International Medical Society
http://imedicalsociety.org

INTERNATIONAL ARCHIVES OF MEDICINE
SECTION: ENDOCRINOLOGY
ISSN: 1755-7682

2017
Vol. 10 No. 144
doi: 10.3823/2414

Acute Effects of Oral Calcium Carbonate with and Without the Addition of Omeprazole and Fiber Enriched Milk on Serum Calcium Concentrations in Postmenopausal Women

ORIGINAL

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Abstract

Introduction: In recent years, some studies have shown an increase in cardiovascular risk due to the use of calcium supplements in excess of the recommended doses. One hypothesis is that some calcium supplements lead to a more pronounced elevation of serum calcium concentrations.

Objectives: The aim of this study was to evaluate the serum calcium responses after ingestion of calcium carbonate, with and without the prior use of omeprazole, and after ingestion of soluble fiber enriched milk (SFM).

Method: Five postmenopausal women were evaluated in three phases. For each phase, the serum calcium responses were determined at 0h (baseline), 1h, 2h, 3h and 4h. After ingestion of 1200mg of calcium, both for the patients who received the calcium carbonate and for those who received SFM.

Results: The rise in serum calcium observed after ingestion of calcium carbonate with a calcium peak of 0.56 mg/dl (p=0.032), and it was higher when compared to SFM 0.26 mg/dl (p=0.284). There was no significant elevation of serum calcium after ingestion of SFM. The calcium responses were negative after the administration of omeprazole in comparison with the use of calcium carbonate and SFM, reaching 7.06mg/dl vs 9.04mg/dl vs 9.12mg/dl at 0h, 5.30mg/dl vs 9. 32mg/dl vs 9.00mg/dl at 1hr, 5.52mg/dl vs 9.48mg/dl vs 9.32mg/dl at 2hr, 5.18mg/dl vs 9.48mg/dl vs 9.34mg/dl at, respectively, p<0.001.

International Archives of Medicine
Section: Endocrinology
ISSN: 1755-7682
2017
Vol. 10 No. 144
doi: 10.3823/2414

Conclusion: In conclusion, our data showed that the same amount of SFM induced a lower serum calcium response when compared to calcium carbonate. The use of omeprazole significantly reduced the intestinal absorption of calcium carbonate.

Keywords
Calcium; Milk; Fiber; Postmenopausal Women; Proton Pump Inhibitor.

Introduction

Calcium (Ca) intake, particularly during childhood, is a key determinant for bone gain and peak bone mass in adulthood, as well as for bone loss during aging. Osteoporosis is characterized by bone fragility and fractures. A low calcium intake is associated with an increased risk of bone fracture, especially in patients from countries with a high incidence of osteoporotic fractures [1, 2].

There are different formulas of calcium supplementation. Calcium from carbonate and citrate are the most common forms of calcium supplements. Calcium carbonate ($CaCO_3$) is the most cost-effective option; by contrast, calcium citrate does not depend on food for better absorption, and can be used in patients with hypocloridia and achlorhydria without diminishing its optimal absorption [2].

The presence of other dietary components in the intraluminal area affects calcium absorption efficacy [3]. Although the indication of fiber-rich foods for individuals with dyslipidemias, diabetes mellitus and chronic intestinal constipation has intensified, the use of a higher amount of dietary fiber may interfere with the absorption of various minerals, including calcium [4].

The benefits of calcium for bone health are partially attributed to bone resorption inhibition, secondary to increased calcium serum levels and parathyroid hormone (PTH) suppression [2, 5]. Several studies have attempted to demonstrate the influence of postprandial metabolism on different dietary calcium supplementation. However, there is some controversy concerning the postprandial bioavailability of different calcium formulations. For example, Yang et al showed no differences in the acute metabolic response when they compared calcium carbonate and tricalcium phosphate [6]. On the other hand, Reginster et al, using a similar protocol, showed that the use of calcium carbonate has resulted in higher levels of serum calcium and increased bone resorption inhibition when compared to other formulations, including tricalcium phosphate [7]. Zikán et al demonstrated that calcium carbonate suspended in water is more effective in reducing bone resorption compared to SFM [8]. Martini and Wood studied calcium absorption with the ingestion of industrialized orange juice enriched with calcium citrate-malate and concluded that the bioavailability of calcium was similar to that of cow´s milk [9]. The impact on bone physiology resulting from the use of different calcium formulations is still poorly understood.

The use of calcium to treat osteoporosis has become widespread and, while some populational studies suggest that calcium intake may prevent vascular diseases, other research indicates that supplements may accelerate vascular calcification [10, 11].

