

ORIGINAL ARTICLE

Thyroxine in Goiter, *Helicobacter pylori* Infection, and Chronic Gastritis

Marco Centanni, M.D., Lucilla Gargano, M.D., Gianluca Canettieri, M.D., Nicola Viceconti, M.D., Antonella Franchi, M.D., Gianfranco Delle Fave, M.D., and Bruno Annibale, M.D.

ABSTRACT

BACKGROUND

Malabsorption of thyroxine has been described in patients treated with drugs that modify an acidic environment. We determined whether there is an increased need for thyroxine in patients with euthyroid multinodular goiter and impaired secretion of gastric acid.

METHODS

We assessed the dose of thyroxine required to obtain a low level of thyrotropin (0.05 to 0.20 mU per liter) in 248 patients with multinodular goiter. Of these 248 patients, 53 also had *Helicobacter pylori*-related gastritis and 60 had atrophic gastritis of the body of the stomach (31 with evidence of *H. pylori* infection and 29 without such evidence). The reference group comprised 135 patients with multinodular goiter and no gastric disorders. In addition, variation in the level of serum thyrotropin was prospectively studied in 11 patients treated with thyroxine before and after *H. pylori* infection and both before and during treatment with omeprazole in 10 patients treated with thyroxine who had gastroesophageal reflux.

RESULTS

The daily requirement of thyroxine was higher (by 22 to 34 percent) in patients with *H. pylori*-related gastritis, atrophic gastritis, or both conditions than in the reference group. In prospective studies, the occurrence of *H. pylori* infection in the 11 patients treated with thyroxine led to an increase in the level of serum thyrotropin ($P=0.002$), an effect that was nearly reversed on eradication of *H. pylori* infection. In a similar way, omeprazole treatment was associated with an increase in the level of serum thyrotropin in all 10 patients treated with thyroxine, an effect that was reversed by an increase in the thyroxine dose by 37 percent.

CONCLUSIONS

Patients with impaired acid secretion require an increased dose of thyroxine, suggesting that normal gastric acid secretion is necessary for effective absorption of oral thyroxine.

From the Endocrinology Unit, Department of Experimental Medicine and Pathology, University La Sapienza, Polo Pontino, Latina (M.C., L.G., G.C., N.V., A.F.); and the Department of Digestive and Liver Diseases, Sant'Andrea Hospital, University La Sapienza, Rome (G.D.F., B.A.) — both in Italy. Address reprint requests to Dr. Centanni at the Department of Experimental Medicine and Pathology, Policlinico Umberto I, Viale Regina Elena 324, 00161 Rome, Italy, or at marco.centanni@uniroma1.it.

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THE DAILY DOSE OF THYROXINE IN THE treatment of patients with thyroid disease has been studied extensively, mainly as replacement therapy for hypothyroidism.¹⁻⁶ Efficient absorption of oral thyroxine appears to be important to ensure optimal treatment.^{7,8} Oral thyroxine is absorbed through the intestinal mucosa^{7,8} at the level of the jejunum and ileum.^{7,8} Absorption of thyroxine ranges from 62 to 82 percent of the ingested dose, with a peak between the first and third hours.⁸ Intestinal absorption of thyroxine is a key determinant of the effectiveness of therapy and is influenced by several factors, including the age of the patient,^{7,9} adherence to therapy,⁶ dietary habits,⁶ absorption kinetics,^{7,8} malabsorption,^{6,10} and interference of other drugs.^{6,11-14}

The study of interference of some of these drugs has highlighted the role of an acidic environment in thyroxine absorption.^{11,12} The normally acid environment of the stomach becomes altered in patients with gastritis related to *Helicobacter pylori* infection, atrophic gastritis of the body of the stomach, or both,¹⁵⁻¹⁸ as well as in patients who are receiving long-term treatment with proton-pump inhibitors.¹⁹ Both *H. pylori* infection and treatment with proton-pump inhibitors are frequent in Western countries,^{20,21} and the association of thyroid diseases with atrophic gastritis has been reemphasized.^{16,22} The concomitant presence of such gastric disorders with thyroid diseases may lead to uncertainty about the daily dose of thyroxine and, thus, to a continuous need for care and monitoring. This study was aimed at analyzing the dose of thyroxine that is required to lower levels of thyrotropin in patients with goiter who have impaired secretion of gastric acid.

