Clinical study of the tolerability of calcium carbonate–casein microcapsules as a dietary supplement in a group of postmenopausal women

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Abstract

**Background:** Calcium is an essential macronutrient; however, currently supplements are often associated with gastrointestinal (GI) adverse events. The authors investigated the tolerability of a new delivery system for calcium supplementation, based on the functionalization of calcium carbonate (CaCO₃) particles by casein proteins, in a randomized, prospective, double-blind, active comparator clinical trial.

**Methods:** Around 208 postmenopausal women were enrolled and randomized 1:1:1:1 to one of the four calcium supplements, taken for 30 days: (1) microencapsulated CaCO₃ (microCaCO₃) with a 90:10 mineral to protein ratio; (2) microCaCO₃ with a 95:5 mineral to protein ratio; (3) conventional CaCO₃ tablets; and (4) calcium citrate tablets (CaCitr). The Gastrointestinal Symptom Rating Scale (GSRS) questionnaire was used to evaluate the GI tolerability and the Treatment Satisfaction Questionnaire for Medication (TSQM) to analyze the satisfaction of the participants with the use of the calcium supplements.

**Results:** The mean GSRS scores at baseline differed among the groups from 3.95 to 5.35 without statistical significance. After 1 month use of supplements, the group given microCaCO₃ with a 90:10 mineral to protein ratio, showed the lowest mean GSRS score (6.07), while the group given conventional CaCO₃ showed the highest score (11.86). According to the completed TSQM questionnaire, the use of supplements was easier for both microCaCO₃ groups in comparison with conventional supplements.

**Conclusions:** The microCaCO₃ supplement has shown promising results in the context of GI tolerability and patient satisfaction in the use of supplements compared to conventional calcium supplements. The reduction of GI adverse events may increase the compliance to calcium supplements especially important among groups at risk of calcium deficiency.

**Keywords:** casein-functionalized calcium carbonate microcapsules, dietary calcium supplements, gastrointestinal adverse events, microencapsulated calcium carbonate, postmenopausal women.

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**Introduction**

Calcium is an essential macronutrient required by humans that must be provided by the diet. It is a basic constituent of hydroxyapatite crystals, the mineral component of bones. Insufficient calcium accrual, leading to a suboptimal bone mass peak and low bone mineralization, is an important factor that leads to osteoporosis and fractures. An important population group at risk for dietary calcium deficiency is postmenopausal women, whose estrogen deficiency impairs the bone turnover cycle, leading to a disproportionate increase in bone resorption compared with formation. The average reduction in bone mass density (BMD) is about 10% during the menopausal transition period, with an average loss of 200 mg of daily calcium in the first 3–4 years. Osteoporosis is the most prevalent disease in postmenopausal women, and is strongly associated with low quality of life. The International Osteoporosis Foundation estimated that approximately 30% of all postmenopausal women have osteoporosis in Europe and in the USA, and at least 40% of these women will experience one or more fragility fractures in their remaining lifetime. The major goals of treatment for osteoporosis are the prevention of fractures and the maintenance or increase in BMD by consumption of an adequate amount of dietary calcium. The recommended daily calcium intake for postmenopausal women is 1200 mg, and calcium supplementation is usually required to correct the deficiency and guarantee an appropriate daily intake of calcium.
The currently most used calcium dietary supplements are calcium carbonate (CaCO$_3$) and calcium citrate (CaCitr), which are often associated with gastrointestinal (GI) adverse events such as constipation, excessive abdominal cramping, bloating, abdominal pain, or diarrhea. Specifically, they are related to a high release rate of carbon dioxide when CaCO$_3$ particles are subjected to gastric acidic conditions. The inconvenience and the frequency of such adverse events appear to contribute to low compliance. Therefore, a new delivery system for calcium supplements is highly desirable to reduce CaCO$_3$ ionization in the stomach and the associated adverse events, which could increase the compliance to calcium supplements especially among the population at risk of calcium deficiency.

