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ENDOCRINE TRIALS

Thyroxine softgel capsule in patients with gastric-related T_4 malabsorption

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Abstract The key role of an intact gastric acid secretion for subsequent intestinal T_4 absorption is supported by an increased requirement of thyroxine in patients with gastric disorders. A better pH-related dissolution profile has been described in vitro for softgel T_4 preparation than for T_4 tablets. Our study was aimed at comparing softgel and tablet T_4 requirements in patients with gastric disorders. A total of 37 patients with gastric-related T_4 malabsorption were enrolled, but only 31 (28F/3M; median age = 50 years; median T_4 dose = 2.04 μg/kg/day) completed the study. All patients were in long-lasting treatment (>2 years) with the same dose of T_4 tablets when treatment was switched to a lower dose of softgel T_4 capsules (−17 %; $p = 0.0002$). Assessment of serum FT_4 and TSH was carried out at baseline and after 3, 6, 12, and 18 months after the treatment switch. In more than 2/3 of patients (good-responders $n = 21$), despite the reduced dose of T_4, median TSH values were similar at each time point ($p = 0.3934$) with no change in FT_4 levels. In the remaining patients (poor-responders $n = 10$), TSH levels were significantly higher at each time point than at baseline ($p < 0.0001$). To note, in five of them intestinal comorbidity was subsequently detected. Comorbidity associated with poor-responders status was the only significant predictor in multivariate analysis (OR = 11.333). Doses of softgel T_4 capsules lower than T_4 tablet preparation are required to maintain the therapeutic goal in 2/3 of patients with impaired gastric acid secretion.

Keywords Thyroxine · Hashimoto's thyroiditis · Nodular goiter · T_4 malabsorption · *Helicobacter pylori*

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Introduction

The long-lasting use of oral thyroxine treatment requires care regarding dose management and hormone absorption which are crucial to obtaining the therapeutic goal. The detrimental effects of overt or subclinical hypothyroidism, even due to T_4 undertreatment, are exhaustively described in previous studies [1, 2]. Old habits in thyroid hormone administration have been challenged by novel concepts on oral thyroxine treatment [3–7]. Convincing evidence now supports the hypothesis that a dose of levothyroxine, when individually tailored [6, 8, 9], allows easier attainment of the therapeutic goal. Despite these improvements, however, some patients fail to show an adequate chemical and clinical response to the "appropriate" dose of T_4, requiring larger doses of levothyroxine and improper and/or expensive diagnostic procedures [3].

Historically, these large variations of T_4 dosage were explained by the poor compliance of patients with the prescribed regimen (pseudomalabsorption) [10]. Several physiological (pregnancy and weight) and/or paraphysiological

(behavioral, nutritional, and pharmacological) interferences have since been identified [see 11 for ref]. Recently, the use of an individually tailored dose of T4, adjusted by age, body weight or body mass index [8, 12–14], also led to the detection of thyroxine malabsorption associated with gastrointestinal disorders [15]. In fact, oral thyroxine is absorbed at the level of the duodenum, jejunum, and ileum [16], and some inflammatory disorders of the small intestine may cause hormone malabsorption (celiac disease, lactose intolerance, small intestine bacterial overgrowth etc.,) [9, 13, 17–19]. However, an increased need for oral thyroxine has also been identified in gastric disorders (*Helicobacter pylori* infection, chronic gastritis etc.,) [14], highlighting a novel role for the stomach in subsequent intestinal T_4 absorption [14, 15]. The naïve thyroxine has a hydrophobic structure with an alanine side chain which results in its low permeability [20]. Conversely, pharmaceutical T_4 preparation is a hydrophilic sodium salt and its physico-chemical characteristics as well as that of the environment in which it dissolves, may be relevant for intestinal absorption. Softgel preparation is a new formulation of levothyroxine and consists in a pearl-shaped capsule, in which T_4 is dissolved in glycerin and has a protecting shell made of softgel gelatin [21]. This preparation has been proven to be bioequivalent to traditional T_4 in tablet form [21], but with a different dissolution profile [20]. Pabla et al. in fact, showed that the dissolution profile of softgel was clearly superior with the progressive increase of pH, when compared with that of other T_4 preparations from different brands [20]. So far, in patients with gastric disorders, where larger doses of thyroxine tablets are required [14] and gastric pH is less acidic than normal [22], lower doses of softgel T_4 preparation may be sufficient to maintain the therapeutic target. Our study aimed to assess this hypothesis by comparing the effects of tablet and softgel preparation of T_4 in patients with proven gastric disorders.