METHODS

PATIENT POPULATION

We conducted our study in a cohort of 269 outpatients with nontoxic multinodular goiter who were seen at a referral center for thyroid disease from 1999 to 2004. Approval was granted from the institutional review board, and written informed consent was obtained from all participants. The patients in this study were treated with thyroxine in an attempt to reduce the size of their goiters or at least to minimize further growth, although the efficacy of this practice has been debated.²³ The diagnosis of nontoxic multinodular goiter (increased thyroid volume, presence of mul-

iple nodules, and normal levels of thyrotropin and serum free thyroxine) was based on clinical and sonographic examination, the measurement of thyrotropin and serum free thyroxine, the presence of serum thyroid peroxidase antibodies, radioiodine uptake, and thyroid scanning.²³ None of the patients had received previous treatment, and all had normal thyroid function (i.e., with levels of thyrotropin and serum free thyroxine in the normal range) (Table 1). All patients had stage 1A or 1B goiter (according to the World Health Organization classification), with at least two nodules whose diameters were more than 1 cm and less than 3 cm, and all had clinical features suggestive of impaired gastric acid secretion (e.g., anemia caused by cobalamin deficiency or iron deficiency; long-standing uninvestigated dyspepsia, as indicated by bloating, fullness, or burning; or a combination of these conditions).²¹

These findings are the specific clinical features that have been described in association with atrophic gastritis and *H. pylori*-related nonatrophic gastritis, which are both related to hypochlorhydria and achlorhydria.^{16,24,25} Patients with high levels of serum thyroid peroxidase antibodies were not excluded from the study. Exclusion criteria were the presence of low levels of serum thyrotropin (less than 0.20 mU per liter) in untreated patients, nonsuppressible nodules at scintigraphy, or both; or celiac disease and intestinal malabsorption, recent drug treatments (e.g., with estrogens or antisecretory drugs), or both.

STUDY GROUP

A total of 123 euthyroid patients with nontoxic multinodular goiter met the inclusion criteria and entered the study after informed consent was obtained. Gastrin levels were measured after an overnight fast, and the patients were tested for parietal-cell antibodies and *H. pylori* antibodies. A carbon-13-labeled urea breath test was performed. Patients who presented with hypergastrinemia underwent tests of basal and stimulated acid secretion and gastroscopy with antral and corporal biopsies. *H. pylori*-related nonatrophic gastritis was diagnosed in 53 patients, primarily on the basis of histologic examination, results on the urea breath test, or both, along with the presence of *H. pylori* antibodies as a subsidiary test. Atrophic gastritis was diagnosed in 60 patients on the basis of histologic criteria (inflammation, oxyntic atrophy, and intestinal metaplasia), low

Table 1. Baseline Characteristics of Patients with Multinodular Goiter.*

Group	No. of Patients	Age yr	Male: Female Ratio	Thyrotropin†	Serum Free Thyroxine‡	Gastrin	Increased Level of Serum Parietal-Cell Antibodies	Increased Level of Serum <i>H. pylori</i> Antibodies	Increased Level of Serum Thyroid Peroxidase Antibodies
				mU/liter	ng/dl	pg/ml		no. of patients	
Reference patients	135	48±13	9/126	1.83±0.68	1.19±0.21	18±13	0	0	0
Patients with <i>Helicobacter pylori</i> -related nonatrophic gastritis	53	50±11	1/52	1.71±0.59	1.22±0.23	51±35	7	45§	0
Patients with atrophic gastritis	29	55±12	2/27	1.97±0.67	1.38±0.32	563±358	20	0	18
Patients with <i>H. pylori</i> -related nonatrophic gastritis and atrophic gastritis	31	53±12	2/29	1.78±0.52	1.19±0.25	670±297	22	31	21

* Plus-minus values are means ±SD. Patients in the reference group had multinodular goiter and no evidence of gastritis or *H. pylori* infection.