Controlled delivery systems, such as microcapsules, are promising candidates for encapsulating, delivering, and controllably releasing active ingredients including drugs and dietary supplements. In the development of innovative controlled-release systems, the use of natural polymers derived from biological systems, including protein, DNA, lipids and polysaccharides, holds much promise as biocompatible and biodegradable options. They have favorable pharmacokinetics and low toxicity. Casein, the major milk protein, is an inexpensive, non-toxic, and highly stable biomolecule with structural and physicochemical properties, which facilitate its use as a natural polymer for controlled release. Properties that facilitate the use of caseins as drug-delivery agents include binding to ions and small molecules, surface-active and stabilizing properties, self-assembly properties, and excellent gelation and water-binding capacities.

The authors postulated that microencapsulation of CaCO$_3$ particles by a natural polymer such as casein protein should reduce and slow down the ionization of CaCO$_3$ under gastric acidic conditions, preventing the associated adverse GI symptoms, compared to bared CaCO$_3$ particles. Taking advantage of the suitable properties of the casein as a coating material, CaCO$_3$ particle surface was functionalized with sodium caseinate by an ionic gelation process followed by spray drying as described by Casanova and coworkers. Two types of microcapsules, with different mineral to protein ratios, were studied (i.e. 95:5 and 90:10 ratios). Figure 1 shows...
electron microscope images for both systems. Scanning electron microscope images indicate the formation of spherical aggregates of primary calcium carbonate particles sizing 3–15 µm (Figure 1A). The 95:5 system had an average particle size (d32) of 7.5 µm, whereas the 90:10 system showed a value of 9.0 µm. The transmission electron microscope image of both systems revealed the presence of a continuous milk protein layer covering the calcium carbonate particles with a thickness between 5 and 8 nm (Figure 1B). The dissolution study, following Method 701 USP, of CaCO₃ systems demonstrated that microCaCO₃ particles 90:10 had the lowest solubilization grade (i.e. 63%) in comparison with the microCaCO₃ particles 95:5 or the bare CaCO₃ particles, having values of 81 and 96%, respectively. Herein, the authors report the use of this new calcium delivery system, used as a dietary supplement in a group of healthy postmenopausal women with a low intake of dietary calcium. The primary objective of the study was to evaluate the GI tolerability of microCaCO₃. The secondary objectives comprised the comparison of the GI tolerability and the efficacy between microCaCO₃ and the conventional supplements of CaCO₃ and CaCitr. In this work, the authors described the results related to the GI tolerability and patient satisfaction after 1-month usage of dietary calcium supplements.

**Methods**

**Study design and study population**

The study was a randomized, prospective, double-blind clinical trial (CALCIMIP, NCT03452696) that compared microCaCO₃ with standardized CaCO₃ and CaCitr salts. A group of 208 healthy postmenopausal women was consecutively recruited for 6 months by a gynecologist from the medical center specialized in women health at the Instituto Palacios located in Madrid, Spain. The main inclusion criteria of the study consisted of postmenopausal females (postmenopausal criteria: older than 45 years with amenorrhea for at least 1 year) between 45 and 70 years old, low daily intake of dietary calcium (<900 mg/day), and no presence of any pathologies that would prevent participation in the study according to the study protocol. Eligible participants were also required to be able to read and understand the informed consent form. Exclusion criteria included hypersensitivity to the active substances to test (i.e. calcium carbonate or calcium citrate) or to any of the excipients (i.e. milk proteins or added flavors), renal insufficiency, history of kidney or urinary stones, use in the last month of diuretics (furosemide, ethacrynic acid), aluminum salts, and/or thyroid hormones, or use of any other drug or experimental device during the 30 days prior to the selection.

The protocol was approved on April 20, 2018, by the Ethics Committee of clinical research of the Princess University Hospital, located in Madrid in Diego de León, 62 (CP: 28006). The study was performed in accordance with the Helsinki Declaration (1964) and subsequent amendments and with current Spanish regulations (Real Decreto 1090/2015, 4th December; Circular 07/2004 on research with health products), Good Clinical Practices standards and code of ethics. All participants volunteered for the study and signed an informed consent form. No personal data were recorded to guarantee the confidentiality of the participants’ data.