Patients and methods

Patients and study design

This study was conducted from 2008 to 2012 in a tertiary outpatient Endocrinology unit on a sequentially examined cohort of 795 patients who had been referred for thyroid diseases and were in need of thyroxine treatment. Following the initial clinical examination, patients were treated with an individually tailored dose of thyroxine in replacement (target serum TSH = 0.4–2.5 mU/l; median T_4 dose: 1.37 μg/kg body weight/day) or semi-suppressive mode (target serum TSH = 0.1–0.4 mU/l; median T_4 dose: 1.57 μg/kg body weight/day) according to the thyroid disorder diagnosed, as previously described [9, 14]. All patients were treated with the same brand of oral levothyroxine sodium in tablet form (Eutirox, Bracco, Milan, Italy) and agreed to take thyroxine under fasting conditions, abstaining from eating or drinking anything other than water for at least 1 h after treatment. The dose of thyroxine required to obtain the therapeutic goal was normalized by patient's body weight/day.

If patients failed to reach the expected target serum TSH in two or more consecutive measurements, the T_4 dose was adjusted until the target TSH level was steadily attained. At the same time, this group of patients entered diagnostic workup to assess whether the presence of a gastrointestinal disorder resulted in an increased need of T_4 [15]. Of the patients examined, a sample was then selected to be enrolled in the study according to the following criteria:

Inclusion criteria: (1) patients with an increased need of thyroxine [9, 13–15, 17, 18]; (2) patients with a histologically diagnosed gastric disorder impairing gastric acid secretion.

Exclusion criteria: (1) patients who were pregnant or nursing; (2) patients who had recently used substances or drugs known to interfere with T_4 metabolism [23]; (3) patients who had been treated with drugs interfering with levothyroxine absorption and action in the last 12 months, including proton pump inhibitors [see ref. 11 for the list]; (4) patients with BMI >30; (5) patients who had undergone thyroid and/or gastrointestinal surgery; (6) patients with clinical evidence of intestinal disorders at the beginning of the study.

Phase 1

Based on the above-mentioned criteria, 37 patients (34 women and 3 men, median age = 50 years; IQ1–IQ3 = 43–59 years) were selected and accepted to be enrolled in the study.

In these patients, the diagnosed gastric disorders were treatment-refractory *H. pylori* infection, *H. pylori*-related chronic gastritis and gastric atrophy. Once the target TSH level had been reached, the dose of thyroxine remained unchanged and serum TSH was measured every 6 months for 2 years. Only patients who maintained target TSH levels without further changes to the already increased dose of T_4 proceeded to phase 2. Patients' compliance was checked by a questionnaire which was read and accepted both at the beginning of the study and at the end of phase 1, and confirmed by the stability of serum TSH at constant dose. 31 of 37 patients completed the first phase, while 6 patients did not due to supervening pregnancy ($n = 1$), poor compliance with T_4 treatment ($n = 2$) or the necessary use of interfering drugs for concomitant but unrelated disorders ($n = 3$).

Phase 2

In the remaining 31 patients who entered phase 2, we checked the ability of a reduced dose of T_4 softgel preparation (Tirosint®, IBSA, Lugano, CH) to maintain, in each patient, the same target TSH value obtained with conventional T_4 tablet. To this end, the tablet T_4 dose, established during phase 1, was switched in each patient to the immediately lower dose of T_4 softgel closer to the commercially available preparation (median reduction of T_4 dose = 17 %) and was thereby maintained throughout the study. All other criteria for T_4 assumption were identical to phase 1. TSH and free T_4 (FT_4) were measured at the beginning of phase 2 (time 0) and after 3, 6, 12, and 18 months. Patients gave morning blood samples prior to T_4 administration which were immediately frozen at −20° until assayed. Again, the enrolled patients' compliance with T_4 treatment was secured by a questionnaire 6 months after the pharmacological switch and confirmed at the end of the study.