† The normal range for this assay is 0.2 to 4.0 mU per liter.

‡ The normal range for this assay is 0.8 to 1.8 ng per deciliter.

§ The eight patients who did not have increased serum *H. pylori* antibodies had positive results on the urea breath test.

acid output, and the presence of *H. pylori* antibodies. Another 10 patients without evidence of either hypergastrinemia or *H. pylori* infection presented with recurrent heartburn; they also underwent gastroscopy with biopsy. The presence of hyperemia of the lower esophagus in the absence of gastric disorders was considered a confirmation of the diagnosis of gastroesophageal reflux disease.

REFERENCE GROUP

A total of 146 patients with nontoxic multinodular goiter without signs or symptoms of impaired gastric acid secretion (i.e., an absence of anemia caused by cobalamin deficiency or iron deficiency or dyspepsia) were screened in a manner similar to that used in the study patients, and their consent was obtained. Atrophic gastritis and *H. pylori* infection were ruled out on the basis of normal fasting gastrin levels, the absence of parietal-cell antibodies and *H. pylori* antibodies, and negative results on urea breath tests (Table 1). However, 4 to 19 months after the start of the study, 11 of these 146 previously asymptomatic patients began to have dyspeptic symptoms. For this reason, the urea breath test was repeated, and *H. pylori* infection was diagnosed in all 11 patients, who were then removed from the reference group. Their daily requirement of thyroxine was then analyzed prospectively before and after the eradication of *H. pylori*. Thus, a total of 135 patients served as the gastric disease-free reference group; their baseline characteristics are shown in Table 1.

STUDY DESIGN

All 269 patients who were enrolled in the study were advised and agreed to take thyroxine (Eutirox, Bracco) under fasting conditions, waiting at least one hour before eating or drinking (except water) to avoid the potentially confounding influence of food. The initial dose of thyroxine in all subjects was 50 µg per day, and responses were followed for at least 30 months. The thyroid-pituitary axis was evaluated every four months. When indicated, treatment was promptly and progressively increased until a low serum thyrotropin level (0.05 to 0.20 mU per liter) was obtained on at least two consecutive measurements (more than eight months apart). The dose of thyroxine that was required at the time of the most recent thyrotropin assay was normalized according to body weight (in kilograms). At the time of sampling, all 269 patients appeared to be adherent to the study protocol. Multinodular goiter is more prevalent in women than in men and fewer men than women provided consent to participate in the study, factors that account for differences in the usual male-to-female ratio.

THYROXINE REQUIREMENTS

The daily thyroxine dose that was required to achieve a low thyrotropin level was assessed in 135 patients (126 women and 9 men) from 15 to 74 years of age with euthyroid multinodular goiter and no evidence of gastric disorders (reference patients) (Table 1). The values in these patients were compared with those in 113 patients with

multinodular goiter and impaired secretion of gastric acid. Of the latter group, 53 had *H. pylori*-related nonatrophic gastritis (52 women and 1 man) with an age range from 22 to 58 years. An additional 60 patients had atrophic gastritis (56 women and 4 men), with an age range from 22 to 74 years. Of the patients with atrophic gastritis, 31 also had evidence of *H. pylori* infection, and 39 had high levels of serum thyroid peroxidase antibodies, suggesting that chronic thyroiditis may coexist within a goiter. The characteristics of these patients are shown in Table 1.

