Acute and 3-month effects of microcrystalline hydroxyapatite, calcium citrate and calcium carbonate on serum calcium and markers of bone turnover: a randomised controlled trial in postmenopausal women

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Abstract
Ca supplements are used for bone health; however, they have been associated with increased cardiovascular risk, which may relate to their acute effects on serum Ca concentrations. Microcrystalline hydroxyapatite (MCH) could affect serum Ca concentrations less than conventional Ca supplements, but its effects on bone turnover are unclear. In the present study, we compared the acute and 3-month effects of MCH with conventional Ca supplements on concentrations of serum Ca, phosphate, parathyroid hormone and bone turnover markers. We randomised 100 women (mean age 71 years) to 1 g/d of Ca as citrate or carbonate (citrate–carbonate), one of two MCH preparations, or a placebo. Blood was sampled for 8 h after the first dose, and after 3 months of daily supplementation. To determine whether the acute effects changed over time, eight participants assigned to the citrate dose repeated 8 h of blood sampling at 3 months. There were no differences between the citrate and carbonate groups, or between the two MCH groups, so their results were pooled. The citrate–carbonate dose increased ionised and total Ca concentrations for up to 8 h, and this was not diminished after 3 months. MCH increased ionised Ca concentrations less than the citrate–carbonate dose; however, it raised the concentrations of phosphate and the Ca–phosphate product. The citrate–carbonate and MCH doses produced comparable decreases in bone resorption (measured as serum C-telopeptide (CTX)) over 8 h and bone turnover (CTX and procollagen type-I N-terminal propeptide) at 3 months. These findings suggest that Ca preparations, in general, produce repeated sustained increases in serum Ca concentrations after ingestion of each dose and that Ca supplements with smaller effects on serum Ca concentrations may have equivalent efficacy in suppressing bone turnover.

Key words: Calcium supplements; Serum calcium; Bone turnover; Randomised trials

Ca supplements have been widely used for treating or preventing osteoporosis, however, recent evidence suggests that they increase cardiovascular risk. In a meta-analysis of randomised controlled trials, Ca supplements, with or without vitamin D, significantly increased the risk of myocardial infarction1. The findings of this meta-analysis have been questioned, primarily because cardiovascular events were not a primary endpoint in any of the included trials, and cardiovascular events were therefore not ascertained in a standardised manner. In contrast to supplemental Ca, high intakes of dietary Ca do not appear to be associated with increased cardiovascular risk2–4. A key difference between supplemental Ca and dietary Ca is their effects on serum Ca concentrations. While Ca supplements are taken in large doses that acutely raise serum Ca concentrations for at least 6 h following their ingestion5,6, Ca from the diet tends to be consumed in smaller amounts over a day, and even large amounts of dietary Ca have smaller effects on serum Ca concentrations7. It may be the elevation in serum Ca concentrations, after ingestion of Ca supplements, that underlies the increase in cardiovascular risk. In observational studies, higher serum Ca concentrations within the normal range have been associated with increased cardiovascular risk8–10. There are several possible mechanisms by which increased serum Ca concentrations could influence cardiovascular risk, perhaps involving the activity of vascular smooth muscle cells or endothelial cells, or by influencing blood coagulation11.

However, Ca remains an essential nutrient for bone health. Some observational studies have shown lower bone mineral density and an increased risk of fracture among those with the lowest intakes of Ca12,13. In light of the adverse

Abbreviations: CTX, C-telopeptide; MCH, microcrystalline hydroxyapatite; PINP, procollagen type-I N-terminal propeptide; PTH, parathyroid hormone.
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cardiovascular risks associated with Ca supplementation, it has been recommended that individuals meet the recommended intakes of Ca through diet alone, or that smaller doses of supplements are used\(^\text{14,15}\). Although dietary intakes of Ca often fall below the recommended levels\(^\text{16-19}\), it would be theoretically possible for most people to meet these intakes through dietary sources alone. However, there are others, such as the elderly or those who are unable to or choose not to consume dairy products, who may be at risk of inadequate intakes\(^\text{19,20}\), and for whom supplementation may be recommended. Therefore, there exists a need for a safer form of supplemental Ca. Microcrystalline hydroxyapatite (MCH), derived from bovine bone, contains Ca and phosphate in the form of hydroxyapatite, as well as collagenous and non-collagenous bone proteins. MCH has previously been shown to have a smaller effect on serum Ca concentrations than conventional Ca supplements 4 h post-ingestion\(^\text{21}\). MCH could potentially provide a safer form of supplemental Ca to the cardiovascular system than conventional supplements. However, documentation of the acute and medium-term effects of different types of Ca supplements on serum Ca concentrations and related variables in carefully conducted randomised trials is scant, particularly using currently accepted markers of bone turnover.

