

Effect of Calcium Carbonate on the Absorption of Levothyroxine

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LEVOthyroxine sodium is commonly prescribed for the treatment of hypothyroidism and thyroid neoplasia. The absorption of levothyroxine is approximately 80% after oral administration.^{1,2} Certain drugs have been shown to interfere with the absorption of levothyroxine. These include ferrous sulfate,³ sucralfate,^{4,5} bile acid sequestrants used to treat hypercholesterolemia,⁶ and aluminum hydroxide given as an antacid.^{7,8} In addition, high-fiber diets may impair thyroxine (T₄) absorption,⁹ and in some cases, food may delay or impair levothyroxine absorption.¹⁰ Other drugs may accelerate the disposal of T₄ and thus increase the dose requirement; these include phenytoin (Dilantin),¹¹ carbamazepine (Tegretol),¹¹ and sertraline (Zoloft).¹²

Calcium carbonate is taken by postmenopausal women for prevention or therapy of osteoporosis. In general, the use of calcium carbonate is increasing because of concern about osteoporosis. The largest group of patients taking T₄ is postmenopausal women. Calcium carbonate has been shown to prevent osteoporosis induced by thyrotropin-suppressive doses of levothyroxine in postmenopausal women.¹³

There is concern that calcium carbonate may reduce the absorption of levothyroxine. Although there are anecdotal claims to this effect, a MEDLINE search revealed no published prospective research studies of this potentially important interaction. Therefore, we

Context The effect of calcium carbonate on the absorption of levothyroxine has not been studied systematically. Such a potential drug interaction merits investigation because concurrent treatment with both drugs is common, particularly in postmenopausal women.

Objective To investigate the potential interference of calcium carbonate in the absorption of levothyroxine.

Design Prospective cohort study conducted from November 1998 to June 1999, supplemented with an in vitro study of thyroxine (T₄) binding to calcium carbonate.

Setting Veterans Affairs Medical Center in West Los Angeles, Calif.

Patients Twenty patients (age range, 27-78 years; n=11 men) with hypothyroidism who were taking a stable long-term regimen of levothyroxine were included in the study. All patients had serum free T₄ and thyrotropin values in the normal range before beginning the study.

Intervention Subjects were instructed to take 1200 mg/d of elemental calcium as calcium carbonate, ingested with their levothyroxine, for 3 months.

Main Outcome Measures Levels of free T₄, total T₄, total triiodothyronine (T₃), and thyrotropin, measured in all subjects at baseline (while taking levothyroxine alone), at 2 and 3 months (while taking calcium carbonate and levothyroxine), and 2 months after calcium carbonate discontinuation (while continuing to take levothyroxine).

Results Mean free T₄ and total T₄ levels were significantly reduced during the calcium period and increased after calcium discontinuation. Mean free T₄ levels were 17 pmol/L (1.3 ng/dL) at baseline, 15 pmol/L (1.2 ng/dL) during the calcium period, and 18 pmol/L (1.4 ng/dL) after calcium discontinuation (overall $P < .001$); mean total T₄ levels were 118 nmol/L (9.2 µg/dL) at baseline, 111 nmol/L (8.6 µg/dL) during the calcium period, and 120 nmol/L (9.3 µg/dL) after calcium discontinuation (overall $P = .03$). Mean thyrotropin levels increased significantly, from 1.6 mIU/L at baseline to 2.7 mIU/L during the calcium period, and decreased to 1.4 mIU/L after calcium discontinuation ($P = .008$). Twenty percent of patients had serum thyrotropin levels higher than the normal range during the calcium period; the highest observed level was 7.8 mIU/L. Mean T₃ levels did not change during the calcium period. The in vitro study of T₄ binding to calcium showed that adsorption of T₄ to calcium carbonate occurs at acidic pH levels.

Conclusions This study of 20 patients receiving long-term levothyroxine replacement therapy indicates that calcium carbonate reduces T₄ absorption and increases serum thyrotropin levels. Levothyroxine adsorbs to calcium carbonate in an acidic environment, which may reduce its bioavailability.