PATIENTS WITH NEWLY DIAGNOSED *H. PYLORI* INFECTION

In 11 patients with multinodular goiter (all women, with a median age of 44 years), *H. pylori* infection was diagnosed 4 to 19 months after the study began. These patients were evaluated prospectively, and their serum thyrotropin levels were measured before, at the time the infection was diagnosed without altering the dose of thyroxine, and on eradication of *H. pylori* infection. In this group, the diagnosis of infection was based primarily on the results of the urea breath test. After the diagnosis of *H. pylori* infection, all patients were treated with a combination of clarithromycin (Klacid, Abbott), amoxicillin (Zimox, Pharmacia), and omeprazole (Mepral, Bracco) for two weeks. Negative results on a urea breath test at least two months later were considered proof of eradication of the bacteria. At that point, thyrotropin levels were reassayed and the dose of thyroxine was adjusted to achieve low levels of serum thyrotropin.

PATIENTS TREATED WITH OMEPRAZOLE

Ten women with multinodular goiter and recurrent heartburn were initially treated with thyroxine alone to achieve low levels of serum thyrotropin. When gastroesophageal reflux disease was diagnosed and other gastric diseases were ruled out, omeprazole (at a dose of 40 mg per day) was administered along with thyroxine. Serum thyrotropin levels were prospectively measured before and during omeprazole treatment, and the dose of thyroxine remained unchanged for at least six months. At that time, the dose of thyroxine was increased to achieve low levels of serum thyrotropin.

ASSAYS

Levels of serum free thyroxine were assayed by radioimmunoassay (Ares-Serono) (normal range,

0 to 23 pmol per liter, which is the equivalent of 0.8 to 1.8 ng per deciliter). Serum thyrotropin levels were measured by immunoradiometric assay (Ares-Serono) (normal range, 0.2 to 4.0 mU per liter; sensitivity, 0.01 mU per liter; intraassay and interassay variation, 4.2 percent). Serum thyroid peroxidase antibodies were measured by radioligand assay (intraassay variation, 3.6 percent; interassay variation, 4.6 percent). The diagnoses of iron-deficiency anemia and cobalamin-deficiency anemia were made on the basis of serum hemoglobin levels (under 12 g per deciliter in women and under 14 g per deciliter in men); low levels of ferritin, vitamin B₁₂, or both; and the mean corpuscular volume.^{15,17,24} Mean corpuscular volume and hemoglobin were measured with an automated counter (Technicon H3, Bayer). The urea breath test was performed with the use of an acid meal composed of 75 mg of ¹³C-labeled urea that was dissolved in 200 ml of orange juice. Breath samples were analyzed by infrared spectroscopy (Iris, Wagner-Analysen-Technik). A change from baseline of more than 4.5 percent at 30 minutes was considered to indicate the presence of *H. pylori* infection.²⁶

H. pylori antibodies were detected by a commercial enzyme-linked immunosorbent assay kit (GAP test, Biorad). Levels of serum *H. pylori* antibodies were determined with the use of a solid-phase immunosorbent assay (Autostat, Cogent Diagnostics). Fasting plasma gastrin levels were measured by a radioimmunoassay with the use of antibody 4562 (courtesy of J.F. Rehfeld, University of Copenhagen, Copenhagen),¹⁵ and basal acid output and pentagastrin-stimulated acid output were determined as described previously.¹⁵ At gastroscopy, three biopsy specimens were obtained from the midbody mucosa and three from the antrum. Histologic analysis was performed on serial paraffin sections (5 μm) stained with hematoxylin and eosin and, for *H. pylori* detection, with Giemsa.

STATISTICAL ANALYSIS

Data are expressed as means ±SD or as medians (with interquartile ranges). InStat Graphpad software, version 3.06 (2003) for Windows, was used in the statistical analysis. The Friedman test was used for the analysis of variance. The Mann-Whitney test was used to compare pairs of groups, and the Wilcoxon signed-rank test was used to evaluate changes within subjects.

