# Comparison of the Absorption of Calcium Carbonate and Calcium Citrate after Roux-en-Y Gastric Bypass

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## Abstract

**Introduction—**Roux-en-Y gastric bypass (RYGB) restricts food intake. Consequently, patients consume less calcium. In addition, food no longer passes through the duodenum, the main site of calcium absorption. Therefore, calcium absorption is significantly impaired. The goal of this study is to compare two common calcium supplements in gastric bypass patients.

**Method—**Nineteen patients were enrolled in a randomized, double-blinded, crossover study comparing the absorption of calcium from calcium carbonate and calcium citrate salts. Serum and urine calcium levels were assessed for peak values ($C_{max}$) and cumulative calcium increment (area under the curve [AUC]). Serum PTH was assessed for minimum values ($PTH_{min}$) and cumulative PTH decrement (AUC). Statistical analysis was performed using a repeated analysis of variance model.

**Results—**Eighteen subjects completed the study. Calcium citrate resulted in a significantly higher serum $C_{max}$ (9.4+0.4 mg/dl vs. 9.2+0.3 mg/dl, $p$=0.02) and serum AUC (55+2 mg/dl vs. 54+2 mg/dl, $p$=0.02). Calcium citrate resulted in a significantly lower $PTH_{min}$ (24+11 pg/ml vs. 30+13 pg/ml, $p$=0.01) and a higher AUC (−32+51 pg/ml vs. −3+56 pg/ml, $p$=0.04). There was a

non-significant trend for higher urinary AUC in the calcium citrate group (76.13+36.39 mg/6 h vs. 66.04+40.82, *p*=0.17).

**Conclusion**—Calcium citrate has superior bioavailability than calcium carbonate in RYGB patients.

### Keywords

Roux-en-Y gastric bypass; Obesity; Calcium citrate; Calcium carbonate

## Introduction

The prevalence of obesity in the US is escalating [1]. Lifestyle interventions or pharmacological interventions remain inadequate in lowering the risk of comorbid conditions and mortality in this population [2–6]. Roux-en Y surgery has recently substituted the JI bypass procedure [7–9]. This procedure has been shown to be effective in sustaining weight loss [3, 10–14], diminishing multiple associated coexisting conditions, including hypertension, glucose intolerance, and dyslipidemia, and consequently improving the quality of life [3, 13–17]. However, several studies reported the increased risk of bone loss and kidney stones with this procedure [18–28]. Impaired intestinal calcium absorption from rapid intestinal transit time and derangement in vitamin D metabolism is likely to occur and may be responsible for secondary PTH stimulation, which ultimately increases the risk of bone loss [24, 25, 27–30]. Moreover, hyperoxaluria from intestinal fat malabsorption and hypocitrituria due to metabolic acidosis from diarrheal state may increase the risk of kidney stone formation [18, 20]. To date, the differential effects of two commonly used calcium supplements, calcium citrate and calcium carbonate, in the reversal of secondary hyperparathyroidism following gastric bypass has not been fully elucidated.

This study was undertaken to explore whether calcium supplementation may play a beneficial role in post-surgical RYGB patients.

## Materials and Methods

### Subjects

Eighteen healthy volunteers following RYGB surgery were enrolled into the study. The study sample included 17 Caucasian females and one Caucasian male. The mean age was 44.2 years (range, 30–61 years), and the mean BMI was 30.3 kg/m$^2$ (range, 20–40 kg/m$^2$). All the subjects underwent RYGB surgery (either open or laparoscopic) approximately 1 year prior to enrollment in the study (mean, 22.7 months; range, 11–35 months).

Men or women, aged 18–75 years, who had a gastric bypass operation at least 12 months prior were included in the study. Patients with a previous oophorectomy, liver disease, renal disease, hypercalcemia, hyperthyroidism or parathyroid disorders; use diuretics, bisphosphonates, calcitonin, corticosteroids, anabolic steroids, or anticonvulsants within 3 months of the study; and are heavy smokers (>10 cigarettes/day) or abusing alcohol (>70 ml/day) were excluded from the study. All participants were given a written informed

consent for protocol that was approved by the University of Texas Southwestern Medical Center Institutional Review Board.