A meta-analysis was performed to evaluate the influence of calcium supplementation on cardiovascular risk in patients over 40 years of age, followed for at least one year while taking calcium supplements (>500mg/day). The rate of adherence to the treatment was above 75%. Studies on the relation between calcium and vitamin D versus placebo were not included, since the use of vitamin

D is associated with reduced mortality [11]. Cardiovascular events analysed included acute myocardial infarction (AMI), stroke and sudden death. The selected studies involved 12,843 patients, followed for an average of 3-4 years. Over 85% of the participants were females, with a mean age of 75 years. A 27-31% increase in risk of AMI has been observed in patients on a calcium supplement, according to the type study analyzed ($p = 0.03$). In addition, calcium supplementation was associated with an increased risk of AMI in individuals with calcium intake above average (805 mg/day). There was no significant increase in the incidence of stroke or composite outcomes, including sudden death. The rate of women using hormone replacement was less than 3% [12].

The use of proton pump inhibitors (PPIs) is common in clinical practice; however its use may be associated with decreased bioavailability of calcium. Ivanovich et al. studied Ca absorption in individuals with milk-alkali syndrome or hypochlorhydria, and concluded the necessity of gastric acidity to dissolve the calcium carbonate [13]. Although these conclusions are based, apparently, on a single hypochlorhydria patient, they have led to the belief that the of the low pH of the stomach is crucial to the bioavailability of Ca [13, 14].

The effect of proton pump inhibitors on the absorption and metabolism of calcium recently received more attention. One study described the association between the long-term therapy with PPIs, particularly at high doses, with increased risk of fractures, and this risk is significantly accentuated when proton pump blockers are being used [15].

The present study was designed to demonstrate whether the use of SFM would result in slower calcium absorption in comparison to calcium carbonate supplementation, and whether the use of a proton pump inhibitor, after ingestion of calcium carbonate, would decrease its bioavailability.

Material and Methods

Selected subjects and study design

Five patients who granted written consent were eligible for the study, which was approved by the Ethics Committee of Agamemnon Magalhães Hospital. The body mass index (BMI) was obtained by dividing body weight in kg by the square of their height in meters, using scales and a stadiometer to measure each patient. The waist and hip circumferences were measured with a flexible measuring tape. Blood pressure was measured using a normal sphygmomanometer.

Patients were excluded from the analysis if they were: taking bisphosphonates, thiazide diuretics, anticonvulsants and lithium; suffering from renal failure with a glomerular filtration rate of less than 40 ml/min, using the formula Modification of Diet in Renal Disease Study (MDRD). Also excluded were individuals with metabolic bone diseases, gastroenterological diseases associated with malabsorption, liver disease and those whose data records were incomplete.

The patients attended the clinic on three different days at one week intervals. The patients were given fiber enriched milk on the first study day and two pills of calcium carbonate ($CaCO_3$ + cholecalciferol 200 UI 600mg) on the second study day, resulting in a total dose of 1,200 mg calcium carbonate and 400 UI of vitamin D3 (cholecalciferol). On the third and final day, the patients received the same dose of calcium carbonate, but had previously taken high doses of proton pump inhibitor (omeprazole) 40 mg daily for 7 days. The amount of SFM (1.200mg calcium) used was 60g and, since it contains only 144 UI of cholecalciferol, two drops of vitamin D3 (Addera Mantecorp, Brazil) were added (equivalent to 256UI, the remainider necessary to complete 400 IU) **(Table 1)**.

For all three phases of the study, five blood samples were obtained. The first was collected before the intake of the calcium supplementation of the

Table 1. Nutrition facts of fiber enriched milk powder Serving Size 25g* (2 tablespoons).

Amount per serving		DV %
Energy	80kcal=338kJ	4
Carbohydrates	14g	5
Proteins	5.2g	7
Total fat	0g	0
Trans fat	None	***
Saturated fat	0g	0
Dietary fiber	2.4g	10
Soluble fiber	2.4g	***
Sodium	75mg	3
Calcium	500mg	50
Iron	4.3mg	31
Vitamin A	141µg	24
Vitamin D	1.5µg	30
Vitamin E	4.7mg	47
Vitamin C	23mg	51
Folic Acid	120µg	50

DV: daily values; Kcal: kilocalories; kJ: kilojoules; g: grams; mg: milligrams; µg: microgram

chosen formulation (baseline), while the remaining four samples were collected after ingestion of the supplement. The patients fasted for at least 12 hours before the test.