**Dietary supplements**

Eligible participants were randomized to one of the four calcium supplements arms depicted in Table 1 in a 1:1:1:1 proportion.

**Intervention procedures**

Participants, who met the initial eligibility criteria and agreed to participate in the study, attended two visits. During Visit 1, inclusion and exclusion criteria were confirmed while participants were informed about all the aspects related to the study and signed the informed consent form. The medical history of the participants was gathered including any health conditions and current treatment. A physical exploration comprising

| Table 1. Type of calcium supplements, their content, and the total daily intake of elemental calcium per treatment arm. |
|---------------------------------------------------------------|
| **Treatment arm** | **Type of calcium supplement** | **Content per tablet** | **Tablets per day** | **Total daily intake of elemental calcium (mg)** |
| Arm A | MicroCaCO₃ oral chewable tablet | • Protein: 10%  
• CaCO₃: 90%  
• Elemental calcium: 500 mg | 2 | 1000 |
| Arm B | MicroCaCO₃ oral chewable tablet | • Protein: 5%  
• CaCO₃: 95%  
• Elemental calcium: 500 mg | 2 | 1000 |
| Arm C | CaCO₃ oral chewable tablet | • Elemental calcium: 500 mg | 2 | 1000 |
| Arm D | CaCitr oral chewable tablet | • Elemental calcium: 315 mg | 3 | 945 |

CaCitr, calcium citrate; CaCO₃, calcium carbonate; microCaCO₃, microencapsulated calcium carbonate.
weight, height, blood pressure, and heart rate was performed together with the determination of vitamin D status. A vitamin D supplement was prescribed in case participants showed levels of vitamin D below 30 ng/mL. To evaluate GI tolerability, participants were asked to fill in the Spanish version of the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire. The scale is a disease-specific instrument of 15 items combined into 5 symptom clusters, such as reflux, abdominal pain, indigestion, diarrhea, and constipation. The GSRS has a 7-point graded Likert-type scale where 1 represents the absence of troublesome symptoms and 7 represents very troublesome symptoms. Its reliability and validity are well documented.24

After 30 days, physical exploration was performed during Visit 2. Data of adverse events and concomitant medication were also gathered. Participants filled in again the GSRS questionnaire, and their satisfaction with the calcium supplements was self-reported by completing the Spanish version of the Treatment Satisfaction Questionnaire for Medication (TSQM). This is a widely used generic measure of satisfaction with medication that has a Likert-type scale from 1 (extremely dissatisfied) to 7 (extremely satisfied).25 Only the results obtained by both questionnaires related to the GI tolerability and the satisfaction with the use of calcium supplements are discussed subsequently.

**Study outcomes and statistical analysis**

The primary outcome was defined as the prevalence of patients who reported GI symptoms during the second visit per arm of treatment. The secondary outcome was defined as the prevalence of participants with GI symptoms in the A and B treatment arms compared with the C and D treatment arms in Visit 2. The scores of the questionnaire GSRS provided by the participants were analyzed to determine both outcomes. For the primary outcome, the scores of the GSRS of both visits were analyzed per arm treatment, while for the secondary outcome, the GSRS scores of the four treatment arms from the second visit were comparatively analyzed.

The satisfaction grade of the participants with the usage of calcium supplements was analyzed as an exploratory outcome. The scores of the questionnaire TSQM were analyzed to compare the results between the treatment arms.

**Sample size and statistical analysis**

The sample size calculation was based on a similar study.26 The present randomized, double-blind clinical trial was powered considering a type I error (α) of 0.05 and type II error (β) of 0.20 (power was 80%). Additionally, 20% of dropouts were expected; therefore, more than 30 women in each group were recruited as a precaution. Data were analyzed using the analysis of variance (ANOVA) test to detect statistical differences. A $p$-value $< 0.01$ was considered statistically significant. The results were expressed as mean values ± standard deviation (SD) and calculated based on a per-protocol analysis.