**Study Design**—This is a randomized, double-blind, crossover trial comparing the absorption of calcium carbonate to calcium citrate. Each subject participated in two phases of the study and was assigned a supplement order using a block randomization scheme. In the first phase, the participants ingested a single dose of 500 mg calcium citrate as Citracal® 250 mg + D (two tablets of Citracal, each containing 250 mg of elemental calcium and 62.5 IU of vitamin D, retailed by the Mission Pharmacal Company, San Antonio, TX, USA). In the second phase, subjects took a single dose of 500 mg calcium carbonate as Os-Cal®500+D (one tablet containing 500 mg elemental calcium and 125 IU of vitamin D, marketed by SmithKline Beecham Consumer Healthcare, Pittsburgh, PA, USA). For 1 week prior to each phase and between the first and second phases, participants were instructed to maintain dietary calcium (400 mg/day) and sodium (100 mEq/day) restrictions. None of the patients was on H2 receptor antagonists or proton pump inhibitor during the study.

The day prior to the test phase, each subject fasted after 6 P.M. and ingested 300 ml of distilled water at 8 P.M. and 11 P.M. The morning of the test day, subjects ingested 600 ml of distilled water at 6 A.M. and then 300 ml at 8 A.M., 10 A.M., and noon. At 8 A.M., one of the test medications was given with a standard breakfast (prepared by the GCRC dietician). The breakfast meal provided 403 kcal: 9.4 g of protein, 18.6 g of fat, 49.6 g of carbohydrate. The mineral composition was 97 mg calcium, 130 mg potassium, 19 mEq of sodium, 13 mEq of potassium, 40 mg of magnesium, 17 mEq of chloride, and 2 mg of oxalate. An intravenous heparin line was placed at 7:30 A.M., which was used to draw blood at 7:55 A.M. and 8 A.M., and then hourly from 8 A.M. to 2 P.M. A fasting urine sample was collected from 6 A.M. to 8 A.M. Urine was then collected in 2-h pools for 6 h after the calcium load (from 8 A.M. until 2 P.M.). The blood samples were evaluated for calcium and PTH levels. Urine was analyzed for calcium and creatinine.

**Assays**—Serum and urine calcium levels were measured by atomic absorption spectrophotometry, and urine creatinine was measured on an autoanalyzer using the Jaffe rate method. Serum intact PTH was determined using an immunoradiometric assay kit (ALPCO Diagnostics, Windham, NH, USA). Assays were performed without knowledge of treatment phase.

## Statistical Analysis

Statistical analysis of the two-phase crossover trial was performed using mixed linear model and repeated measures analysis to assess order or carryover effects. The targeted sample size was 16 to 19 subjects, estimated to detect a difference between supplements of 0.80 mg/dl h for the serum calcium delta area under the curve. The estimated standard deviation was 1.0 mg/dl h for a desired power between 85% and 90% at the 0.05 level of significance. For the hourly timed measurements, repeated measures models were used to assess the effect of calcium supplement, time, and the interaction between supplement and time. Serum and urine calcium levels were assessed for peak values ($C_{max}$) and area under the curve (AUC), cumulative excretion for urinary calcium. Serum parathyroid suppression was assessed with

minimum PTH values ($PTH_{min}$) and PTH decrement (AUC). Time ($t_{max}$ and $t_{min}$) to achieve serum and urinary $C_{max}$ and serum $PTH_{min}$ were also derived from the hourly time course data. For these pharmacokinetic variables, the calcium supplements were compared with repeated measures models, which included factors to assess the effect of treatment order and the interaction between supplement and order. $p$ values less than 0.05 were considered statistically significant. Results are expressed as mean and standard deviation. Analyses were performed using SAS® statistical software version 9.1.3 (SAS Institute, Cary, NC, USA).

## Results

### Serum Calcium

At the baseline, serum calcium levels were similar (Table 1 and Fig. 1a). The mean serum calcium values for the calcium citrate and calcium carbonate phases were 9.1+0.4 and 9.0+0.3 mg/dl, respectively ($p$=0.22). The serum calcium levels for calcium carbonate were not significantly different throughout the experiment. For calcium citrate, the calcium levels increased considerably at hours 5 and 6. When the responses between phases were compared, serum calcium was notably higher with calcium citrate (ANOVA $p<0.0001$). In addition, the $C_{max}$ was significantly higher with calcium citrate compared to calcium carbonate (Table 1 and Fig. 1a) with 11 patients having a higher $C_{max}$ after calcium citrate than after calcium carbonate. Moreover, the length of time to achieve the $C_{max}$ was considerably longer for the calcium citrate group (3.60+2.30 h vs. 2.10+2.10 h, $p$=0.016). Calcium citrate also yielded a significantly greater AUC compared to calcium carbonate ($p$=0.02; Table 1 and Fig. 2b).