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studied the potential interference of calcium carbonate in the absorption of levothyroxine. A study was performed in 20 patients with hypothyroidism. In addition, a study of T₄ binding to calcium carbonate was performed in vitro.

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METHODS

Study of Patients With Hypothyroidism

Study Population. Study subjects were recruited at the Veterans Affairs Medical Center in West Los Angeles and at UCLA Medical Center from patients in the endocrinology clinics. Twenty patients (11 men, 9 women), ages 27 to 78 years, with hypothyroidism secondary to Hashimoto thyroiditis, surgical thyroidectomy, or radioiodine ablation of the thyroid who took levothyroxine in a dose of 1.0 µg/kg or greater were selected for study. They had an initial screening visit, which consisted of medical history and physical examination. All patients had normal free T₄ values and serum thyrotropin levels in the normal range of 0.6 to 4 mIU/L. Patients taking the following medications were excluded: aluminum hydroxide antacids, iron preparations, sertraline or similar drugs, phenytoin, carbamazepine, colestipol or cholestyramine, and fiber-supplemented diets. Study and consent procedures were reviewed and approved by the institutional review board of the Veterans Affairs Greater Los Angeles Healthcare System, and each patient gave informed, written consent.

Data Collection. Patients had initial baseline measurement of thyroid function tests. If the initial free T₄ and thyrotropin levels fell within the normal range, they were maintained on the pre-study dose of levothyroxine. If the initial free T₄ and thyrotropin levels were not normal, then the dose of levothyroxine was adjusted. Patients were advanced to the next stage of the study once they had normal free T₄ and thyrotropin levels after at least 6 weeks on a stable dose of levothyroxine. The dose of levothyroxine was not changed during the remainder of the study. The levothyroxine preparation used throughout the study was Synthroid.

Each patient then was given 1200 mg of calcium (as calcium carbonate, Goldmine brand) with instructions to ingest it daily with the levothyroxine in the morning on an empty stomach. The patients returned for follow-up measure-

ment of serum free T₄, total T₄, total triiodothyronine (T₃), and thyrotropin at 2 months and 3 months after beginning calcium. The calcium carbonate was discontinued at the 3-month follow-up visit and levothyroxine was continued. The patients returned 2 months after discontinuing calcium for thyroid function tests. Pill counts, brief histories, and physical examinations were carried out at each visit. The patients did not take the calcium and levothyroxine before the blood was sampled on the day of the visit. Most blood samples were collected during the morning.

Laboratory Studies. Free T₄ and total T₄ levels were determined by the Coat-A-Count radioimmunoassay methods (Diagnostic Products Corporation, Los Angeles, Calif). The T₃ level was determined by radioimmunoassay (Magic T₃ Radioimmunoassay, Bayer Corporation Diagnostic Division, Tarrytown, NY). Measurement of serum thyrotropin was done by immunoassay with 3 monoclonal antibodies (Nichols Institute Diagnostics, San Juan Capistrano, Calif).

Statistical Analyses. Mean values for the thyroid function tests (free T₄, total T₄, total T₃, and thyrotropin) for the initial visit while taking levothyroxine, 2 visits while taking calcium plus levothyroxine, and the final visit while taking levothyroxine were compared using the repeated measures multivariate analysis of variance test. *P* values from this test were computed for the overall difference between the groups (baseline levothyroxine vs 2 visits while taking levothyroxine plus calcium vs final levothyroxine) and for specific contrasts between the groups (baseline levothyroxine vs 2 visits while taking levothyroxine plus calcium, final levothyroxine vs 2 visits while taking levothyroxine plus calcium).

Timeline. The timeline for the study was as follows: (1) 0 months: baseline taking levothyroxine, add calcium at visit; (2) 2 months: visit No. 1 taking levothyroxine plus calcium; (3) 3 months: visit No. 2 taking levothyroxine plus calcium, discontinue calcium at visit; and (4) 5 months: final visit taking levothyroxine, after calcium discontinuation.