**Results**

A total of 208 participants were recruited, and 177 finished the study. The age of the participants was between 45 and 72 years (59.5±6.6 years). The participants were randomized to one of the four treatment arms shown in Figure 2. In total, 31 women ceased participation in the study. In the group using microCaCO$_3$ (arm A), 7 women discontinued because of the recommendation of their physician and none of them due to adverse events caused by the supplement. In the other three treatment arms, the main reason for discontinuation was GI symptoms and the difficulty of chewing the tablet. In total, 12 women interrupted the study because of GI adverse events taking microCaCO$_3$ 95:5 (arm B: 6), CaCO$_3$ supplement (arm C: 4), or CaCitr (arm D: 2).

For all participants, age and clinical data including calcium intake, the mean arterial pressure (MAT), and the body mass index (BMI) were collected. In Table 2, the different variables are presented as an average per treatment group with no statistically significant differences between them ($p>0.01$) according to the ANOVA test. The women of arm A were on average the oldest participants (60.85 years), while the women in group B were the youngest (57.24 years). The lowest mean BMI corresponded to group D (26.77 kg/m$^2$), and was highest in group C (30.28 kg/m$^2$). MAT was overall the same in all the groups, at around 90 mmHg. Related to the dietary calcium intake, group D had the highest intake of calcium with an average of 701.4 mg/day, and group A the lowest with 638.61 mg/day.

For the study of the evolution of the GSRS questionnaire between the treatments, the two-way ANOVA test was performed on two factors (time and supplement) with repeated measures in one of them (supplement). The results showed a significant effect on GSRS score before and after the use of the supplements, independently of the treatment ($F=40.76; p<0.001$). The interaction between the type of treatment and the changes in the GSRS score was also significant ($F=4.03; p=0.008$), indicating the influence of the type of supplement on the evolution of the GSRS score.

The tolerability of the calcium supplements was evaluated by comparison of the mean score of the GSRS survey from Visit 1 and Visit 2 per treatment arm (Table 3). In Visit 1, the overall score in all arms was between 3.95 and 5.35, while in the Visit 2, higher scores were reported in the B, C, and D groups. The highest score was reported in the group treated with conventional CaCO$_3$ (arm C: 11.86). The groups treated with microCaCO$_3$ 95:5 or CaCitr had a score of 9.5, while group A had the lowest score (6.07) with an insignificant increase of the mean GSRS score from Visit 1 to Visit 2 ($p=0.628$) between the two visits. In the other treatment groups, the absolute difference of GSRS score between Visit 2 and 1 was $>5$ points, with arm C being the highest difference of $−7.91$ ($p<0.001$; Table 3).

The difference in mean GSRS score among treatment arms before the use of supplements was minimal ($p=1$). However, after 30 days of supplement consumption, the difference of mean GSRS...
Table 2. Age and clinical data of the 177 participants gathered during Visit 1.

| Treatment arm, mean (SD) | F(3;173) | p-value |
|--------------------------|----------|---------|
| A                        |          |         |
| Age, y                   | 60.85 (7.02) | 57.24 (6.77) |
| Calcium intake, mg/day   | 638.61 (185.23) | 650.93 (181.4) |
| MAP, mmHg                | 89.98 (13.34) | 90.62 (6.61) |
| BMI, kg/m²               | 28.73 (10.05) | 27.07 (4.39) |
| B                        |          |         |
| Age, y                   | 60.27 (5.8)  | 60.27 (5.8) |
| Calcium intake, mg/day   | 664.7 (158.18) | 701.4 (139.54) |
| MAP, mmHg                | 91.91 (6.48)  | 91.24 (5.24) |
| BMI, kg/m²               | 30.28 (16.15) | 26.77 (5.12) |
| C                        |          |         |
| Age, y                   | 60.27 (5.8)  | 60.27 (5.8) |
| Calcium intake, mg/day   | 664.7 (158.18) | 701.4 (139.54) |
| MAP, mmHg                | 91.24 (5.24)  | 91.24 (5.24) |
| BMI, kg/m²               | 26.77 (5.12)  | 26.77 (5.12) |
| D                        |          |         |
| Age, y                   | 59.47 (6.3)  | 59.47 (6.3) |
| Calcium intake, mg/day   | 701.4 (139.54) | 701.4 (139.54) |
| MAP, mmHg                | 91.24 (5.24)  | 91.24 (5.24) |
| BMI, kg/m²               | 26.77 (5.12)  | 26.77 (5.12) |
| Total                    |          |         |