Serum calcium and ionized calcium were determined in duplicate by an automated computerized analysis system.

Statistical analysis

Data analysis was done by means of descriptive statistics and presented as mean and standard deviations, as well as by inferential statistical techniques, through the F test (ANOVA) with repeated measurements for comparison between groups at each assessment time and between times of evaluation in each group. The Bonferroni test, which is suitable for determining individual differences between multiple groups of data, was applied to indicate a significant difference shown by F-test (ANOVA).

The level of significance adopted for the statistical tests was 5%. Data were entered on an Excel spreadsheet, and statistical calculations were made using SPSS 17.

Results

The physical characteristics of the vonlunteers are shown in **Table 2**.

Table 2. Baseline characteristics of the study patients.

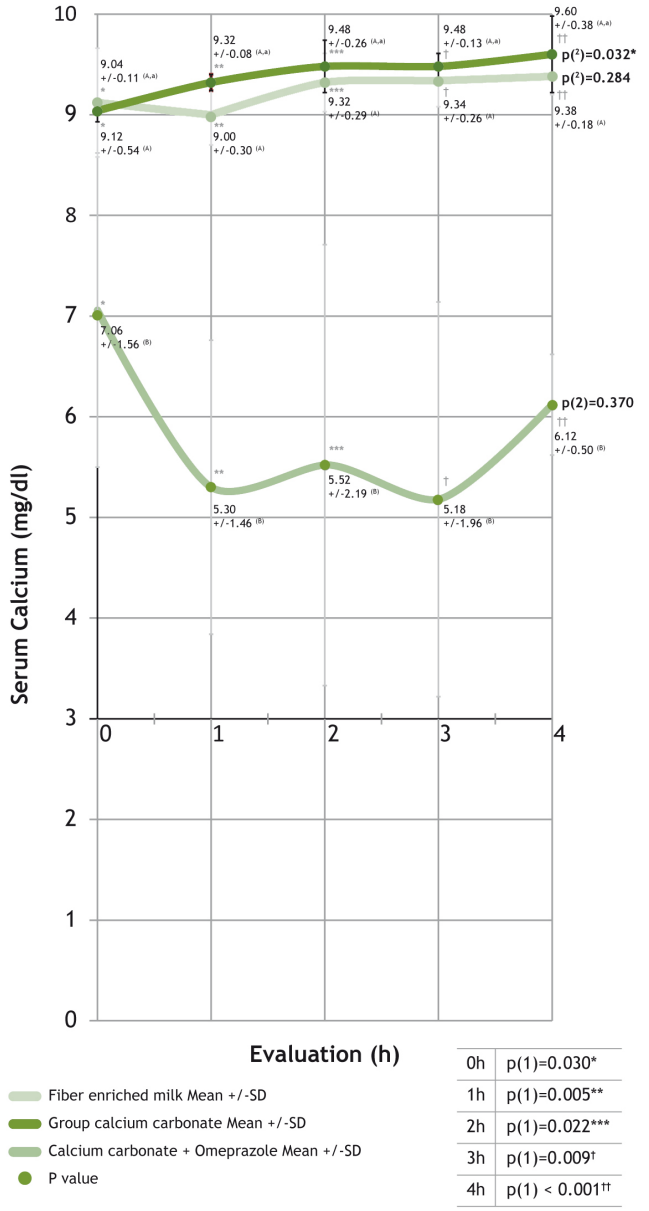
	Mean/SD	Median
Age (years)	57.20/10.62	56.00
BMI (Kg/m^2)	30.91/2.34	30.34
AC	101.20/3.55	101.50
HC	104.00/2.18	104.50
AC/HC	1.03/0.04	1.02
SAP	130/17.32	120
DAP	80/7.07	80

BMI: Body Mass Index; AC: Abdominal Circumference; HC: Hips Circumference; SAP: Systolic Arterial Pressure; DAP: Diastolic Arterial Pressure

The calcium curves (serum and ionized) were determined at the same time points 0h, 1h, 2h, 3h and 4h, at one-hour intervals. There was a one-week interval between all phases, and the dose of calcium used was equivalent to 1,200mg.