The study has been approved by the local Ethical Committee (Santa Maria Goretti Hospital, Latina, Italy) according to the local ethical rules and to the guidelines in the Declaration of Helsinki. Written informed consent from all patients was obtained before the start of the study.

Methods

Assessment of serum TSH and free T_4 was made at the time of the first examination and following 3, 6, 12, and 18 months of treatment. Serum TSH and FT4 were each assayed in a single run.

Levels of serum free thyroxine were detected by commercial assay (Thermo Scientific, BRAHMS FT_4 RIA, Hennigsdorf, Germany) (normal range: 10 to 25 pmol/l which is the equivalent of 7.8–19.4 pg/ml). Serum TSH levels were assayed by commercial assay (Thermo Scientific, BRAHMS TSH RIA, Hennigsdorf, Germany) (normal range, 0.4–4.0 mU/l: sensitivity: 0.04 mU/l; intra-assay and inter-assay variation were 2.5 and 4.1 %, respectively).

Serum anti-thyroid peroxidase antibodies were measured by commercial assay (Thermo Scientific, BRAHMS anti-TPO, Hennigsdorf, Germany) (normal range: <60 U/ml).

The diagnosis of thyroid disorders

The diagnosis of Hashimoto's thyroiditis

The diagnosis of Hashimoto's thyroiditis was based on the presence of at least two of the following three criteria: characteristic ultrasonographic pattern, hypothyroidism, and high titers of anti-thyroperoxidase antibodies (anti-TPOAb).

The diagnosis of non-toxic multinodular goiter

The diagnosis of non-toxic multinodular goiter (NTMG) was based on clinical and ultrasonographic features, normal serum iodothyronines and TSH, the absence of serum antiperoxidase antibodies, normal radioiodine uptake, and thyroid scan. All patients had goiter WHO stage 1A or 1B and at least 2 nodules >1 cm. Untreated goitrous patients with low serum TSH (<0.5 mU/l) and/or T_3 non-suppressible nodules at the thyroid scan were not enrolled in the study.

The diagnosis of gastric disorders

The diagnosis of atrophic chronic gastritis and *Helicobacter pylori*-related gastritis was performed as previously described [14, 22] and was based on histological examination. Briefly, at gastroscopy, three biopsy specimens were collected from the midbody mucosa and three from the antrum. Histological evaluation was on serial paraffin Sects. (5 μm) stained with hematoxylin–eosin and, for *H. pylori* detection, with Giemsa. Colonization by H. Pylori, inflammatory infiltrate and activity, atrophy grading and intestinal metaplasia were assessed by the Sydney system score [24] to diagnose and distinguish gastritis subtypes. Atrophy of the fundic mucosa was defined as focal or complete replacement of oxyntic glands by metaplastic pyloric or intestinal glands. Atrophy of the antral mucosa was defined as focal or complete disappearance of antral glands or their replacement by intestinal metaplastic epithelium [25].

The persistence of *H. pylori* infection was diagnosed by using a urea breath test, as previously described [14]. The presence of *H. pylori* autoantibodies was measured by an Elisa commercial kit (G.A.P. test, Biorad, Milan, Italy). Serum anti-parietal cell antibodies were determined using a solid phase immunosorbent assay kit (Autostat, Cogent Diagnostics, Ltd, Edinburgh, Scotland). Fasting plasma gastrin levels were measured by a radioimmunoassay.

