)	69.6±12	87.81±27	0.04[a]
Time to maximum ΔTT4 (minutes)	212.3±87	245.4±73	NS
AUC_{240} ΔTT4 (nmol/L)	10,560±2,621	13,090±3,610	NS
AUC_{300} ΔTT4 (nmol/L)	14,010±2,815	17,800±4,924	0.027[a]
Maximum ΔFT4 (nmol/L)	13.2±5	16.8±7	NS
Time to maximum ΔFT4 (minutes)	200.0±86	244±61	NS
AUC_{240} ΔFT4 (nmol/L)	1,986±599	2,650±981	0.033[a]
AUC_{300} ΔFT4 (nmol/L)	2,665±887	3,592±1,368	0.036[a]

ΔTT4 Increase in TT4; *ΔFT4* increase in FT4, calculated by subtracting the basal value from the peak value; AUC_{240} area under the curve up to 240 min of LT4 dose; AUC_{300} area under the curve up to 300 min of LT4 dose

[a] Significant difference between groups

and carrier-mediated processes, energy, temperature, and is also probably Na^+ dependent [24].

Maximal intestinal absorption of LT4 tablets occurs 2 h after ingestion [17] and depends on its dissolution in gastric acid secretion [15]. Impaired duodenal absorption due to low LT4 dissolution in the gastric cavity has been observed in patients with atrophic or chronic gastritis [15]. The RYGB consisted of transecting the upper stomach to create a small (≤30.0 ml) proximal gastric pouch, which was anastomosed to the proximal jejunum in a Roux-en-Y fashion. This bypasses almost the entire stomach so that there is a minimal contact of the LT4 with hydrochloric acid. Malabsorption of LT4 has been described in a few patients following jejunoileal bypass for morbid obesity [26, 27]. However, the methods for evaluating LT4 absorption in these studies were not convincing. Therefore, we decided to study morbidly obese patient's ability to absorb LT4 before and within 3 months of the surgical procedure using a precise nonisotopic methodology [6].

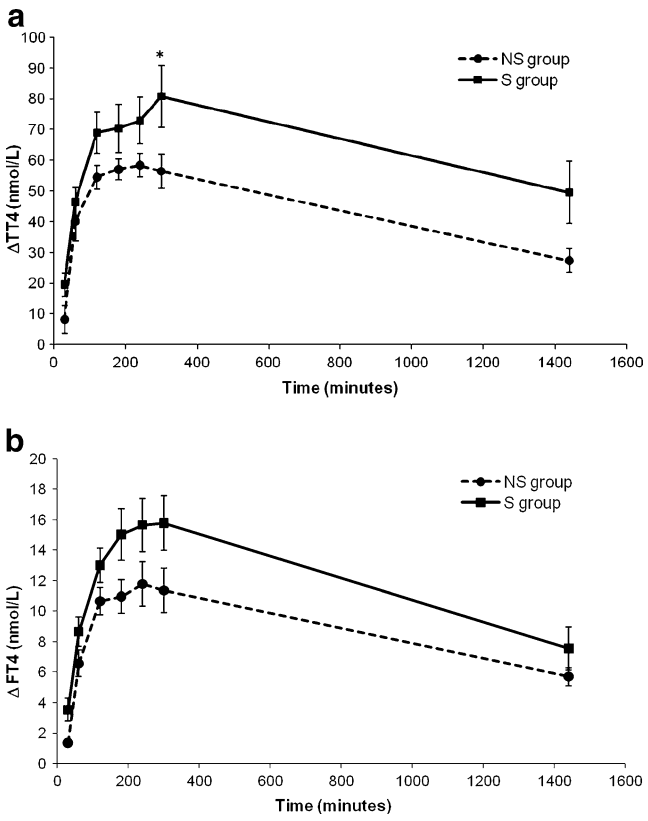

Fig. 1 Increase in **a** TT4 (ΔTT4) and **b** FT4 (ΔFT4) in patients before Roux-en-Y gastric bypass (RYGB) (NS group) and after RYGB surgery (S group). The values presented are means±SD, *$p<0.04$

In our study, mean weight and BMI reduction between 2 and 3 months after surgery was 15.8% and 13.4%, respectively. Santini et al. [19] have reported that individuals with increased BMI require higher doses of LT4 to achieve a similar degree of TSH reduction as lean subjects. Similarly, we detected a negative correlation between ΔTT4 peak and BMI, as well as ΔTT4-AUC_{300} and BMI, suggesting an influence of increased BMI in the absorption of LT4.