The results for serum calcium according to group and time of evaluation are shown in Figure 1. At each assessment time, the average serum calcium levels were lower in the group on calcium carbonate + Omeprazole than in the other groups (0h=7.06mg/dl vs 9.04mg/dl vs 9.12mg/dl) (1h=5.30mg/dl vs 9.32mg/dl vs 9.00mg/dl) (2h=5.52mg/dl vs 9.48mg/dl vs 9.32mg/dl) (3h=5.18mg/dl vs 9.48mg/dl vs 9.34mg/dl) (4h=6.12mg/dl vs 9.60mg/dl vs 9.38mg/dl) $p < 0.001$ and were similar in the milk powder and calcium carbonate groups (0h= 9.12mg/dl vs 9.04mg/dl) (1h=9.00mg/dl vc 9.32mg/dl) (2h=9.32mg/dl vs 9.48mg/dl) (3h=9.34mg/dl vs 9.48mg/dl) (4h=9.38mg/dl vs 9.60mg/dl) $p = 0.032$.

Figure 1: Total serum calcium responses after 1.2g of elemental calcium plus 400UI of vitamin D3 intake, as calcium carbonate with and without previous omeprazole use and soluble fiber-enriched powder milk, in 5 posmenopausal women.



Note:

†: Difference 5.0%.

1: By F test (ANOVA) with repeated measures form comparison between groups at each time. If all uppercase letters are distinct, there are significant differences between the corresponding groups through Bonferroni comparisons.

2: By F test (ANOVA) with repeated measures form comparison between the time points in each group. If all lowercase letters are distinct, there are significant differences between the corres- ponding time in each group by the Bonferroni test.

When the first two groups were compared with each other, the serum calcium values were higher in the calcium carbonate group **(Figure 1)**, presenting significant differences between the assessment time points.

In the milk powder group, the mean was lower at baseline (9.12mg/dl) and highest at 4h (9.38mg/dl), but with no significant differences between time points (p = 0.284). In the calcium carbonate group, the mean increased with the assessment time, with a significant difference between 0h and each of the other times (9.04mg/dl, 9.32mg/dl, 9.48mg/dl, 9.48mg/dl, 9.60mg/dl). In the calcium carbonate + Omeprazole group, the mean was highest at 0h (7.06mg/dl) and varied at other time points, with no significant differences between time points (p = 0.370).

The mean of ionized calcium ranged from 1.21mg/dl to 1.30mg/dl, with no significant differences between groups in each assessment time (p> 0.05) and between the time of evaluation in each group (p> 0.05).

Discussion

The present study demonstrated that the same amount of calcium intake from SFM induced a lower calcemia curve than the calcium carbonate supplementation. Serum calcium levels decresead significantly after one week of administration of high doses of omeprazole.

Lower levels of calcium after milk intake could be due to the presence of fiber in its composition. There are data in the literature suggesting that soluble fiber supplementation in the diet could decrease urinary calcium excretion, yet the effect on its absorption and bioavailability is still very controversial. A study performed in male patients taking oat bran (21g) over 32 days revealed a significant decrease in urinary calcium excretion, though no change in intestinal absorption was observed [16]. Another study reported an apparent decrease in calcium

absorption in elderly persons with a daily intake of wheat bran (30g) for 21 days [17].

Behall et al. reported no change in calcium balance (intake versus fecal and urinary excretion) in subjects with type 2 diabetes mellitus after consumption of a diet enriched with a type of legume 32 g/day for 6 months [18]. A study conducted by Coudray et al. reported a positive balance of calcium in healthy men who consumed inulin or beets, a source of 58g of fiber, for 28 days [19].

Another study evaluated 13 patients with type 2 diabetes mellitus who received a high content of dietary fiber (24g). In these patients there was a decrease in urinary calcium excretion at 24 hours, but no significant effect on its absorption [20].

In the present study, SFM serum calcium values were higher after ingestion of calcium carbonate when compared to SFM, thus demonstrating the importance of fiber in reducing calcium bioavailability.

Since the low serum calcium values obtained after ingestion of high doses of proton pump inhibitor omeprazole (40 mg), our study demonstrated the important role of proton pump inhibitor (omeprazole) in calcium absorption.

Regarding the effects of acid reduction therapy for peptic diseases, Bo-Linn et al evaluated the absorption of calcium in subjects on supplementation with calcium carbonate before and after the use of cimetidine, a potent histamine blocker. There was no evidence of the influence of gastric acidity on the absorption of dietary calcium [21]. The authors speculated how the relatively insoluble $CaCO_3$ would have been absorbed in the absence of gastric acid: 1) luminal pH of the jejunum is usually 6.1, which releases 37% of calcium from $CaCO_3$ within two hours; 2) The micro-environment surface of the enterocyte acid might have been low enough to provide another possible site of $CaCO_3$ dissolution; 3) Pancreatic and biliary stimulation in response to the meal could result in the secretion of factors that would dissolve $CaCO_3$ [21].