### Serum PTH

At the baseline, serum PTH values were also similar between the two phases (Table 1 and Fig. 2a). However, during the study, the serum PTH levels dropped dramatically in the calcium citrate group. These values were lower at hours 1, 2, 5, and 6 when compared to the baseline. Serum PTH for the calcium carbonate phase showed no notable difference throughout the experiment. In a comparison between the two calcium supplement phases, serum PTH was significantly lower for calcium citrate (ANOVA, $p<0.0001$). As shown in Table 1, calcium citrate was associated with a considerably lower $PTH_{min}$ ($p$=0.011) in which 12 of the 18 patients had a lower $PTH_{min}$ after calcium citrate than after calcium carbonate. Calcium citrate was also associated with a lower AUC (Table 1). The time required to achieve the $PTH_{min}$ was not drastically different between the two phases (2.30+1.70 vs. 1.80+ 1.80, $p$=0.32), and these results were not affected by the order in which the calcium supplements were given.

### Urinary Calcium

Urinary calcium values were similar at the baseline for both of the phases (Table 1). During the study, the urine calcium levels increased significantly following calcium citrate ingestion ($p$=0.002) but remained unchanged during the calcium carbonate phase ($p$=0.52). This differential response between the calcium supplements was statistically significant ($p$=0.03, phase by hour interaction; Fig. 3a and b).

### Urinary Calcium/Creatinine (Ca/Cr)

Urinary Ca/Cr values were similar at the baseline for each of the two phases (Table 1). During the study, the urine Ca/Cr levels increased significantly following ingestion of both calcium citrate ($p<0.001$) and calcium carbonate ($p=0.02$). However, over time, the responses between the phases showed a distinct difference ($p=0.001$, phase by hour interaction) with a larger increase in urinary Ca/Cr sustained at hour 6 during the calcium citrate phase (Fig. 4a and b).

## Discussion

Poor intestinal calcium absorption and disturbances in calciotropic hormone metabolism have been shown to play a major role in increasing the risk of bone loss and kidney stones following bariatric surgery [18–29]. This study for the first time explored the main differences in calcemic and calciuric responses between the two commonly used calcium supplements. In this study, the mean serum calcium concentration and peak basal variations in serum calcium were significantly higher for calcium citrate than calcium carbonate. Moreover, the cumulative increment in urinary calcium following the test load from baseline was significantly greater for calcium citrate than calcium carbonate (Table 1). It was also noteworthy that calcium citrate lowered the serum PTH concentration significantly as displayed by a greater cumulative fall in peak serum PTH concentrations. Thus, both the greater increment in serum calcium concentration and urinary calcium excretion in parallel with greater suppression of serum PTH suggest both the pharmacokinetic and pharmacodynamic superiority of calcium citrate.

Several studies have shown that the absorption of calcium carbonate is more dependent on gastric acid secretion than calcium citrate [31–36]. A previous study in healthy, postmenopausal women with varying degrees of gastric acid secretion reported a 2.5-fold higher intestinal calcium absorption following a single test load of calcium citrate than calcium carbonate [37]. Although it has been never tested, limited gastric acid secretion after RYGB could, in part, be a possible explanation for the similar findings in this study. In addition, other factors as a result of RYGB surgery, including diminished calcium absorption from both decreased intestinal absorptive capacity and from vitamin D derangements as a result of intestinal fat malabsorption, may also have influenced the findings [20, 39]. A recent year-long, prospective, longitudinal study showed that RYGB surgery is associated with high serum PTH, low serum 25-hydroxy vitamin D concentrations, and evidence of increased bone turnover with a rise in urinary N-telopeptide and serum osteocalcin [38]. A factor which influences the bioavailability of various calcium salts is gastric acid secretion. In contrast to the dependency of calcium carbonate solubility on an acidic environment, calcium citrate has even been shown to be partially soluble in water [32]. It is conceivable that this superior intestinal bioavailability of calcium citrate in the face of limited gastric acid secretion may compensate for both diminished intestinal absorptive capacity [40] and deranged vitamin D metabolism detected after RYGB [38].

