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## TRABAJO ORIGINAL

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# Vitamin C improves the apparent absorption of levothyroxine in a subset of patients receiving this hormone for primary hypothyroidism

## La vitamina C mejora la absorción aparente de levotiroxina en ciertos pacientes que reciben esta hormona por hipotiroidismo primario

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### ABSTRACT

As in some patients with hypothyroidism, because of unknown reasons, large doses of levothyroxine are required to achieve a therapeutic endpoint, and preliminary observations have indicated that an hypoacidic gastric environment is associated with a reduction in levothyroxine bioavailability, and that co-administration of vitamin C might enhance absorption of certain drugs, we assessed whether this effect would be obtained taking levothyroxine with vitamin C.

**Design:** We studied 28 patients (24 women and 4 men, age range 26-76 years; mean  $48.0 \pm 17.75$ ) treated with levothyroxine at doses of  $>1.70 \mu\text{g}/\text{kg}$  but failing to achieve their target TSH level. During the control period, each patient had at least two determinations of TSH indicating inadequate dosage. Interfering factors that could alter levothyroxine absorption such as celiac disease, calcium, iron, or antacid use, among others, and non-compliance were excluded. During the study period, the patients continued on the same dose of levothyroxine but took the tablet with 1 g of vitamin C in 200 cc of tap water, instead of the same volume of water alone. Serum TSH levels were prospectively measured 6-8 weeks after starting co-administration with vitamin C, and two months later.

**Main outcome:** After six-eight weeks of taking levothyroxine with vitamin C, serum TSH decreased in all 28 patients (average reduction  $69.79 \pm 22.19 \%$ ), and the target or desired level of TSH was achieved in 19/28 patients. The difference between TSH levels before and after treatment with vitamin C was significant: Basal TSH (IFMA) was  $9.01 \pm 5.51$  mIU/L vs. a mean TSH on vitamin C treatment of  $2.27 \pm 1.61$  mIU/L ( $p < 0.0001$ ).

**Conclusions:** 1) Vitamin C enhances oral absorption of levothyroxine; 2) Co-administration of Vitamin C with levothyroxine should be considered in patients with difficulties in the absorption of levothyroxine. **Rev Argent Endocrinol Metab 48: 16-24, 2011**

No financial conflicts of interests exist.

**Key words:** vitamin C - absorption - levothyroxine

### RESUMEN

Como algunos pacientes con hipotiroidismo requieren altas dosis de levotiroxina para lograr el objetivo terapéutico, y existen observaciones de que el medio gástrico hipoácido se asocia a reducción en la biodisponibilidad de la levotiroxina, y que la coadministración de vitamina C puede mejorar la absorción de ciertas drogas, se evaluó si este efecto se podía lograr tomando la levotiroxina con vitamina C.

Se estudiaron 28 pacientes (24 mujeres y 4 hombres, edad 26-76 años; media  $48.0 \pm 17.75$ ) **tratados con levotiroxina en dosis  $>1.70 \mu\text{g}/\text{kg}$  pero que no lograban el nivel deseable de TSH.** Durante el período de control, cada paciente tuvo al menos dos determinaciones de TSH que indicaron dosis inadecuada. Se ex-

cluyeron pacientes que presentaran factores que pudieran alterar la absorción de levotiroxina o con falta de cumplimiento del tratamiento. Durante el período de estudio, los pacientes continuaron con la misma dosis de levotiroxina pero tomaron la tableta con 1 g de vitamina C diluida en 200 cc de agua corriente, en lugar del mismo volumen de agua corriente sola. Se midió TSH plasmática prospectivamente a las 6-8 semanas de coadministrar la levotiroxina con vitamina C, y en una segunda oportunidad dos meses después.

**Resultados:** Luego de 6-8 semanas de tomar la levotiroxina con vitamina C, la TSH se redujo en todos los pacientes (promedio de reducción  $69.79 \pm 22.19\%$ ), y el nivel deseable de la misma se logró en 19/28 pacientes. La diferencia entre los niveles de TSH antes y después del tratamiento con vitamina C fue estadísticamente significativa: la TSH (IFMA) basal fue  $9.01 \pm 5.51$  mIU/L vs. una TSH media con vitamina C de  $2.27 \pm 1.61$  mIU/L ( $p < 0.0001$ ).