To evaluate MCH as a form of supplemental Ca, we compared its acute effects on serum Ca concentrations with those of conventional Ca supplements, and assessed their medium-term effects on bone turnover. There are a number of ways in which MCH preparations may be produced with respect to the degree of protein hydrolysis and granule size, so, as a secondary aim, we determined whether differences in these variables influenced the effects on serum Ca concentrations or bone turnover. Finally, we examined the duration of the elevation in serum Ca concentrations following the ingestion of a Ca supplement, as few trials have continued beyond 4–6 h, and determined whether these acute effects were attenuated with long-term use.

Methods

Participants

The present study was a trial of 100 women, at least 5 years postmenopause. We recruited women from those who had volunteered for other osteoporosis studies, but had been ineligible for those studies because they had normal bone density. We excluded women with a history of CVD, a 5-year cardiovascular risk of >15%, or a major ongoing systemic illness; or if they had taken any medication known to affect Ca concentrations or bone metabolism in the past year, or were taking >2000 IU/d (50 μg/d) of vitamin D. Participants who regularly used more than 100 mg/d of Ca supplements required a 6-month withdrawal period before entering the study. We reviewed the medical history questionnaires of approximately 1000 women, of whom 415 met the inclusion and exclusion criteria and were invited to participate. Women who expressed interest in participating were asked to complete a self-administered medical history questionnaire, which was reviewed by study staff to ensure they still met these criteria. The flow of the participants through the study is presented in Fig. 1. Of the participants, three with phlebotomy difficulties withdrew after randomisation but before receiving their first dose of treatment. These women did not contribute data to the study, and by convention, those participants who were randomised but who withdrew before receiving the study intervention were excluded from the intention-to-treat analysis.

Study design

Participants were randomised to the treatment with Ca (1 g/d) as citrate or carbonate (citrate–carbonate), one of two MCH preparations, or a Ca-free placebo, for 3 months. A 1 g dose of Ca was studied as this has been most commonly studied in relation to fracture and cardiovascular risk\(^\text{1,22}\). For the present study, two MCH preparations (denoted MCHA and MCHB) were supplied by Waitaki Biosciences. The MCHA preparation had a smaller particle size and a greater degree of protein hydrolysis compared with MCHB. New Zealand cattle are free of BSE. Calcium carbonate (Kirsch Pharma) and calcium citrate (Jost Chemical Company) were purchased from Hawkins Watts. All four treatments and placebo were given as powders encapsulated in identical gelatin capsules. Each capsule contained 125 mg Ca or placebo. TriPLICATE samples of each of the four treatments and placebo were analysed to verify Ca content. Treatment was randomly assigned using a computer-generated variable-block randomisation schedule prepared by staff not in contact with participants. Participants were blinded to the treatment that they received for the duration of the study. Study staff were not blinded throughout the study. This was to allow further measurements to be carried out on only those participants allocated to calcium citrate and placebo (data to be presented elsewhere).

On day 1 of the study, participants attended an 8 h session at our research clinic after an overnight fast. A baseline blood sample was collected between 07.00 and 09.00 hours, after which participants immediately received the first dose of their allocated treatment with water. Further blood samples were collected 2, 4, 6 and 8 h after the treatment was ingested. To permit the effects of the allocated treatment to be examined in isolation, participants were asked to consume only the standardised low-Ca meals provided during the 8 h period. A light breakfast (peaches in juice and toast with margarine and jam, marmalade or honey) was provided immediately after the treatment was ingested; a light lunch (fruit salad in juice and bread with margarine and jam, honey, marmalade or peanut butter) was provided at 4 h, followed by an optional snack (plain biscuits and decaffeinated tea) at 6 h. Meals were provided after the blood sampling was completed for that time point. The breakfast meal provided an additional 74 mg Ca, the lunch 74–80 mg Ca, and the snack 6 mg Ca, by calculation. Water and non-caffeinated tea without milk were allowed ad libitum throughout the day.