However, there are some limitations to this study. We were unable to quantify gastrointestinal absorption of calcium isotopically since commercial calcium salts could not be labeled with calcium isotopes. Another limitation to this study was that we used only

serum PTH levels as a surrogate marker of the patient's response to calcium supplementation. However, a recent study showed a marked rise in urinary N-telopeptide commensurate with a significant rise in serum PTH immediately following RYGB [38]. It would have been ideal to simultaneously measure both urinary and serum markers of bone turnover in order to predict the magnitude of skeletal response to calcium citrate. Previous studies with calcium citrate alone [41] or comparing both the supplements showed a significant decrease in bone turnover markers with calcium citrate [42]. Our data suggest that in tablet formulation, calcium citrate is more bioavailable than calcium carbonate in lowering serum PTH levels and may prove to be superior in the reversal of secondary hyperparathyroidism, a condition which may accompany RYGB procedures. Long-term longitudinal studies to confirm the superiority of calcium citrate supplementation in patients following RYGB, preferably using different oral preparations, is needed to integrate these results to clinical practice.

## Acknowledgments

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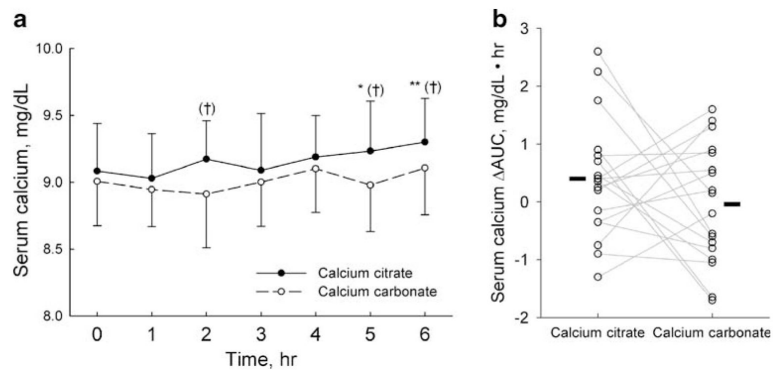
**Fig. 1.**

Serum calcium. **a** Data are presented as mean and standard deviation. The omnibus difference between the calcium supplements were statistically significant ($p<0.0001$, repeated measures analysis). *Filled circles p<0.05, \*\*p<0.01 vs. time 0; †p<0.001 vs.* calcium carbonate. **b** Symbols and lines represent individual subjects. *Solid bars* indicate the mean AUC of each phase
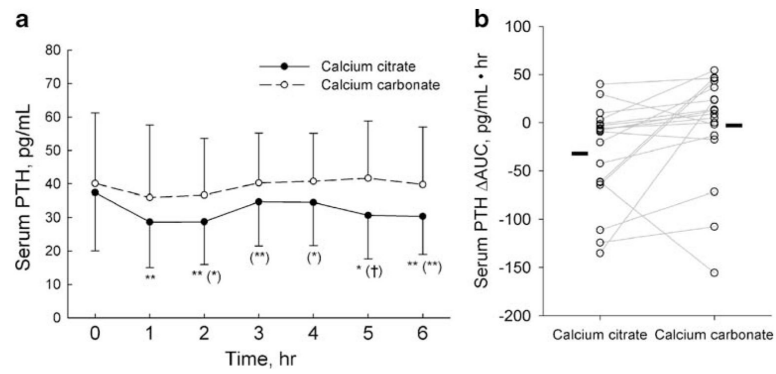
**Fig. 2.**
Serum PTH. **a** Data are presented as mean and standard deviation. The omnibus difference between the calcium supplements were statistically significant ($p<0.0001$, repeated measures analysis). *$p<0.05$, **$p<0.01$ vs. time 0; (*)$p<0.05$, (**)$p<0.01$, (†) $p<0.001$ vs. calcium carbonate. **b** Symbols and lines represent individual subjects. *Solid bars* indicate the mean AUC of each phase
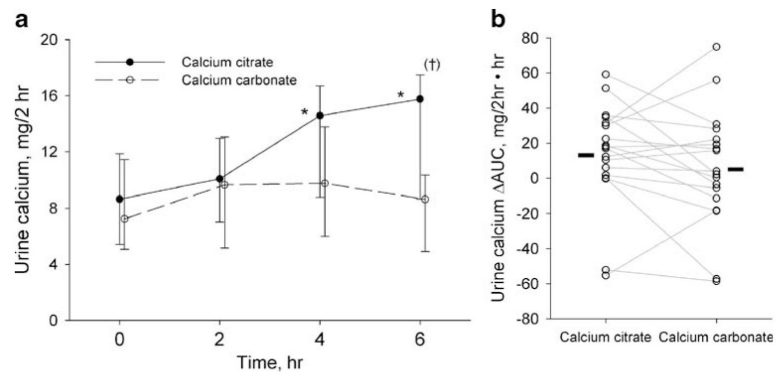
**Fig. 3.**
Urine calcium. **a** Data are presented as geometric mean and 95% confidence interval. *$p$=0.001 compared Time 0 within phase, (†)$p$=0.01 compared to calcium carbonate. The response differences over time between the calcium supplements were statistically significant ($p$=0.03, supplement by hour interaction). **b** Symbols and lines represent individual subjects. *Solid bars* indicate the mean AUC of each phase