**Conclusiones:** 1) La vitamina C aumenta la absorción oral de levotiroxina; 2) La coadministración de vitamina C con levotiroxina sería de utilidad en pacientes con dificultades en la absorción de levotiroxina. **Rev Argent Endocrinol Metab 48: 16-24, 2011**

Los autores declaran no poseer conflictos de interés.

**Palabras clave:** vitamina C - absorción - levotiroxina

## INTRODUCTION

Levothyroxine sodium is commonly prescribed for the treatment of hypothyroidism and thyroid neoplasia. As a result of hypofunction or absence of the thyroid gland, the level of serum thyroid stimulating hormone (TSH) is elevated because of the absence of the regulatory negative feedback mechanism. Patients with hypothyroidism are supplemented with synthetic thyroxine (i.e. levothyroxine, LT4) in oral doses to achieve physiological T4 and TSH serum levels. The mean treatment dosage of LT4 is  $1.6 \mu\text{g}/\text{kg}$  body weight/day<sup>(1)</sup>. The absorption of levothyroxine is approximately 50-100 % after oral administration<sup>(2-6)</sup>, but there is considerable inter-individual and intra-individual variability<sup>(7)</sup>. On occasions, when extraordinarily large doses of LT4 are required to achieve a therapeutic endpoint, clinicians should suspect either some interference with absorption or non-compliance. Many causes of LT4 malabsorption have been reported (Table I) and the more common causes are listed in Table 1 including gastrointestinal diseases, liver diseases, pancreatic diseases, certain gastrointestinal surgical procedures, many drugs and dietary interactions, heart disease or pregnancy<sup>(7-37, 43-51)</sup>. Other drugs may accelerate the disposal of LT4 and therefore increase the dose requirement<sup>(38-42)</sup>. In some rare patients, hypothyroidism persists despite seemingly adequate or even supraphysiologic LT4 doses, even after having excluded the above-mentioned possible causes as well as pseudomalabsorption or noncompliance<sup>(1, 52-57)</sup>.

Indeed, there are several case reports in the literature in which euthyroidism could only be

achieved through parenteral LT4 administration and the underlying pathophysiologic mechanism for malabsorption remained unresolved<sup>(58-60)</sup>.

Because serum TSH levels are usually normalized in patients with primary hypothyroidism with a mean daily LT4 dose of about  $1.6 \pm 0.4 \mu\text{g}$   $\text{kg}^{-1}$   $\text{day}^{-1}$ <sup>(1)</sup>, malabsorption may be suspected once the patient requires more than  $2.4 \mu\text{g}$   $\text{kg}^{-1}$   $\text{day}^{-1}$ <sup>(7)</sup>. However, some patients with apparent dose requirements between  $1.6 \pm 0.4 \mu\text{g}$   $\text{kg}^{-1}$   $\text{day}^{-1}$  and  $2.4 \mu\text{g}$   $\text{kg}^{-1}$   $\text{day}^{-1}$  should be considered as having malabsorption as well.

Of note in this regard are the several factors relating to LT4 absorption in the stomach, including the role of gastric acid secretion, timing of food ingestion, gastric pH impairment, and the effect of the latter on facilitating LT4 absorption in the gut<sup>(18)</sup>. Dissolution of LT4 is a crucial step in its oral absorption and bioavailability<sup>(61)</sup>, and tablets of LT4 need intragastric acid pH in order to achieve an adequate dissolution. Decreased dissolution of LT4 with higher gastric pH as described by Pabla et al confirmed the relationship of LT4 absorption to alterations in gastric pH and the importance of variable dissolution of LT4 on the bioavailability of LT4<sup>(61)</sup>. The normally acid environment of the stomach becomes altered in patients with gastritis related to *Helicobacter pylori* infection, atrophic gastritis or both<sup>(62-66)</sup> as well as in patients who are receiving long-term treatment with proton-pump inhibitors<sup>(67)</sup>. Centanni et al described that patients with impaired acid secretion require an increased dose of LT4<sup>(18)</sup> and LT4 requirements are higher in hypochlorhydric goiter with *H pylori*-gastritis and thyrotropin levels decreased by 94 % after treatment<sup>(66)</sup>.