In Vitro Studies

An in vitro study of T₄ binding to calcium was modified after that of Liel et al.⁹ The buffer solution consisted of 0.1% bovine serum albumin, phosphate-buffered saline, and T₄ (at a concentration of 0.8 µg/dL). Four hundred milligrams of calcium carbonate (Sigma, reagent grade) was added to 1 mL of the buffer solution and serially diluted (with buffer solution containing 0.1% bovine serum albumin, phosphate-buffered saline, and cold T₄) to achieve the following concentrations: 400 mg/mL, 100 mg/mL, 25 mg/mL, 6.25 mg/mL, 1.56 mg/mL, and 0.39 mg/mL. Ten microliters of ¹²⁵I-T₄ (NEN Life Science Products, Boston, Mass, specific radioactivity 5700 µCi/µg, 10 µL containing 25 000 to 30 000 cpm) was added to the serial dilutions of calcium carbonate as well as to a buffer solution without calcium. Tubes were incubated in a shaking bath for 2 hours at 37° C. At the end of the incubation period, samples were centrifuged at 1000 g for 10 minutes. Two hundred microliters of supernatant was transferred to a second set of tubes and tubes were counted for 2 minutes in a gamma well counter.

Adsorption to calcium carbonate was examined by calculating the percentage change in ¹²⁵I-T₄ in the supernatant (in cpm) in serial dilutions of calcium carbonate compared with buffer plus ¹²⁵I-T₄ alone. Four trials were carried out with the buffer adjusted to a pH of 7.4. Five trials were carried out with the buffer adjusted with hydrochloric acid to a pH of 2.0 to simulate gastric acidity.

RESULTS

The mean free T₄ level was significantly reduced as a result of calcium treatment from a baseline of 17 pmol/L (1.3 ng/dL) to 15 pmol/L (1.2 ng/dL) during the calcium period, and increased to 18 pmol/L (1.4 ng/dL) after calcium discontinuation (overall *P* < .001). The mean total T₄ level was also significantly reduced as a result of calcium treatment from 118 nmol/L (9.2 µg/dL) at baseline to 111 nmol/L

(8.6 µg/dL) during the calcium period, and increased to 120 nmol/L (9.3 µg/dL) after calcium discontinuation (overall $P=.03$) (TABLE). The mean serum thyrotropin level increased significantly from 1.6 mIU/L to 2.7 mIU/L with calcium treatment, and then dropped to 1.4 mIU/L after calcium discontinuation (overall $P=.008$) (Table). Mean T_3 did not change as a result of calcium treatment ($P=.82$).

Thirteen of 20 patients had a reduction in free T_4 during the calcium phase, and 7 patients had no change (FIGURE 1, left). Thirteen of 20 patients had an increase in thyrotropin level during the calcium phase and in 4 patients, it rose

above the normal range. Four of the remaining 7 patients had no substantial change in thyrotropin level and 3 had a slight decrease (Figure 1, right). Pill counts were carried out at each visit and confirmed patient compliance.

In the in vitro study in which $^{125}\text{I-T}_4$ was incubated with serial dilutions of calcium carbonate, at pH 7.4 the fraction of $^{125}\text{I-T}_4$ recovered in the supernatant after calcium was added was not different from $^{125}\text{I-T}_4$ alone. The mean percentage of added T_4 recovered in the supernatant at pH 7.4 for different concentrations of calcium carbonate ranged from 97% to 109% (FIGURE 2). At pH 2.0, however, over 5 trials, the mean percent-

age of $^{125}\text{I-T}_4$ in the supernatant was reduced to 52% at 400 mg/mL of calcium carbonate and to 90% at 100 mg/mL (Figure 2). At 400 mg/mL and 100 mg/mL, calcium carbonate was present in a slurry rather than a clear solution.