RESULTS

DAILY THYROXINE REQUIREMENTS

The daily dose of thyroxine that was required to achieve low levels of thyrotropin (0.05 to 0.20 mU per liter) in the 135 patients in the reference group was compared with the dose for 53 patients with *H. pylori*-related gastritis, for 60 patients with atrophic gastritis, for 31 patients with evidence of *H. pylori* infection, and for 29 patients without such infection. The baseline characteristics of these patients are shown in Table 1. In the reference group, a median thyroxine dose of 100 µg per day (which corresponded to a dose of 1.53 µg per kilogram of body weight per day) was sufficient to obtain a low level of serum thyrotropin. At a similar dose, 52 of 53 patients with *H. pylori*-related gastritis and all of those with atrophic gastritis had thyrotropin values in the normal range. The daily dose of thyroxine in these patients was thus increased until the desired low level of serum thyrotropin was achieved in all patients (a dose in-

crease of 22 percent, $P < 0.001$ for the comparison with the reference group) (Table 2). A higher median dose of thyroxine (27 percent, $P < 0.001$) was also necessary to obtain a low level of serum thyrotropin in patients with atrophic gastritis (Table 2). In these patients, an increased level of serum thyroid peroxidase antibodies was not associated with the daily thyroxine requirement (Table 2). In contrast, in patients with atrophic gastritis who also presented with evidence of *H. pylori* infection, the requirement for thyroxine was one third more than in the reference group (34 percent, $P < 0.001$).

Since atrophic gastritis is more frequent in elderly persons¹⁶ (a period of life characterized by a reduced need for daily thyroxine¹¹), we examined the thyroxine requirement of patients in the reference group and patients with gastritis after arbitrarily subdividing them into two age-related groups: under 60 years of age and 60 years of age or older. Twenty-three of 60 patients with atrophic gastritis and 20 of 135 patients in the reference group were at least 60 years of age. A

Table 2. Daily Thyroxine Requirement in Patients with Multinodular Goiter and *Helicobacter pylori*-Related Gastritis or Atrophic Gastritis, with or without Evidence of *H. pylori* Infection.*

Group	No. of Patients	Thyrotropin†	Serum Free Thyroxine‡	Median Dose of Thyroxine (interquartile range)§		Median Increase in Thyroxine Dose Required	P Value¶
		mU/liter	ng/ml	µg/day	µg/kg/day	%	
Reference patients	135	0.12±0.05	1.48±0.26	100 (86–100)	1.53 (1.40–1.62)	NA	NA
Patients with <i>H. pylori</i> -related nonatrophic gastritis	53	0.11±0.04	1.53±0.22	125 (112–125)	1.87 (1.78–2.03)	22	<0.001
Patients with atrophic gastritis	60	0.11±0.06	1.50±0.24	125 (113–150)	1.95 (1.81–2.25)	27	<0.001
Patients with concurrent <i>H. pylori</i> -related nonatrophic gastritis	31	0.11±0.04	1.53±0.22	150 (125–150)	2.05 (1.87–2.34)	34	<0.001
Patients without concurrent <i>H. pylori</i> -related nonatrophic gastritis	29	0.12±0.05	1.49±0.25	125 (100–150)	1.90 (1.72–2.04)	24	<0.001
Patients with increased level of serum thyroid peroxidase antibodies	39	0.11±0.06	1.51±0.19	125 (122–150)	1.95 (1.81–2.27)	27	<0.001
Patients without increased level of serum thyroid peroxidase antibodies	21	0.11±0.05	1.49±0.26	125 (109–156)	1.98 (1.82–2.17)	29	<0.001

* Plus-minus values are means ±SD. NA denotes not applicable.

† The normal range for this assay is 0.2 to 0.4 mU per liter.

‡ The normal range for this assay is 0.8 to 18 ng per deciliter.

§ Daily doses of thyroxine (expressed in micrograms per day and normalized according to body weight) are expressed as median values with interquartile ranges. Median thyroxine doses are the doses at which patients maintained thyrotropin concentrations of 0.05 to 0.20 mU per liter in at least two consecutive measurements, obtained more than eight months apart. Data refer to the thyroxine doses that were administered before the last thyrotropin measurement.