TABLE I. Causes of LT4 malabsorption

Gastrointestinal diseases and surgeries			
Coeliac disease	8, 9	Jejunostomy	14
Lactose intolerance	8, 10, 11	Jejunioileal bypass	15,16
Vitamin B12 deficiency	12	Short bowel syndrome	17
Intestinal infections (Giardia lamblia)	13	Autoimmune gastritis and H. pylori infection	18, 19, 20
Liver diseases			
cirrhosis		Obstructive liver disease	4
Pancreatic diseases			
Pancreatic insufficiency	20, 21		
Medication interference			
Cholestyramine	22	Activated charcoal	37
Colestipol	23	Anion exchange resins	20
Aluminum hydroxide antacids	24, 25	Phenytoin	38, 39
Ferrous sulphate	26, 27	Phenobarbital	38, 39
Sucralphate	28, 29	Carbamazepine	40
Propranolol	30	Rifampin	41
Laxatives	31	Sertraline	42
Calcium carbonate	32, 33	Amiodarone	43
Lovastatin	34, 35	Oestrogen therapy	44
Sevelamer hydrochloride	36	Raloxifene	45
Chromium picolinate	36	Cimetidine	7
Bile acid sequestrants	22	Herbal remedies	46
Dietary interference			
Walnuts	47	Prunes	47
Soybean	48	Fiber	50, 51
Coffee	49		
Heart disease			
Congestive Heart failure	20		
Pregnancy	44		

Conceivably, even physiological variations in intragastric pH might determine differences in LT4 tablets dissolution, and therefore LT4 absorption. Preliminary observations indicated that co-administration of acidic compounds –as official HCl- might enhance absorption of LT4. Similarly, a favourable effect of taking certain drugs with orange juice has been described; thus, in H pylori- and HIV-positive hypochlorhydric subjects, delavirdine absorption increased by 57 % with orange juice administration<sup>(68)</sup>. Although controversial, in certain cases it has been found that vitamin C improves iron absorption<sup>(69)</sup>.

In this study we evaluated whether a beneficial effect on LT4 absorption of co-administration of Vitamin C, an acidic compound, might be observed in patients with hypothyroidism refractory to oral LT4 alone.

## METHODS

### Subjects

Twenty eight patients, 24 women and 4 men, aged 26–76 years (mean  $48,0 \pm 17.75$  years), taking LT4 treatment for primary hypothyroidism who failed to achieve TSH levels at the desired target in spite of increasing their dose of LT4 (Levotiroxina Glaxo, GlaxoSmithKline) were included in the study. The target TSH level was considered, as usual practice, between low and half normal value, i.e. 0.4 and 2.0 mU/L. Because serum TSH levels are usually normalized in patients with primary hypothyroidism with a mean daily LT4 dose of about  $1.6 \pm 0.4 \mu\text{g kg}^{-1} \text{day}^{-1}$ (1), we included patients that required more than  $1.6 \mu\text{g kg}^{-1} \text{day}^{-1}$  to achieve TSH levels between 0.4 and

2.0 mU/L (ie  $\geq 1.7 \mu\text{g kg}^{-1} \text{ day}^{-1}$ ). This situation was present in 33 of 2450 patients who attended our center, with a prevalence of 1.34 %; the other 8 patients did not want to participate in the study. The mean daily dose was  $147.19 \pm 36.47 \mu\text{g/day}$ , and the mean body weight  $69.43 \pm 14.59 \text{ kg}$ . None of the patients were taking medication known to interfere with LT4 absorption/metabolism (Table I), nor were they known to have gastrointestinal diseases that could alter LT4 absorption (Table I). Gastrointestinal or liver diseases were excluded by absence of symptoms of impaired gastric acid secretion or intestinal malabsorption and, when possible, through laboratory investigations. All 28 patients had normal liver function tests and antibodies against gliadin and endomysium were negative, and 8/28 had parietal-cell antibodies measured and were negative. Carbon-13-labeled-urea breath test, used to diagnose *Helicobacter pylori* infection, was performed in 14/28 patients and was negative in all cases. Twenty of the 28 patients had psychiatric evaluation in order to exclude non-compliance. Five patients had been on a lactose-free diet before vitamin C co-administration, with no change in TSH level. Other potential causes of LT4 malabsorption or accelerated LT4 metabolism were not studied.