The divergent results may be due to the amount of carbohydrates in the test meals. Many studies have shown that various sugar supplements, when administered together with calcium, increase its absorption by lowering the pH of the microintestinal environment [14].

Although short-term studies have suggested that PPI could decrease calcium absorption, this effect has not been demonstrated in the analysis of long-term results. One of the first studies on the influence of omeprazole in calcium absorption was performed in healthy subjects and in patients undergoing dialysis, both receiving Omeprazole 20 mg. The report suggested that short exposures to this drug, ranging from three days to 20 months, caused a decrease in calcium absorption [22]. However, a randomized clinical trial in healthy subjects, over 17 days did not show any relation between the administration of omeprazole (40 mg) and intestinal calcium absorption, which was measured by gastrointestinal wash [23].

The effects of prolonged use of PPI on bone health have been evaluated in several studies. An increased risk of hip fractures was evidenced in patients on PPIs, as well as a relationship with time of use. Those patients who had been using the drug for longer periods had a decrease in gastric acidity, resulting in a lower absorption of calcium [24].

Subsequent studies yielded inconsistent results when BMD was evaluated on the bases of bone densitometry examinations [24, 25]. One study showed no changes in total hip BMD rate between users and non-users of PPI [25]. Gray showed that both users and non-users had an increase in hip BMD, from baseline to three years. However, the increase in BMD was lower in PPI users than in non-users [26]. Targownik was unable to demonstrate any relationship between BMD of the lumbar spine and hip and exposure to PPIs. In this study, the use of PPIs was not associated with a faster decline in BMD [27].

Several meta-analyses have assessed the risk of PPIs and fractures in recent years. Most of those studies concluded that the risk of hip fracture increased moderately in PPI users (relative risk, 1.2 to 1.30),

and spine fractures (relative risk 1.6). However, the studies have been limited by significant heterogeneity, and when studies were adjusted to take into account other risk factors for fracture, the use of PPI was not considered to be the cause. Histamine receptor antagonists do not appear to be associated with the risk of fractures [28, 29, 30].

Based on these studies, low BMD may be a marker for other comorbidities that predispose individuals to use PPI and other medical treatments, rather than a direct result of PPI therapy [30].

Given the findings of an increased risk of fractures in patients with chronic use of PPIs, it is questionable whether all patients with a diagnosis of gastroesophageal reflux disease (GERD) chronically using PPI should initiate replacement of vitamin D and calcium, as well as undergo a DXA examination [30]. Based on a recent study by Targownuk et al., a patient without comorbidities or risk of fracture should not be subjected to DXA or start treatment with calcium and vitamin D [27].

Regarding the acute effects of different way of calcium supplementation, a randomised cross-over trial of ten women with a mean age of 69 years examined the effects of calcium from different sources on serum calcium. Fasting participants received a single dose of 500mg of calcium as citrate, citrate with a meal, fortified juice or a dairy product meal. Blood was sampled before and 1, 2, 4 and 6 h after each ingestion of calcium [30].

The authors compared the changes in serum calcium after 500 mg of calcium in the form of citrate with the effects of 1000mg of calcium in the form of citrate or carbonate in their previous study [30]. They found that changes in ionized calcium were similar and that the changes in total calcium were slightly fewer after 500mg of calcium as citrate in comparison with 1000 mg of calcium as citrate or carbonate (with a light meal) in their previous study [30].

Total calcium was higher than baseline between 1 and 6h after citrate-fasting (all P<0·02), fortified juice (p<0·0001) and the dairy-meal (p<0·05) and between 2 and 6h after citrate-with-a-meal (p<0·0001). The rise in both ionised and total calcium after citrate-with-a-meal was delayed but not diminished in extent as fortified juice was indistinguishable from citrate-fasting for both indices. The dairy-meal generally caused smaller increases in serum calcium than did citrate-fasting [30].

In our patients there were no significant changes in serum ionized calcium between the groups whereas with omeprazole there were no changes at all. This may well be due to the narrow detection range of serium-ionized calcium as compared with total calcium.

Conclusion

In conclusion our data suggest that different sources of calcium have different acute effects on serum calcium and support recommendations that dietary calcium might be safer than supplements in terms of cardiovascular effects.

Acknowledgments

The authors are indebted to the preceptors and colleagues at Agamenon Magalhães Hospital for all their support throughout the study.

Conflict of interest

The authors have no conflicts of interest or financial ties to report.

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