After day 1, participants were instructed to take their treatment at home in two divided doses, with their morning and evening meals. Midway through the study, participants...
were telephoned to encourage compliance. After 3 months, participants returned to our clinic having taken their final dose of treatment the evening before, and a final fasting blood sample was collected. As it is unknown whether the acute effects of conventional Ca supplements on serum Ca concentrations are different after long-term use, we invited participants allocated to calcium citrate to repeat the 8 h sampling protocol as carried out on day 1. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human participants were approved by the New Zealand Northern Regional X Ethics Committee. Written informed consent was obtained from all participants. The present study was registered with the Australia New Zealand Clinical Trials registry (ACTRN12611000232932).

**Measurements**

Ionised Ca concentration was measured on anaerobically handled specimens using an ABL800 FLEX blood gas analyser (Radiometer) within 60 min of collection. The samples for the measurement of total Ca and phosphate concentrations were batch-analysed at the end of each 8 h session using a Cobas modular analyser (Roche Diagnostics). The samples for the measurement of parathyroid hormone (PTH) and bone turnover markers were stored at −70°C and batch-analysed at the completion of the study. Roche autoanalysers were used for the measurement of PTH, serum procollagen type-I N-terminal propeptide (PINP) and serum C-telopeptide (CTX) concentrations (Roche Diagnostics). Baseline 25-hydroxyvitamin D concentration was measured using the API400 LC/MS/MS System (ABSciex).

Body weight was measured using electronic scales, and height using a Harpenden stadiometer (Holtain). Dietary Ca intake was assessed using a validated FFQ (23). Compliance was assessed at the final visit by capsule count and calculated as the number of capsules taken as a percentage of the number that should have been taken.

**Statistical analyses**

The present study was adequately powered (80%) at the 5% significance level to detect a between-group difference in either of the bone turnover markers of at least one standard deviation. Effects of this size have previously been observed with Ca supplementation and are likely to be of clinical significance.

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**Fig. 1. Flow of the participants through the study. MCH, microcrystalline hydroxyapatite.** *Three participants were unable to be cannulated. These participants did not receive the study intervention, did not contribute data to the study and were not included in the analysis.*
Data were analysed on a modified intention-to-treat basis (three participants who were randomised but who did not commence the study treatment were excluded) using a mixed-model approach to repeated measures (Proc Mixed, SAS version 9.2; SAS Institute, Inc.). The assumptions of normality and homogeneity of variance were met, and all models were inspected for adequacy of fit. Exact methods were employed where appropriate. The change from baseline was the dependent variable and baseline value of the appropriate variable was included as a covariate (ANCOVA). Significant main (time or treatment allocation) and interaction effects (time × treatment allocation) were further explored using the method of Tukey to construct honestly significant differences; however, since these comparisons were pre-planned, the pairwise P values were not adjusted for multiplicity. The areas under the ionised Ca, total Ca or phosphate concentrations over time functions (AUC) were calculated using a trapezoidal method and provided the dependent variable as indicated.

All tests were two-tailed and P < 0·05 was considered significant.

Results

The baseline clinical and biochemical characteristics of participants are presented in Table 1. The groups were comparable in all indices at baseline. Over the 3-month study period, 85% of participants took 80% or more of their allocated capsules. Median compliance was not different between the groups (P = 0·10).

Acute effects on serum calcium and phosphate concentrations

Changes in the concentrations of serum ionised Ca (ANCOVA, treatment × time interaction, P = 0·0001) and phosphate (treatment × time interaction, P < 0·0001) were different among the five groups. Changes in the concentrations of ionised Ca, total Ca and phosphate were not different at any time point between the calcium citrate and calcium carbonate groups (all P > 0·20), or between the MCHA and MCHB groups (all P > 0·34, expect for changes in ionised Ca concentrations at 6 h, P = 0·07). To allow for comparison between conventional Ca supplements (citrate and carbonate) and MCH, the results from these groups were pooled for subsequent analyses.