As expected, serum TSH and leptin concentrations of morbidly obese patients in the NS group were significantly higher when compared with those in the S group. Higher serum TSH concentrations in morbidly obese patients have been attributed to persistently elevated stimulation by hypothalamic TRH [28]. Elevated serum leptin acts on the paraventricular nucleus (PVN) in the hypothalamus inducing expression of mRNA for TRH [29]. Ultimately,

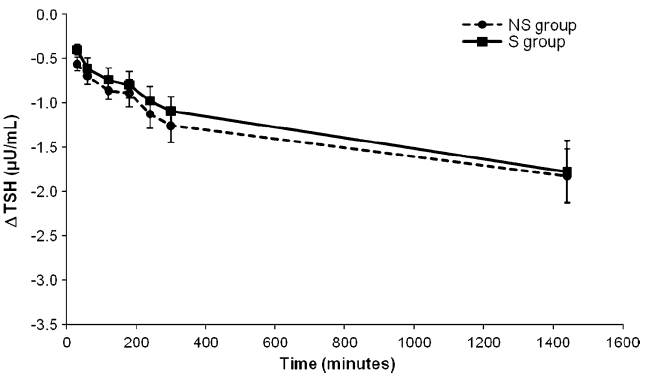

Fig. 2 ΔTSH values in patients before RYGB surgery (NS group) and after RYGB surgery (S group), values presented are means±SD

more TRH is produced with subsequent stimulation of pituitary thyrotrophs that might lead to moderately elevated serum TSH (Table 1). Morbidly obese patients, however, do not present abnormal decrease in FT4. This laboratory configuration of relatively high-serum TSH and normal FT4 has been erroneously denominated "subclinical hypothyroidism" but is actually a reflex of hypothalamic stimulation by leptin of TRH-producing neurons in the PVN [30]. Following weight loss after RYGB surgery, there was a concomitant decline in circulating leptin, leading to reduced stimulation of the TRH-producing neurons in the PVN. As a consequence, serum TSH returns to normal levels, as clearly shown in our patients after RYGB surgery.

The results of LT4 absorption were somewhat unexpected. As shown in Table 2 and Fig. 1, there were higher values of ΔTT4 peak, ΔTT4-AUC_{300}, ΔFT4-AUC_{240}, and ΔFT4-AUC_{300} in patients who underwent Roux-en-Y surgical procedure in spite of the diminished volume capacity of the gastric pouch and, presumably, very low levels of gastric acid secretion. Although speculative, it is tempting to bring forward a hypothesis that the new configuration of the gut after Roux-en-Y bypass, with the jejunoileal segment placed immediately below the gastric pouch, might create a new situation favorable to LT4 absorption. Indeed, it has been postulated that in normal conditions, 53% of the LT4 absorption after gastric dissolution is observed mainly in the upper and lower parts of the jejunoileal segment [23]. Even in the absence of a normal gastric dissolution, the LT4 tablets will be normally absorbed by a close and direct contact with the jejunoileal portion of the upper intestinal tract. In patients in the S group, there was some delay of LT4 absorption, but maximum ΔTT4 and ΔFT4 did not differ from the values obtained before RYGB surgery.

The clinical significance of our findings is related to the fact that obesity is being considered a risk for thyroid autoimmunity [5], thus establishing a link between the main cause of acquired thyroid failure (hypothyroidism) and obesity. Indeed, many obese patients (before or after RYGB) will be on need of LT4 replacement therapy, and accordingly to our findings, LT4 therapy does not have to be modified for a hypothetical defective absorption. Possibly, due to the marked weight loss after RYGB the attending physician will have to adjust the LT4 dosage considering the new weight (but not for lack of normal LT4 absorption).

In conclusion, we have demonstrated that LT4 absorption after Roux-en-Y bypass surgery does not diminish LT4 absorption. A small delayed absorption of LT4, however, was observed in some patients due to placement of the jejunoileal segment in close attachment to the gastric pouch. As a corollary to this observation, some individual variations regarding LT4 absorption and/or weight loss may occur after RYGB, it is advisable to closely monitor thyroid function parameters in patients who are in need of LT4 treatment.