The cause of hypothyroidism was primary autoimmune hypothyroidism in 18 subjects, primary non-auto-immune hypothyroidism in 4 subjects, previous radioiodine treatment given for hyperthyroidism-Graves' disease in 1 subject and autonomous nodule in 1 subject-, and thyroidectomy because of a nodular goitre in 4 subjects.

None of the patients had any contraindication for receiving 1 g/day of vitamin C.

### Study design

All subjects gave informed written consent, and the protocol was approved by a local ethics committee. Before the study, all subjects were taking LT4 in the morning, with 200 cc of tap water, at least an hour before breakfast. Hypothyroidism as indicated by elevated TSH (on at least two occasions) was persistent despite administration of high oral LT4 doses (ie  $\geq 1.7 \mu\text{g kg}^{-1} \text{ day}^{-1}$ ). After an interval of at least two months, all patients were asked to ingest the same LT4 dose, at the same time, but along with vitamin C (1 g in 200 cc of tap water; Redoxon 1g®, Bayer). Serum TSH levels were prospectively measured 6-8 weeks after starting

co-administration with vitamin C, and another measurement was performed at least two months later (Figure 1). All blood samples were drawn in an ambulatory Center, and the LT4 preparation used throughout the study was Levo-tiroxina GlaxoSmithKline®.

The main outcome measurement was the median change in serum TSH levels. Serum TSH (normal range 0.4 - 4.0 mU/l) was measured by chemiluminescence (Bayer-Centauro), with a detection limit of 0.01 mU/l. The interassay variation was 7.5 and 3.1 6.4 % at mean TSH values of 0.5 and 7.5 mU/ml, respectively.

### Statistical analysis

Data are expressed as mean  $\pm$  SD, and TSH pre and post vitamin C are expressed as median as well. Student's t -test (paired) and Wilcoxon signed rank test were used to detect significant differences between TSH levels before and after co-administration with vitamin C. For all the tests,  $P < 0.05$  was considered to be a significant difference. In all cases, statistical analyses were performed on absolute values.

Although it was not a randomized double-blind study, information as to which patients were taking LT4 alone or LT4 with Vitamin C was not available when hormone measurements were being performed.

## RESULTS

Table II shows, for each patient, the mean values of two or more levels of serum TSH before and after

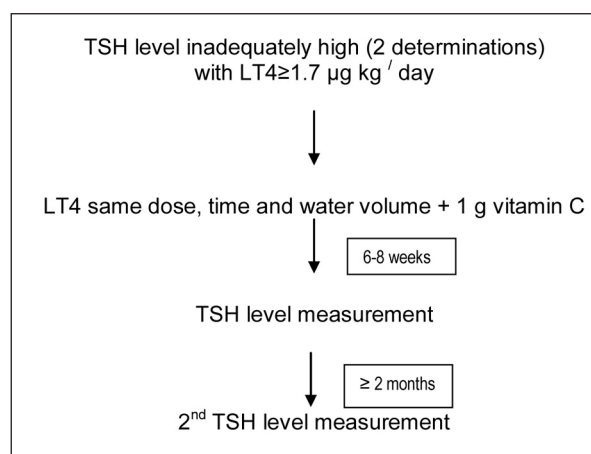


Figure 1. Study design.

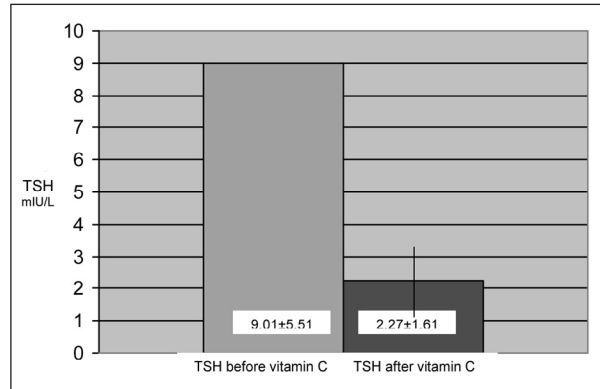
**TABLE II.** Individuals values of LT4 dose, TSH pre and post vitamin C, and % of TSH reduction