¶ The Mann-Whitney test was used to compare the value in each group with the value in the reference group.

|| Patients in the reference group had multinodular goiter and no evidence of gastritis or *H. pylori* infection.

Table 3. Effect of Age on the Daily Thyroxine Requirement in Patients with Multinodular Goiter, with or without Concomitant Atrophic Gastritis.*

Variable	No. of Patients	Age yr	Thyrotropin mU/liter	Serum Free Thyroxine ng/ml	Median Dose of Thyroxine (interquartile range)† μg/kg/day	Median Increase in Thyroxine Dose Required %	P Value
Age <60 yr							
Reference patients‡	115	40±10	0.12±0.05	1.48±0.26	1.58 (1.43–1.66)	NA	NA
Patients with atrophic gastritis	37	46±8	0.11±0.07	1.57±0.30	2.08 (1.90–2.38)	32	<0.001§
Age ≥60 yr							
Reference patients‡	20	65±4	0.13±0.05	1.51±0.26	1.37 (1.21–1.46)	NA	NA
Patients with atrophic gastritis	23	67±4	0.12±0.06	1.58±0.31	1.81 (1.68–1.93)	32	<0.001¶

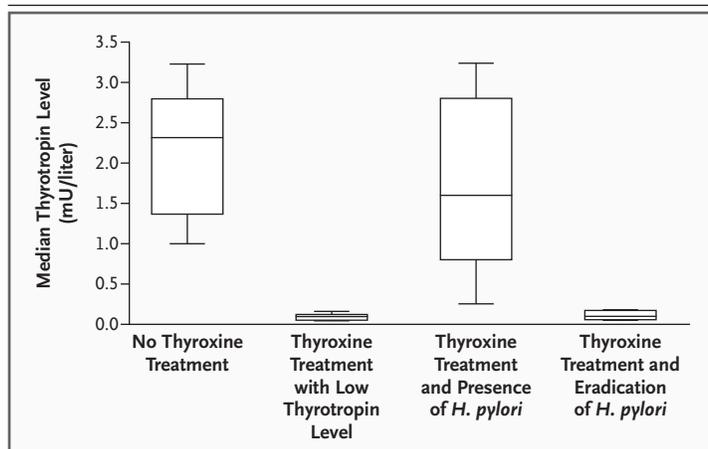
* Plus-minus values are means ±SD. The 53 study patients with *Helicobacter pylori* infection were not included in the analysis. NA denotes not applicable.

† Daily doses of thyroxine (normalized according to body weight) are expressed as median values with interquartile ranges. Median thyroxine doses are the doses at which patients maintained thyrotropin concentrations of 0.05 to 0.20 mU per liter in at least two consecutive measurements, obtained more than eight months apart. Data refer to the thyroxine doses that were administered before the last thyrotropin measurement.

‡ Patients in the reference group had multinodular goiter and no evidence of gastritis or *H. pylori* infection.

§ The Mann-Whitney test was used to compare patients with atrophic gastritis with patients in the reference group under the age of 60 years.

¶ The Mann-Whitney test was used to compare patients with atrophic gastritis with patients in the reference group 60 years of age or older.

**Figure 1.** Effect of Newly Diagnosed *Helicobacter pylori* Infection on Thyrotropin Levels in Patients with Multinodular Goiter Treated with Thyroxine.

The box plots show levels of thyrotropin in patients who received no treatment with thyroxine, in patients receiving thyroxine treatment (median dose, 1.56 μg per kilogram per day) and in whom a low level of thyrotropin (0.05 to 0.20 mU per liter) was stably achieved, in patients with *H. pylori* infection (with no change in the dose of thyroxine), and in patients after the eradication of *H. pylori* infection (median dose, 1.70 μg per kilogram per day). Each box plot shows the median (horizontal line within the box), the interquartile range (the horizontal lines at either end of the box), and the SD (I bar). The Friedman test was used for the analysis of variance ($P < 0.001$). $P = 0.002$ (by the Wilcoxon signed-rank test) for the comparison of patients with *H. pylori* infection receiving thyroxine with patients with low levels of thyrotropin receiving thyroxine; and $P = 0.002$ (by the Wilcoxon signed-rank test) for the comparison of patients whose *H. pylori* infection was eradicated with patients with *H. pylori* infection.

similar 32 percent increase in the median dose of thyroxine was required in patients with atrophic gastritis in both age groups, as compared with their age-related reference groups (Table 3).