Ionised Ca concentrations increased in the citrate–carbonate and MCH groups compared with the control group (Fig. 2). Over 8 h, fifteen participants in the citrate–carbonate group, four in the MCH group and none in the placebo group had an ionised Ca measurement above the normal range (> 1·30 mmol/l) at one or more time points. The change in ionised Ca concentrations was more positive in the citrate–carbonate group than in the MCH group, and the corresponding AUC was greater in the citrate–carbonate group than in the MCH group. Total Ca concentrations also increased in both the citrate–carbonate and MCH groups compared with the control group (Fig. 2). The increase in total Ca concentrations was slightly greater in the citrate–carbonate group than in the MCH group; however, the AUC for total Ca concentrations was not different between those two groups. Ionised Ca and total Ca concentrations remained increased from baseline 8 h after the dose was ingested in the citrate–carbonate group (P < 0·0001) and MCH group (P < 0·01).

Serum phosphate concentration was increased in the MCH group compared with the citrate–carbonate and control groups (Fig. 3). The change in phosphate concentration was not different between the citrate–carbonate and control groups, except at 6 h. Phosphate concentration remained increased from baseline at 8 h in the MCH group.

Table 1. Baseline clinical and biochemical characteristics of participants

(Mean values and standard deviations)

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<th>Calcium carbonate (n 20)</th>
<th>MCHA (n 20)</th>
<th>MCHB (n 19)</th>
<th>Control (n 20)</th>
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<td>46·5</td>
<td>19·1</td>
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MCH, microcrystalline hydroxyapatite; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; CTX, C-telopeptide; PINP, procollagen type-I N-terminal propeptide.

* Corrected for albumin.
The concentration of the Ca–phosphate product (ionised Ca \(\times\) phosphate) was increased in the MCH and citrate–carbonate groups relative to the control group, and the increase was greater in the MCH group (Fig. 3).

After 3 months of supplementation, fasting ionised Ca concentration was increased from baseline in the citrate–carbonate group by 0·01 mmol/l (\(P=0·006\)) and fasting total Ca concentration was lower than baseline in the control group by 0·03 mmol/l (\(P=0·02\)). Fasting phosphate concentration was lower than baseline at 3 months in the MCH group by 0·04 mmol/l (\(P=0·01\)). In the eight participants allocated to calcium citrate who repeated the 8 h of blood sampling at 3 months, the changes in ionised and total Ca concentrations were similar to those observed at baseline (Fig. 4).

Acute and long-term effects on parathyroid hormone and markers of bone turnover

Changes up to 3 months in the concentrations of PTH (ANCOVA, treatment \(\times\) time interaction, \(P=0·04\)), CTX (treatment \(\times\) time interaction, \(P=0·006\)) and PINP (treatment \(\times\) time interaction, \(P=0·002\)) were different among the five groups. Changes in the concentrations of PTH, CTX and PINP were not different between the citrate and carbonate groups (\(P>0·25\)) or between the MCHA and MCHB groups (all \(P>0·13\)) at any time point. The results from these groups were therefore pooled as above.

PTH concentration declined over the 8 h after the first dose of citrate–carbonate or MCH compared with the control group, and the reduction in PTH concentration was greater in the citrate–carbonate group than in the MCH group (Fig. 5). CTX concentration declined from baseline in the control group from 2 to 8 h (all \(P<0·0001\)). There was a further reduction in the concentration of CTX in the citrate–carbonate and MCH groups compared with the control group (Fig. 5). The change in the concentration of CTX over 8 h was not different between the citrate–carbonate and MCH groups at any time point. The concentration of PINP increased from baseline in all groups at 8 h (all \(P<0·04\)), and was not different between the groups.

After 3 months, PTH concentration was slightly but significantly lower in the citrate–carbonate and MCH groups relative to the control group (Fig. 5). Both CTX and PINP concentrations were significantly lower than those at baseline in the citrate–carbonate and MCH groups compared with the control group.
group. There were no differences in the reduction in the concentrations of PTH, CTX and PINP at 3 months between the citrate–carbonate and MCH groups.