Diagnosis of additional intestinal disorders

Additional diagnostic workup was initiated only in those patients with supervening intestinal symptoms (bloating, flatus, abdominal discomfort etc.,). The presence of additional intestinal disorders was suspected on clinical grounds and confirmed according to the specific guidelines of each disorder. Indeed, lactose intolerance was diagnosed according to Suchy et al. [26], atypical celiac disease with

Rostom et al. [27] and small intestinal bacterial overgrowth with Rana et al. [19]

Statistical analysis

Frequencies, mean ± standard deviation (SD), and median with relative Interquartile range (IQR) were calculated for each relevant variable. The Mann–Whitney test (with or without Welch's correction) was used to compare non-parametric data. ANOVA and Kruskal–Wallis non-parametric tests were used to test independence of more than two samples at a 0.05 level of significance. Bonferroni's multiple comparison test was used to compare individual groups. A stepwise logistic regression model with backward elimination was performed to identify independent variables associated with the highest TSH percentage increase, using the strategy suggested by Hosmer and Lemeshow [28]. Each variable was examined by univariate analysis using the appropriate statistical test (Student's t test and χ^2 test) and included in the model when the p value was lower than 0.25. Subsequently, a multivariate logistic regression with backward elimination of any variable that did not contribute to the model on the grounds of the Likelihood Ratio test (cutoff at $p = 0.05$) was performed. Variables whose exclusion altered markedly the coefficient of the remaining variables were kept in the model. Interaction terms were tested using a cutoff of 0.15 level significance. Adjusted odds ratio (OR) and 95 % confidence intervals (CI) were calculated. All statistical calculations were performed using Stata version 8.0 (College Station, Texas, Stata Corporation, 2003). For the purpose of analysis, sample division of patients in good-responders and poor-responders was used as the dependent variable (outcome). The following variables were tested as predictors: age, weight, dose/weight, TSH at baseline, thyroid disease (non-toxic multinodular goiter or Hashimoto's thyroiditis), gastric diseases, and intestinal comorbidity.

Results

Thirty-one of 37 patients completed the study (20 patients with Hashimoto's thyroiditis in subclinical hypothyroidism and 11 with non-toxic multinodular goiter). The clinical and biochemical characteristics of these 31 patients are described in Table 1. No significant changes of the body weight of patients were observed during tablet or softgel treatment. All patients who completed the study had a definite gastric disorder (chronic superficial gastritis, $n = 15$; gastric atrophy, $n = 13$; treatment-resistant *H. pylori* infection, $n = 3$) [24, 25, 29]. Biochemical gastric parameters are shown in Table 2. During the last period of the study, eight of these patients with supervening intestinal symptoms were further investigated and, in five of them, a previously unrecognized intestinal disorder was positively ascertained at the time of or immediately following the last examination.

During the first phase, individual serum TSH values were stable in all 31 patients over two years (median TSH = 0.42 mU/l, IQ1–IQ3 = 0.26–1.04) at a median dose of tablet T_4 of 2.04 μg/kg/day (Table 1). At this time, treatment was switched from the tablet to a significantly lower dose of T_4 softgel capsule (median T_4 dose = 1.70 μg/kg/day; IQ1–IQ3 = 1.55–1.81 μg/kg/day; −17 %; $p = 0.0002$). Individual reduction of T_4 dose of each patient is shown in Fig. 1.

The analysis of serum TSH values in each patient at each time point revealed that some 2/3 of patients had no substantial changes of TSH over the entire period. On the contrary, the remaining 1/3 had TSH values significantly different from baseline at each time point, suggesting the possible existence of two different responses to the drug switch. Therefore, patients were divided into two groups on the basis of their percentage increase of TSH over the entire period. Specifically, each patient was classified as either poor-responder or good-responder if he/she fell within the highest tertile of increase or within the lower tertiles, respectively. Based on these criteria, 21 patients with not significant TSH variations following the therapeutic shift from tablet to lower softgel T_4 dose were defined as good-responders. The remaining 10 patients showing significant TSH variations as poor-responders. Their anthropometric and functional characteristics are reported in Table 3.

Median TSH values of good-responder and poor-responder patients are represented in Fig. 2. Data confirmed that no significant differences of TSH are detectable in the good-responders group at each time point of the study (ANOVA test: $p = 0.3934$). By contrast, significant serum TSH variations have been clearly identified in patients defined as poor-responders ($p < 0.0001$) (Fig. 2). In this figure, it appears that significantly increased TSH has already been observed after three months of treatment and at each time point throughout the study, as compared to the baseline value (Fig. 2). Thus, in poor-responder patients, serum TSH values increased early and remained high over time. Interestingly enough, all five patients with additional intestinal disorders belonged to the poor-responders group. Among these five patients, lactose intolerance was diagnosed in two, atypical celiac disease in one, and bacterial overgrowth of the small intestine in the remaining two patients.