Patient	LT4 dose ( $\mu\text{g}/\text{kg}$ )	TSH pre-Vit C (mIU/L)	TSH post-Vit C (mIU/L)	TSH reduction (%)
1	2.4	2.6	1.6	39.3
2	1.8	13.9	0.4	96.8
3	2.9	10.8	5	53.7
4	1.8	5.1	0.8	84.3
5	2.1	2.2	1.4	36.5
6	2.5	10.6	3	71.7
7	1.7	4.8	3.7	22.4
8	2.2	8.2	2.5	69.5
9	2.1	11	0.7	93
10	2	14.9	0.7	95.2
11	2.8	9.6	0.7	92.7
12	1.8	4.8	1.3	71.6
13	2.2	13.2	2.2	83.2
14	2.2	7.2	3.2	55.0
15	1.71	7.4	0.3	95.2
16	2	13.1	4.9	62.6
17	1.9	5.1	3.3	34.9
18	1.7	6.8	0.4	92.9
19	2	31	3.6	88.4
20	1.9	11.1	4.4	60.4
21	1.7	7.1	0.4	94.4
22	1.7	5.2	2.7	46.6
23	1.8	6.7	1.2	80.1
24	3.1	9	3.6	60.1
25	2.4	3.3	0.3	90.4
26	2.4	8	1.3	83.2
27	1.9	8	4.5	43.7
28	2.1	10.9	4.8	56.2

ingestion of levothyroxine along with vitamin C, as well as percentage of TSH level reduction and dose of LT4 required (expressed in  $\mu\text{g kg}^{-1} \text{ day}^{-1}$ ).

Serum TSH levels decreased remarkably and significantly after changing LT4 ingestion from tap water to tap water + vitamin C. After 6 - 8 weeks of taking LT4 along with vitamin C, serum TSH decreased in all 28 patients (average reduction  $69.79 \pm 22.19 \%$ , range: 22.4-96.8 %), and the target or desired level of TSH was achieved in 19/28 patients.

The difference between TSH levels before and after co-administration of LT4 along with vitamin C was significant: mean values  $\pm$  standard deviation (SD) for TSH were,  $9.01 \pm 5.51$  mIU/L (median 8.04; range: 2.22-31.05 mIU/L) vs  $2.27 \pm 1.61$  mIU/L (median 1.92; range: 0.32-5.0 mIU/L), without and with vitamin C, respectively ( $p < 0.0001$  for



**Figure 2.** Difference between TSH levels before and after co-administration of LT4 along with vitamin C was significant: mean values  $\pm$  standard deviation (SD) for TSH ( $p < 0.0001$ ).

Student's t -test (paired) and for Wilcoxon signed rank test) (Figure 2).

No patient experienced any adverse effect related to the ingestion of vitamin C.

## DISCUSSION

Many causes of LT4 malabsorption have been reported and the more common causes are listed in Table I including gastrointestinal diseases, liver diseases, pancreatic diseases, certain gastrointestinal surgical procedures, many drugs and dietary interactions, heart disease or pregnancy<sup>(7-37, 43-51)</sup>. Other drugs may accelerate the disposal of LT4 and therefore increase the dose requirement<sup>(38-42)</sup>. In some rare patients, hypothyroidism persists despite seemingly adequate or even supraphysiologic LT4 doses, even after having excluded the above-mentioned possible causes as well as pseudomalabsorption or noncompliance<sup>(1, 52-57)</sup>. Indeed, there are several case reports in the literature in which euthyroidism could only be achieved through parenteral LT4 administration and the underlying pathophysiologic mechanism for the malabsorption remained unresolved<sup>(58-60)</sup>.