Treatments arms definition: A, microCaCO\(_3\) 90:10; B, microCaCO\(_3\) 95:5; C, CaCO\(_3\); D, CaCitr.
BMI, body mass index; MAP, mean arterial pressure; SD: standard deviation; y = years.

Table 3. Mean GSRS score in Visit 1 and Visit 2 and differences between them per treatment arm.

| GSRS | Mean score (SD) | Visit 1, Mean (SD) | Visit 2, Mean (SD) | Difference Visit 1–Visit 2 | p-value |
|------|----------------|-------------------|-------------------|--------------------------|---------|
| A    |                | 5.35 (7.06)       | 6.07 (7.03)       | −0.72                    | 0.628   |
| B    |                | 4.29 (5.52)       | 9.57 (9.57)       | −5.29                    | 0.001   |
| C    |                | 3.95 (5.63)       | 11.86 (11.85)     | −7.91                    | <0.001  |
| D    |                | 4.20 (4.68)       | 9.51 (9.00)       | −5.23                    | <0.001  |
| Total|                | 4.46 (5.77)       | 9.21 (9.64)       |                          |         |

Treatments arms definition: A, microCaCO\(_3\) 90:10; B, MicroCaCO\(_3\) 95:5; C, CaCO\(_3\); D, CaCitr.
GSRS, Gastrointestinal Symptom Rating Scale; SD, standard deviation.
score of arms A and B compared with arms C and D were more pronounced. The comparison of GSRS scores of microCaCO$_3$ 90:10 (arm A) with the rest of supplements showed the most remarkable differences, being the highest when arm A was compared to conventional CaCO$_3$ (−5.80; p=0.025). Mean difference between arms A and B was −3.51 and between arms A and D was −3.45. Mean differences in GSRS score between women using microCaCO$_3$ 95:5 (arm B) and conventional supplements (i.e. arms C and D) were smaller (−2.29 and 0.06, respectively).

As an exploratory outcome, the results of the TSQM questionnaire were compared. This survey, generally, is designed for patients with chronic diseases who take medication to control the disease and its symptoms. In this case, the participants only answered three relevant questions related to the use of dietary supplements. The questions, referred in Table 4, were: Question 9: “How easy or difficult is it to use the medication in its current form?” Question 10: “How easy or difficult is it to plan when you will use the medication each time?” and Question 14: “Taking all things into account, how satisfied or dissatisfied are you with this medication?”

Answers for TSQM: extremely difficult 1, very difficult 2, difficult 3, somewhat easy 4, easy 5, very easy 6, extremely easy 7.

As an average, participants taking microCaCO$_3$ 90:10 in comparison with the microCaCO$_3$ 95:5 system.

Table 4. Mean TSQM scores of the most relevant questions per treatment arm.

|          | Mean score (SD) | F(3;173) | p-value |
|----------|----------------|----------|---------|
| TSQM_Q9  |                |          |         |
| A        | 4.87 (1.48)    |          |         |
| B        | 4.93 (1.33)    |          |         |
| C        | 3.91 (1.41)    |          |         |
| D        | 3.42 (1.37)    | 12.328   | <0.001  |
| TSQM_Q10 |                |          |         |
| A        | 4.96 (1.38)    |          |         |
| B        | 5.07 (1.18)    |          |         |
| C        | 4.32 (1.44)    |          |         |
| D        | 4.07 (1.27)    | 5.990    | 0.001   |
| TSQM_Q14 |                |          |         |
| A        | 5.02 (1.24)    |          |         |
| B        | 5.24 (0.91)    |          |         |
| C        | 4.64 (0.97)    |          |         |
| D        | 4.27 (1.51)    | 5.744    | 0.001   |

Treatment arms definition: A, microCaCO$_3$ 90:10; B, MicroCaCO$_3$ 95:5; C, CaCO$_3$; D, CaCitr.