To test whether confounding factors might have marred these data, a multiple logistic regression analysis was performed on the whole sample. From this analysis, it emerged that our data were independent from the type of

Table 1 Baseline clinical and biochemical features of patients in the study group

Patients (*n*)	Age (years)	Sex	Weight (Kg)	L-T_4 dose (μg/day)	T_4 dose/weight (μg/Kg/day)	TSH (mU/l)	FT_4 (ng/dl)
31	50 (43–59)	28F/3M	66.0 (63–76)	128.5 (125–150)	2.04 (1.78–2.14)	0.42 (0.26–1.04)	1.45 (1.40–1.55)

Results are expressed as median values and interquartile range (IQ1–IQ3)

Table 2 Functional and immunologic features related to gastric disorders in the study group

Gastric disease	$APCAb^+$ (*n*)	$HpAb^+$ (*n*)	Serum gastrin level (pg/ml)
Gastric atrophy	10/13	7/13	776 ± 591
Superficial gastritis	2/15	14/15	97 ± 52
Treatment-resistant *H. pylori* infection	0/3	3/3	49 ± 13

Serum gastrin levels are expressed as mean ± SD

APCAb$^+$ anti-parietal cell antibodies positive, *HpAb*$^+$ anti-*Helicobacter pylori* antibodies positive

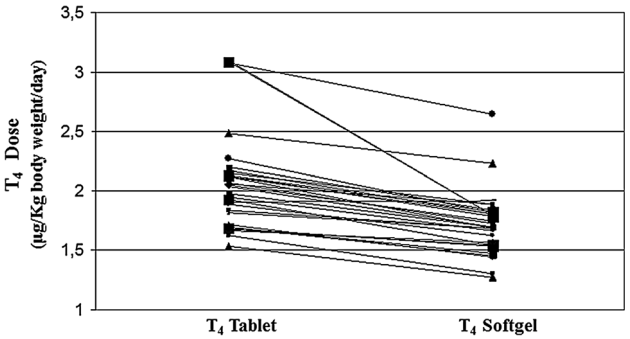

Fig. 1 Individual T_4 dose reduction after shifting from tablet to softgel T_4 preparation ($n = 31$)

Table 3 Clinical features of good-responder and poor-responder patients at baseline

Patients (*n*)	Good-responders 21	Poor-responders 10	*p*
Age (years)	51 (43–59)	50 (43–57)	0.6723
Weight (Kg)	70.0 (64–82)	63.0 (57–65)	0.0179
L-T_4 dose (μg/Kg/day)	129 (125–150)	125 (125–133)	0.0916
Thyroid disease	NTMG = 9 HT = 12	NTMG = 1 HT = 9	0.1064[a]
T_4 dose/weight (μg/Kg/day)	2.04 (1.69–2.14)	2.0 (1.92–2.11)	0.8657
TSH (mU/l)	0.62 (0.26–2.1)	0.39 (0.26–0.46)	0.1629

Results are expressed as median values and interquartile range (IQ1–IQ3). For statistical analysis, the Mann–Whitney test and the [a]Fisher's exact test were used

NTMG non-toxic multinodular goiter, *HT* Hashimoto's thyroiditis

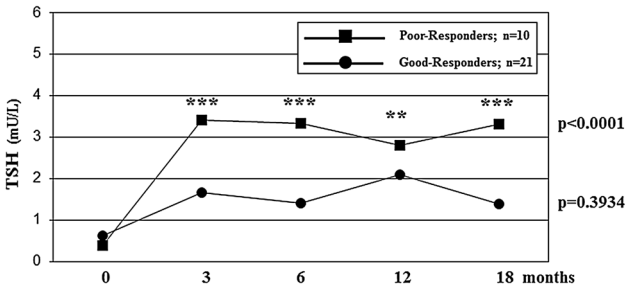

Fig. 2 Median serum TSH values in good-responder ($n = 21$) and poor-responder ($n = 10$) patients at each time point (baseline, 3, 6, 12, and 18 months). ANOVA Test for repeated measures (pairing of data: $p < 0.0001$) and Bonferroni's post test for non-parametric data were used for statistical analysis. $^{**}p < 0.01$, $^{***}p < 0.001$

gastric disorders, the kind of thyroid disease, and/or the anthropometric and functional parameters. The presence of comorbidities (i.e., additional intestinal disorders) associated with poor-responders status was the only predictive condition revealed by multiple logistic regression analysis (OR = 11.333; 95 % CI = 1.048–122.549).