PROSPECTIVE STUDY IN PATIENTS WITH NEWLY DIAGNOSED *H. PYLORI* INFECTION

Levels of serum thyrotropin were measured in 11 patients with multinodular goiter before treatment, once a low level of thyrotropin (0.05 to 0.20 mU per liter) was stably attained on thyroxine treatment, when *H. pylori* infection was diagnosed, and on the eradication of the infection (Fig. 1). In these patients, a low level of serum thyrotropin (median level, 0.11 mU per liter) was achieved at a median dose of thyroxine of 1.56 μg per kilogram per day. When *H. pylori* infection was diagnosed, an increase in the level of serum thyrotropin was observed in all patients (median level, 1.35 mU per liter) before thyroxine treatment was changed (Fig. 1). Once the infection was successfully treated, a low level of serum thyrotropin was reestablished (median level, 0.12 mU per liter) in all patients at a slightly higher median dose of thyroxine (1.70 μg per kilogram per day) (Fig. 1).

PROSPECTIVE STUDY IN PATIENTS TREATED WITH OMEPRAZOLE

Among 10 patients with multinodular goiter and gastroesophageal reflux disease who were treat-

ed with both thyroxine and omeprazole, serum thyrotropin levels were evaluated both before treatment with omeprazole and after treatment. Figure 2 shows the median levels of thyrotropin in untreated patients and once a low level of thyrotropin (median level, 0.1 mU per liter) was attained in all patients at a median thyroxine dose of 1.58 μg per kilogram per day. The addition of omeprazole treatment (at a dose of 40 mg per day) led to a variable increase in thyrotropin levels in all patients (median level, 1.70 mU per liter; $P=0.002$). A low level of serum thyrotropin was reestablished in all patients by an increase in the median dose of thyroxine to a level (2.16 μg per kilogram) that was higher than the dose that lowered thyrotropin in the absence of omeprazole (37 percent, $P=0.001$) (Fig. 2). In addition, patients in whom it was possible to discontinue omeprazole treatment attained a low level of serum thyrotropin at the same dose as did untreated patients.

DISCUSSION

The efficacy of thyroxine treatment in multinodular goiter is debated, but the treatment is administered in numerous centers, especially in Europe.²³ Effective absorption of oral thyroxine is essential for optimal therapeutic management. Substantial data suggest that in several conditions^{6-14,27,28} unusually large doses of thyroxine are required, even in patients who adhere to the prescribed treatment. Our study provides data demonstrating that normal gastric acid secretion is important for the subsequent intestinal absorption of thyroxine. We observed an increase in the requirement of oral thyroxine in all conditions characterized by impaired gastric acid secretion, which was most pronounced in adult patients with atrophic gastritis and concomitant *H. pylori* infection. Severe hypochlorhydria, a hallmark of patients with atrophic gastritis,¹⁵ was associated with an increased need for thyroxine. However, the need for a substantial increase in the dose was observed even in patients with *H. pylori* infection, whose gastric acid secretion varies.¹⁹

The effects of *H. pylori* infection on gastric acid secretion have been attributed to the release of inhibitory cytokines,²⁹ the production of fatty acids inhibiting H^+/K^+ -ATPase activity,³⁰ impaired feedback between gastrin and acid secretion,³¹ damage to the mucosa of the gastric body,^{17,18,31}