**Fig. 4.**
Urine calcium/creatinine. **a** Data are presented as geometric mean and 95% confidence interval. *$p<0.05$ vs. Time 0; (†)$p=0.007$ vs. calcium carbonate. The response differences over time between the calcium supplements were statistically significant ($p=0.001$, supplement by hour interaction). **b** Symbols and lines represent individual subjects. *Solid bars* indicate the mean AUC of each phase
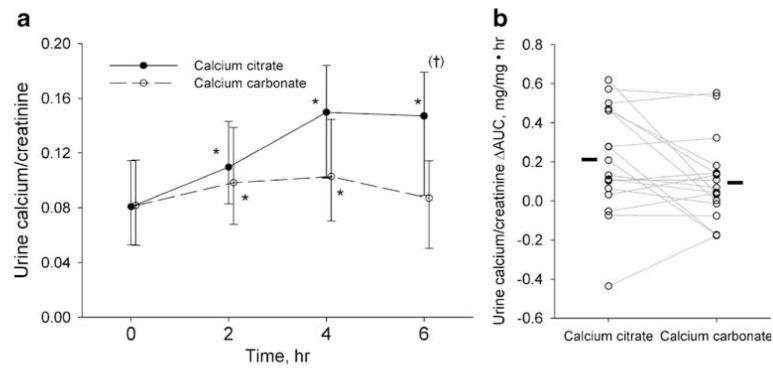
**Table 1**

Calcium citrate vs. calcium carbonate–serum and urine changes

| n=18 | Calcium citrate | Calcium carbonate | p value |
|---|---|---|---|
| Serum calcium | | | |
| Baseline mean mg/dl | 9.1±0.4 | 9.0±0.3 | 0.22 |
| AUC, mg/dl h | 55±2 | 54±2 | 0.02 |
| AUC, mg/dl h | 0.40±1.03 | −0.04±0.02 | 0.24 |
| $C_{max}$, mg/dl | 9.4±0.4 | 9.2±0.02 | 0.02 |
| $T_{max}$, h | 3.6±2.3 | 2.1±0.02 | 0.02 |
| Median | 3.5 | 2 | |
| Peak-baseline, mg/dl | 0.30±0.22 | 0.19±0.11 | 0.11 |
| Serum PTH | | | |
| Baseline mean pg/ml | 37±17 | 40±21 | 0.43 |
| AUC, pg/ml h | 191±73 | 235±94 | 0.001 |
| AUC, pg/ml h | −32±51 | −3±0.01 | 0.04 |
| $C_{min}$, pg/ml | 24±11 | 30±13 | 0.01 |
| $T_{min}$, h | 2.3±1.7 (2.0) | 1.8±1.8 (1.0) | 0.32 |
| Nadir-baseline, pg/ml | −14±−14 | −11±0.22 | 0.22 |
| Urinary calcium | | | |
| Baseline mean mg/2 h | 10.5±8.2 (8.7) | 10.1±7.6 (7.2) | 0.81 |
| AUC, mg/2 h h | 76±36 | 66±41 | 0.17 |
| AUC, mg/2 h h | 13±30 | 5±33 | 0.23 |
| Cumulative increment | 51±25 | 42±25 | 0.07 |
| Urinary Ca/Cr | | | |
| Baseline mean | 0.10±0.08 (0.08) | 0.10±0.07 (0.08) | 1.0 |
| AUC, mg/2 h h | 0.82±0.38 | 0.70±0.45 | 0.13 |
| AUC, mg/2 h h | 0.21±0.27 | 0.09±0.21 | 0.05 |
| Cumulative increment | 0.53±0.25 | 0.45±0.28 | 0.06 |

Results are expressed mean±SD. Medians are presented in parentheses

*AUC* area under the curve, $C_{max}$ maximum concentration, $C_{min}$ minimum concentration, $T_{max}$ time at maximum concentration, $T_{min}$ time at minimum concentration