TSQM_Q9: How easy or difficult is it to use the medication in its current form?; TSQM_Q10: How easy or difficult is it to plan when you will use the medication each time?; TSQM_Q14: Taking all things into account, how satisfied or dissatisfied are you with this medication?

The authors evaluated the GI tolerability profile of microCaCO$_3$ with a 90:10 mineral to protein ratio and 95:5 mineral to protein ratio in postmenopausal women compared with conventional CaCO$_3$ and CaCitr. Their findings showed that supplementation with microCaCO$_3$ after 30 days, produced fewer GI adverse events compared to conventional calcium supplements. Therefore, the microencapsulation of CaCO$_3$ particles by casein protein helps to reduce the formation of carbon dioxide in the stomach and prevent the associated adverse GI symptoms. Between the two types of microcapsules with different mineral to protein ratios, the GSRS score was lower among the women using microCaCO$_3$ 90:10. These results are, also, in concordance with the dissolution test results that indicated the lowest solubilization grade under acidic conditions for the microCaCO$_3$ 90:10 in comparison with the microCaCO$_3$ 95:5 system.

The GI adverse events associated with calcium supplements impact negatively on long-term compliance, which may limit their effectiveness. The better GI tolerability observed
with the use of this new delivery system may contribute to successful compliance in target groups, especially in those with health problems where the GI symptoms could worsen their clinical conditions.\textsuperscript{27,28} In chronic asymptomatic diseases as osteoporosis, overcoming non-adherence presents a challenge. According to recent studies concerning the treatment of osteoporosis, adherence to long-term calcium and vitamin D supplementation varies between 30 and 75%.\textsuperscript{29} Beyond side effects, convenience and satisfaction in the use of supplementation are key aspects in order to increase compliance. The results from the TSQM questionnaire revealed that the microCaCO$_3$ 90:10 delivery system was easy and satisfactory to use compared to conventional supplements. Those two factors may be important for successful adherence to calcium supplements in postmenopausal women and therefore to reduce their risk of fractures.\textsuperscript{30}

The principal limitation of this study was the lack of gathered clinical data related to the presence or absence of GI adverse events after the use of supplements, beyond the patient-reported outcomes via the GRSR questionnaire. Moreover, the study was performed with a small sample and for a short period of time. In order to confirm the good GI tolerability of the microCaCO$_3$ supplement, a long-term study with a bigger sample size should be performed.

The positive result of the microCaCO$_3$ supplement in postmenopausal women could encourage a study using this type of delivery system in different risk groups with additional calcium requirements, such as individuals over 50 years to prevent fractures and bone loss\textsuperscript{28} or individuals with high risk of cancer in the digestive system, especially colorectal cancer.\textsuperscript{6,31}

**Conclusions**

The microCaCO$_3$ delivery system showed promising results in both questionnaires, GSRS and TSQM, compared with the conventional supplements, CaCO$_3$ and CaCitr. The participants who took microCaCO$_3$ supplement reported fewer GI adverse events and were more satisfied than those using calcium supplements. The fewer GI adverse events associated especially with the use of microCaCO$_3$, with a mineral to protein ratio 90:10, might facilitate increased adherence to calcium supplementation, especially important among the groups at risk of calcium deficiency as postmenopausal women.

**Contributions:** All authors contributed extensively to the work presented in this paper. All authors have contributed significantly to the conception, design, or acquisition of data, or analysis and interpretation of data. All authors have participated in drafting, reviewing, and/or revising the manuscript and have approved its submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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