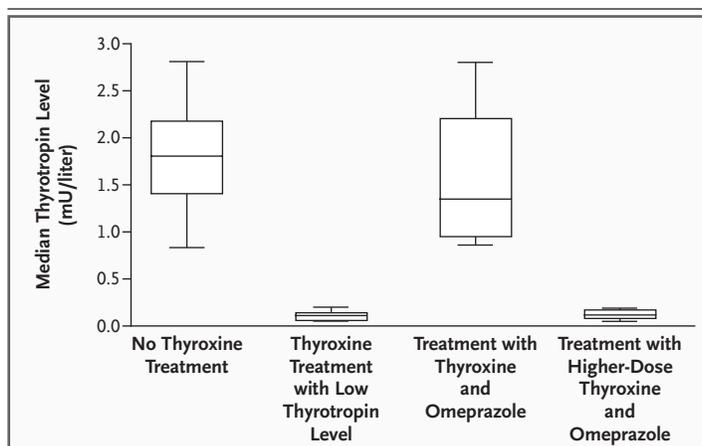


Figure 2. Effect of Long-Term Omeprazole Treatment on Thyrotropin Levels in 10 Patients Simultaneously Treated with Thyroxine.

The box plots show the levels of thyrotropin in patients who received no treatment with thyroxine, in patients receiving thyroxine treatment (median dose, 1.58 μg per kilogram of body weight per day) and in whom a low level of thyrotropin (0.05 to 0.20 mU per liter) was stably achieved, in patients who received simultaneous treatment with omeprazole (at a dose of 40 mg per day) without a change in the dose of thyroxine, and in patients who received an increased thyroxine dose (median dose, 2.16 μg per kilogram) while continuing to receive omeprazole. Each box plot shows the median (horizontal line within the box), the interquartile range (the horizontal lines at either end of the box), and the SD (I bar). The Friedman test was used for the analysis of variance ($P<0.001$). $P=0.002$ (by the Wilcoxon signed-rank test) for the comparison of patients receiving simultaneous treatment with both thyroxine and omeprazole with patients with low levels of thyrotropin receiving thyroxine; and $P=0.002$ (by the Wilcoxon signed-rank test) for the comparison of patients receiving omeprazole and a higher dose of thyroxine with patients receiving omeprazole and a lower dose of thyroxine (median dose, 1.58 μg per kilogram).

and the production of ammonia.³² These mechanisms may well be additive and explain the additive effect of *H. pylori* infection and atrophic gastritis on the daily thyroxine requirement. The complexity of the acid-producing machinery in the stomach³³ may contribute to the individual variability of the response in patients in a longitudinal evaluation. In fact, serum thyrotropin levels rose, though variably, in all patients with newly diagnosed *H. pylori* infection. In some patients, a slightly higher dose of thyroxine was needed to restore thyrotropin suppression. Likewise, the increase in the level of serum thyrotropin was variable in patients treated with omeprazole, although the suppressive effect of thyroxine on thyrotropin disappeared in all patients and was restored only at a substantially higher dose of thyroxine. The similar but reversible effect of omeprazole, which suppresses acid secretion, further supports the hypothesis that normal gas-

tric acid secretion is necessary for effective intestinal absorption of thyroxine.

Although the clinical importance of these findings is fairly clear, the mechanism by which intestinal absorption of thyroxine is impaired in patients with hypochlorhydria is unknown. We may only speculate that oral thyroxine is administered as sodium salt that is less lipophilic than the native hormone, which enters target cells both through passive diffusion and in a carrier-mediated, inhibitable way.^{34,35} In this respect, achlorhydria due to atrophic gastritis,^{15,16,18} the production of ammonia, or both, which are characteristic of *H. pylori* infection,^{19,33} may alter the ionization status and the conformational characteristics of

the thyroxine molecule and thus the efficiency of intestinal absorption of the hormone.

Taken together, our findings indicate that patients with multinodular goiter require an increase in the dose of thyroxine if they have concomitant atrophic gastritis, chronic *H. pylori* infection, or both. These data support the hypothesis that gastric acid secretion is necessary for the effective absorption of oral thyroxine.

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