Other than known explanations for malabsorption of LT4, alternative explanations should also be considered in patients requiring large doses of LT4 to achieve euthyroidism. Often, however, no explanation for reduced bioavailability can be found, and this situation may be addressed with an empirical solution. Preliminary observations indicated that co-administration of acidic compounds –as officinal HCl– might enhance absorption of LT4, and vitamin C as acidic compound has better tolerability. Our study shows that TSH

level decreases reflecting improved LT4 bioavailability after changing the vehicle for ingestion of LT4 from plain water to the same volume of plain water with vitamin C. This observation may have application to those patients who do not achieve their target TSH level in spite of a high dose of LT4. Ingestion of LT4 with vitamin C is safe and was well-tolerated with a resultant desirable salutary effect on LT4 and TSH blood levels.

There may be several explanations for our results. Conceivably, our patients could have had a relatively elevated gastric pH, which in turn might have interfered with dissolution of LT4. Taking LT4 with vitamin C will result in a temporary decrease in gastric pH, which might contribute to a better dissolution of the tablet. This is consistent with recent evidence indicating that a low gastric pH can facilitate LT4 absorption in gut<sup>(18)</sup>. Pabla et al described that dissolution of LT4 decreased considerably with an increase in the pH, which suggests a possible physical interaction in patients concurrently on LT4 and gastric pH alterations. Variable dissolution of LT4 can, therefore, impact the oral absorption and bioavailability of LT4<sup>(61)</sup> and may result in bioequivalence problems. The same commercial form of LT4 was used in all our patients.

The absorption of some drugs, such as delavirdine and iron, has been improved with vitamin C<sup>(68, 69)</sup>. For this study, 1 g of vitamin C was added to 200 cc of plain water producing a solution with a pH of approximately 3.0, a pH associated with an adequate dissolution of LT4 tablets. It was not our intention to supplement vitamin C in deficient subjects, and rather, a clearly safe dose was selected.

We are aware that this study has many limitations. We did not analyze serum T4 levels because determinations of serum TSH levels is the test most clinicians and societies use to judge whether the proper amount of levothyroxine is bioavailable<sup>(70)</sup>.

Although the study did not exclude every cause of malabsorption<sup>(7-51)</sup> in every patient, with laboratory tests (except for coeliac disease, excluded in all), the results were negative in those patients who had them evaluated, and the others were asymptomatic for the known causes of LT4 malabsorption. Some cases of malabsorption of LT4 due to intolerance to lactose have been described<sup>(11)</sup>, but a trial of lactose free diet on some of our patients before the study did not improve serum TSH levels. Checchi et al found that 155 of 391 with autoimmune hypothyroidism were parietal cell antibodies

(PCA)-positive, and that LT4 requirement was significantly higher in them (1.24 +/- 0.40 microg/kg x d) than in PCA-negative patients (1.06 +/- 0.36 microg/kg x d)<sup>(19)</sup>. PCA measured in 8/28 of our patients was negative in all of them, including 5/18 with autoimmune hypothyroidism. Finally, many patients who need to be prescribed high doses of LT4 are not perfectly compliant with their medication, whether unintentional or for secondary gain<sup>(1)</sup>. Non-compliance or pseudomalabsorption was excluded either by psychiatric evaluation or by our subjective impression, and patient errors in LT4 ingestion were excluded by exhaustive and repeated interrogatories.

We did not admit patients to hospital, either to measure gastric pH or serum T4 level after supervised ingestion of LT4 (LT4 absorption study, 54). We considered that patients had values of interindividual variations of gastric pH and of LT4 absorption distributed in the range for a normal population. Intraindividual variations in LT4 absorption might have accounted for the changes, but the measurements in the same subject were repeated at least twice before and after vitamin C as well, and were done within a short period of time, decreasing the possibility of the effect of an intraindividual variation in LT4 absorption.

In conclusion, our study demonstrated that changing the vehicle for ingestion of LT4 from plain water to the same volume of plain water with 1 g vitamin C improves the apparent absorption of LT4 –as it was evaluated indirectly by reduction in TSH level- in a subset of patients receiving this hormone for primary hypothyroidism who do not reach the target TSH level with the usual dose/weight of LT4. The important practical consequence of our finding is that a trial of coadministration of LT4 with vitamin C to enhance LT4 absorption should be considered in patients requiring high doses of LT4 with no obvious cause of LT4 malabsorption. This pilot study needs to be confirmed in a larger randomized, controlled trial.

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