Discussion

Alternative preparations of thyroxine beside the traditional tablet formulation (e.g., softgel capsules, liquid etc.,) have been proposed in the treatment of thyroid disorders [15, 30–32]. Liquid T_4 formulations have been reported to improve the efficiency of treatment in obese patients following bariatric surgery [30] and in patients with congenital hypothyroidism [31] Also Vita et al. reported that the use of softgel T_4 capsules helps to overcome the problem of improper use of coffee close to thyroxine ingestion [32].

In the present study, we observed that a lower dose of softgel T_4 preparation was sufficient to obtain the therapeutic target in about 2/3 of 31 patients with definite gastric disorders, compared with T_4 tablet. The relevance of these data stems from the epidemiological and clinical impact of gastric disorders: *H. pylori* infection, in fact, affects about 50 % of the world population and may trigger chronic gastritis and gastric atrophy [see 33 for Review]. These latter disorders are often concurrent with thyroid diseases [14, 34], and are also associated with autoimmune thyroiditis in the autoimmune polyglandular syndromes [35].

A shared feature of the above-mentioned gastric disorders is an altered gastric acid secretion. Hypo- or achlorhydria is the most frequent sign of chronic gastric disorders, and in hypochlorhydric patients, an increased need for T_4 has been described [14]. However, the mechanism by which the efficiency of intestinal T_4 absorption may be impaired in hypo-achlorhydric patients remains to be elucidated. Differences in chemical structure may be relevant: native iodothyronines are lipophilic and enter target cells through both passive diffusion and/or specific transporters [36] and perhaps in a carrier-mediated sodium-dependent way [37]. Pharmaceutical T_4 preparation, instead, is a sodium salt and the fraction of it reaching the intestinal lumen may be affected by its dissolution rate [20] and by the chemical characteristic of the environment in which it dissolves. An intact gastric acid secretion is key in the absorption of iron and other drugs [38, 39] and may similarly affect thyroxine dissolution profile in vivo. An oral preparation of T_4 which dissolves better in a less acidic environment may be easily absorbed in patients with reduced gastric acid secretion. Remarkably, softgel T_4 formulation showed a better pH-dependent dissolution profile in vitro, compared with tablets [20] and may be the preferred form of T_4 delivery in patients with gastric disorders. On the other hand, not all patients with gastric disorders responded better to the softgel formulation than the tablet formulation. There is no obvious explanation for this discrepancy. In half of the patients in whom TSH increased after treatment switch, we observed the presence of a previously unrecognized intestinal disorder. According to the results of multiple regression analysis, the presence of comorbidities was associated with poor-responders status. So far, we may assume that intestinal disorders are likely to reduce the absorption of thyroxine for reasons intrinsic to the alteration of duodenal mucosa [9]. In the remaining poor-responder patients, however, other still unknown factors may be involved in the impairment of the absorption process. One of these factors may be a different degrees of gastric acid output. Should this be the case, only a direct matching of oral T_4 with the actual level of gastric acid secretion, may help to explain the difference between patients with similar gastric disorders but different responses to softgel treatment.

In conclusion, our findings show that 2/3 of patients with gastric disorders, stabilized on a T_4 tablet regimen, appear to respond similarly in terms of TSH response when they are switched to a significantly lower dose of softgel capsules. Further studies are required to support the hypothesis of a better absorption of the softgel formulation in patients with impaired gastric acid secretion.

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Conflict of interest Marco Centanni received Symposia Honorarium from IBSA Institut Biochimique SA in the years 2010, 2011, and 2012. Nothing to disclose for all other authors.

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