COMMENT

The results of the study of the 20 patients with hypothyroidism receiving T_4 replacement therapy indicate that calcium carbonate has a modest, but significant, effect on thyroid function, most likely due to blocking the absorption of levothyroxine. The administration of calcium and levothyroxine in these patients was associated with a significant reduction in mean serum free T_4 and total T_4 levels during the calcium period. The increase of these values in most patients after calcium discontinuation strengthened the likelihood that the changes were due to calcium ingestion.

The effect of calcium on thyrotropin level was more dramatic than that on free T_4 and total T_4 . The mean thyrotropin level increased significantly from 1.6 to 2.7 mIU/L with calcium treatment, and then dropped to 1.4 mIU/L after calcium discontinuation (overall $P=.008$). Thirteen of 20 patients had an increase in thyrotropin level during the calcium phase. The serum thyrotropin level was

Table. Effect of the Concomitant Administration of Levothyroxine and Calcium on Thyroid Function Tests in 20 Patients With Hypothyroidism*

	Baseline: Levothyroxine	Visit 1: Levothyroxine + Calcium	Visit 2: Levothyroxine + Calcium	Final Visit: Levothyroxine	Overall P†
Free T_4 , ng/dL	1.34 ± 0.04‡	1.23 ± 0.04	1.22 ± 0.05	1.41 ± 0.06‡	<.001
TSH, mIU/L	1.60 ± 0.22‡	2.88 ± 0.41	2.71 ± 0.43	1.44 ± 0.21‡	.008
Total T_4 , µg/dL	9.21 ± 0.46§	8.64 ± 0.43	8.55 ± 0.41	9.31 ± 0.39§	.03
Total T_3 , ng/dL	141.50 ± 4.43	134.40 ± 6.59	142.10 ± 6.54	142.2 ± 7.03	.82

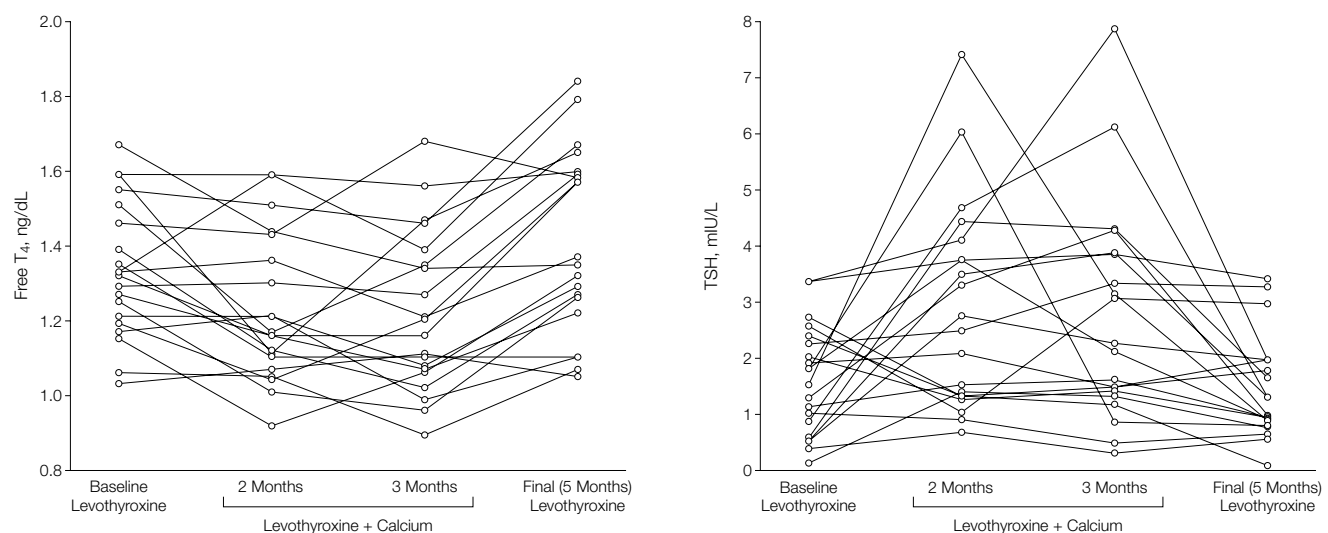
*All values are expressed as mean ±SE. T_4 indicates thyroxine; TSH, thyrotropin; and T_3 , triiodothyronine. To convert free T_4 from ng/dL to pmol/L, multiply by 12.87; to convert total T_4 from µg/dL to nmol/L, multiply by 12.87; and to convert total T_3 from ng/dL to nmol/L, multiply by 0.0154.