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References

1. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. Cancer. 2009;115:3801–7.
2. Camargo RY, Tomimori EK, Neves SC, et al. Thyroid and the environment: exposure to excessive nutritional iodine increases the prevalence of thyroid disorders in Sao Paulo, Brazil. Eur J Endocrinol. 2008;159:293–9.
3. Aoki Y, Belin RM, Clickner R, et al. Serum TSH and total t4 in the United States population and their association with participant characteristics: National Health And Nutrition Examination Survey (NHANES 1999–2002). Thyroid. 2007;17:1211–23.
4. Papavramidis ST, Zisiadis AC, Karamouzis MN, et al. Alterations in thyroid hormones and thyrotropin (TSH) in morbidly obese patients before and after vertical gastroplasty. Obes Surg. 1995;5:298–301.
5. Marzullo P, Minocci A, Tagliaferri MA, et al. Investigations of thyroid hormones and antibodies in obesity: leptin levels are associated with thyroid autoimmunity independent of bioanthropometric, hormonal, and weight-related determinants. J Clin Endocrinol Metab. 2010;95:3965–72.
6. Sherman SI, Malecha SE. Absorption and malabsorption of levothyroxine sodium. Am J Ther. 1995;2:814–8.
7. Liel Y, Sperber AD, Shany S. Nonspecific intestinal adsorption of levothyroxine by aluminum hydroxide. Am J Med. 1994;97:363–5.
8. Northcutt RC, Stiel JN, Hollifield JW, et al. The influence of cholestyramine on thyroxine absorption. JAMA. 1969;208:1857–61.
9. Sherman SI, Tielens ET, Ladenson PW. Sucralfate causes malabsorption of L-thyroxine. Am J Med. 1994;96:531–5.
10. Campbell NR, Hasinoff BB, Stalts H, et al. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. Ann Intern Med. 1992;117:1010–3.
11. Singh N, Weisler SL, Hershman JM. The acute effect of calcium carbonate on the intestinal absorption of levothyroxine. Thyroid. 2001;11:967–71.
12. McLean M, Kirkwood I, Epstein M, et al. Cation-exchange resin and inhibition of intestinal absorption of thyroxine. Lancet. 1993;341:1286.

13. Benvenga S, Bartolone L, Pappalardo MA, et al. Altered intestinal absorption of L-thyroxine caused by coffee. Thyroid. 2008;18:293–301.
14. Chiu AC, Sherman SI. Effects of pharmacological fiber supplements on levothyroxine absorption. Thyroid. 1998;8:667–71.
15. Centanni M, Gargano L, Canettieri G, et al. Thyroxine in goiter, helicobacter pylori infection, and chronic gastritis. N Engl J Med. 2006;354:1787–95.
16. Checchi S, Montanaro A, Pasqui L, et al. L-thyroxine requirement in patients with autoimmune hypothyroidism and parietal cell antibodies. J Clin Endocrinol Metab. 2008;93:465–9.
17. Benvenga S, Bartolone L, Squadrito S, et al. Delayed intestinal absorption of levothyroxine. Thyroid. 1995;5:249–53.
18. Hays MT, Nielsen KR. Human thyroxine absorption: age effects and methodological analyses. Thyroid. 1994;4:55–64.
19. Santini F, Pinchera A, Marsili A, et al. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. J Clin Endocrinol Metab. 2005;90:124–7.
20. Mistry D, Atkin S, Atkinson H, et al. Predicting thyroxine requirements following total thyroidectomy. Clin Endocrinol (Oxf). 2011;74:384–7.
21. Zaninotto P, Head J, Stamatakis E, et al. Trends in obesity among adults in England from 1993 to 2004 by age and social class and projections of prevalence to 2012. J Epidemiol Community Health. 2009;63:140–6.
22. Decker GA, Swain JM, Crowell MD, et al. Gastrointestinal and nutritional complications after bariatric surgery. Am J Gastroenterol. 2007;102:2571–80. quiz 2581.
23. Hays MT. Localization of human thyroxine absorption. Thyroid. 1991;1:241–8.
24. Hennemann G, Docter R, Friesema EC, et al. Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocr Rev. 2001;22:451–76.
25. Wenzel KW, Kirschsieper HE. Aspects of the absorption of oral L-thyroxine in normal man. Metabolism. 1977;26:1–8.
26. Bevan JS, Munro JF. Thyroxine malabsorption following intestinal bypass surgery. Int J Obes. 1986;10:245–6.
27. Azizi F, Belur R, Albano J. Malabsorption of thyroid hormones after jejunoileal bypass for obesity. Ann Intern Med. 1979;90:941–2.
28. Kok P, Roelfsema F, Langendonk JG, et al. High circulating thyrotropin levels in obese women are reduced after body weight loss induced by caloric restriction. J Clin Endocrinol Metab. 2005;90:4659–63.
29. Flier JS, Harris M, Hollenberg AN. Leptin, nutrition, and the thyroid: the why, the wherefore, and the wiring. J Clin Invest. 2000;105:859–61.
30. Hollenberg AN. The role of the thyrotropin-releasing hormone (TRH) neuron as a metabolic sensor. Thyroid. 2008;18:131–9.