†Overall P value from F test of repeated-measures multivariate analysis of variance (MANOVA) analyses that compare the means of the baseline levothyroxine group, the levothyroxine group plus calcium groups, and the final levothyroxine group.

‡ $P<.01$ for between group comparison of levothyroxine plus calcium group (visit 1 + visit 2) from a repeated-measures MANOVA test.

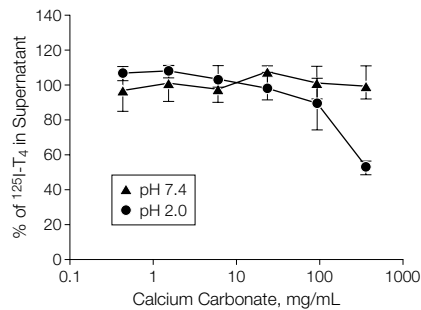
§ $P<.05$ for between group comparison to levothyroxine plus calcium group (visit 1 + visit 2) from a repeated-measures MANOVA test.

Figure 1. Free Thyroxine (T_4) and Thyrotropin (TSH) Levels in 20 Patients With Hypothyroidism: Individual Trends



To convert free T_4 from ng/dL to pmol/L, multiply by 12.87.

Figure 2. In Vitro Studies With Calcium and Thyroxine (T_4)



Error bars indicate the range of y values over 5 trials of in vitro studies (see "Methods").

above the normal range in 4 (20%) of 20 patients, with the highest observed level being 7.8 mIU/L. These 4 patients would have required an increased dose of levothyroxine if they continued to take it with calcium carbonate. Mild thyrotropin elevation indicates subclinical hypothyroidism, in this case due to inadequate replacement therapy. Thyroid hormone treatment of patients with subclinical hypothyroidism may improve lipid profiles and symptoms.^{14,15}

Since the study was not placebo controlled, it is possible that some differences in the thyroid function tests were due to changes in compliance in taking the medication. The study design, however, used each patient as his or her own control and showed that the effects were reversible when calcium was discontinued. In addition, pill counts provided evidence for patient compliance.

The results of the study were similar to the clinical observations made by Schneyer in 1998.¹⁶ However, whereas this study demonstrated a modest influence of calcium ingestion on serum thyrotropin values, the Schneyer data suggest a more profound effect. Schneyer reported that in 3 women with thyroid cancer receiving levothyroxine suppression therapy, the simultaneous ingestion of calcium carbonate and levothyroxine decreased the efficacy of T_4 . The first patient took 1200 mg of calcium (in the form of Tums) and her thyrotropin level rose from 0.08 mIU/L at baseline to 13.2 mIU/L, dropping to 0.6 mIU/L after calcium dis-

continuation. The second and third patients took 1000 mg of calcium (in the form of Os-Cal) and had similar trends in thyrotropin level. The Schneyer data suggest that the effect of calcium on levothyroxine efficacy could be avoided by dosing calcium separately (approximately 4 hours) from T_4 .

Liel et al^{7,8} demonstrated the non-specific adsorptive capacity of aluminum hydroxide for T_4 . The in vitro experiment paralleled a significant increase in serum thyrotropin level in patients given aluminum hydroxide and levothyroxine concomitantly. In our work, the in vitro study at a pH of 7.4 did not demonstrate adsorption of T_4 to calcium carbonate. However, at a pH of 2.0, simulating gastric acidity, there was adsorption of levothyroxine to calcium carbonate, with 52% and 90% of ^{125}I - T_4 in the supernatant (compared with baseline) at calcium concentrations of 400 mg/mL and 100 mg/mL, respectively. The size of the pellet of insoluble calcium carbonate after centrifugation did not vary between the samples at pH 7.4 and at pH 2.0.

Levothyroxine is absorbed mostly in the upper portion of the small intestine.¹⁷ Thus, adsorption at a gastric pH would only partially explain the effect of calcium on the thyroid function studies. There may be other mechanisms operating in the small intestine. Nonetheless, the effect of acidity on the binding of calcium and T_4 may explain why only 13 of 20 patients had a decreased free T_4 level and only 4 of 20 patients had a thyrotropin level above the normal range while taking calcium. It is possible that these patients may have increased acidity in the stomach compared with the others. Alternatively, the patients who did not exhibit the effect of calcium on their thyroid function tests may have had relative achlorhydria. None of the patients were using proton pump inhibitors or histamine H_2 -receptor antagonists on a regular basis. It is recommended that calcium carbonate be taken after a meal to optimize its absorption. Thus, the in vivo study did not exactly simulate the recommended clinical conditions.

The results of the study with 20 patients and the in vitro experiments support the clinical practice of monitoring patients taking both calcium carbonate and levothyroxine carefully for a change in thyroid function tests, especially an elevated thyrotropin level. If an elevated thyrotropin level should occur, it would be advisable to separate the time of ingestion of the calcium and levothyroxine.

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REFERENCES

- Hays MT. Absorption of oral thyroxine in man. *J Clin Endocrinol Metab.* 1968;28:749-756.
- Read DG, Hays MT, Hershman JM. Absorption of oral thyroxine in hypothyroid and normal man. *J Clin Endocrinol Metab.* 1970;30:798-799.
- Campbell NRC, Hasinoff BB, Stalts H, et al. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med.* 1992;117:1010-1013.
- Sherman SI, Tielens ET, Ladenson PW. Sucralfate causes malabsorption of L-thyroxine. *Am J Med.* 1994;96:531-535.
- Havrankova J, Lahaie R. Levothyroxine binding by sucralfate. *Ann Intern Med.* 1992;117:445-446.
- Northcutt RC, Stiel JN, Hollifield JW, Stant EG. The influence of cholestyramine on thyroxine absorption. *JAMA.* 1969;208:1857-1861.
- Sperber AD, Liel Y. Evidence for interference with the intestinal absorption of levothyroxine by aluminum hydroxide. *Arch Intern Med.* 1992;152:183-184.
- Liel Y, Sperber AD, Shany S. Nonspecific intestinal adsorption of levothyroxine by aluminum hydroxide. *Am J Med.* 1994;97:363-365.
- Liel Y, Harman-Boehm I, Shany S. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypothyroid patients. *J Clin Endocrinol Metab.* 1996;81:857-859.
- Benvenega S, Bartolone L, Squadrito S, et al. Delayed intestinal absorption of levothyroxine. *Thyroid.* 1995;5:249-253.
- Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med.* 1993;119:492-502.
- McCowen KC, Garber JR, Spark R. Elevated serum thyrotropin in thyroxine treated patients with hypothyroidism given sertraline. *N Engl J Med.* 1997;337:1010-1011.
- Kung AW, Yeung SS. Prevention of bone loss induced by thyroxine suppressive therapy in postmenopausal women: the effect of calcium and calcitonin. *J Clin Endocrinol Metab.* 1996;81:1232-1236.
- Ross DS. Subclinical hypothyroidism. In: Braverman LE, Utiger RD. *Werner and Ingbar's The Thyroid.* 7th ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1996:1010-1015.
- Tanis BC, Westendorp RGJ, Smelt AHM. Effect of thyroid substitution on hypercholesterolemia in patients with subclinical hypothyroidism: a reanalysis of intervention studies. *Clin Endocrinol.* 1996;44:643-649.
- Schneyer CR. Calcium carbonate and reduction of levothyroxine efficacy [letter]. *JAMA.* 1998;279:750.
- Hays MT. Localization of human thyroxine absorption. *Thyroid.* 1991;1:241-248.