Discussion

In the present study, the ingestion of 1 g Ca as citrate, carbonate or MCH resulted in an acute and sustained elevation of serum Ca concentrations and suppression of bone resorption. In addition, after 3 months of supplementation, there was a reduction in bone turnover (reflected in both CTX and PINP levels). Ingestion of MCH resulted in a smaller increase in serum Ca concentrations than the intake of conventional citrate and carbonate supplements, but increased the concentrations of phosphate and the Ca–phosphate product.

Ionised and total Ca concentrations remained elevated above baseline and the control group 8 h after a 1 g dose of Ca. Some studies have reported elevations in serum Ca concentrations up to 6 h after an oral dose(7,24,25), but few have continued beyond this time point. In postmenopausal women, serum Ca concentration was significantly greater than the control 3–12 h after the ingestion of calcium carbonate and 1–9 h after the ingestion of calcium citrate(6). Similarly, in postmenopausal women, an evening dose of calcium carbonate or citrate raised serum Ca concentrations for at least 12 h(20). Furthermore, in the present study, the serum Ca excursion was not different when calcium citrate was taken at baseline, or after 3 months of continuous supplementation. In longitudinal studies(8), differences in serum Ca concentrations of the magnitude observed in the present study are associated with a 17 % increase in cardiovascular risk, very similar to that found in the trials of Ca supplementation(27).

Few studies have compared the acute effects of MCH with other forms of Ca. Consistent with our findings, these studies have demonstrated smaller increases in serum Ca concentrations and/or reductions in PTH concentrations following the ingestion of MCH compared with other Ca salts(21,24,28). The smaller rise in serum Ca concentrations following the ingestion of MCH may have been due to a lower bioavailability of Ca. This was suggested by the smaller AUC of ionised Ca following the ingestion of MCH compared with citrate–carbonate intake. Alternatively, Ca may have been more slowly absorbed from MCH because of slow dissolution.
of the hydroxyapatite crystal in the gastrointestinal tract, and the need for hydrolysis of the protein matrix. However, it should be noted that MCH was comparably effective in reducing bone turnover, so it does achieve the same therapeutic effect with a lesser increase in serum Ca concentrations. In contrast to the significantly smaller effect of MCH on ionised Ca concentrations, the differences between the groups for total Ca concentrations were less pronounced. Increased serum phosphate concentrations might explain the smaller effect of MCH on ionised Ca concentrations, since Ca complexes with phosphate.

We found no differences between the citrate and carbonate groups, or between the MCH groups. Calcium citrate is more soluble than carbonate, and has been suggested to be more absorbable and/or result in a larger increase in serum Ca concentrations\(^{(26,29,30)}\), although others have found no difference\(^{(5,6,24)}\). Solubility plays a limited role in determining Ca absorption, when Ca is administered with a meal to healthy people\(^{(31,32)}\). Differences between calcium carbonate and citrate in some trials might reflect differences in the physical form in which they were administered (e.g. powder vs. tablet)\(^{(33)}\). In the present study, all preparations were administered as identical encapsulated powders. Similarly, the more finely processed MCH preparation would be expected to be more rapidly absorbed than the less finely processed preparation, due to the greater surface area of the smaller particles, but this was not the observed outcome.

PTH exhibits a marked diurnal rhythm\(^{(34)}\), as do markers of bone resorption, such as CTX\(^{(35–37)}\). Accordingly, we observed significant changes in the concentrations of PTH and CTX in the control group of the present study during the 8 h period; these changes were very similar to those previously reported for PTH\(^{(38)}\) and CTX\(^{(37)}\). The citrate–carbonate and MCH preparations further reduced CTX concentrations over 8 h compared with the control. Markers of bone formation, such as PINP, exhibit a diurnal rhythm similar to those of bone resorption, but one that is less pronounced\(^{(38)}\). PINP concentration was only measured at 8 h, and was elevated in all groups at this time. After 3 months, bone turnover was significantly lower in the citrate–carbonate and MCH groups, reflected by reductions in both CTX and PINP concentrations. Lowered bone turnover is a well-established effect of Ca supplementation\(^{(21,39–41)}\).

Previous studies have compared the acute effects of different Ca preparations on serum Ca and PTH concentrations\(^{(6,21,24,30)}\) under the premise that larger increases in ionised Ca concentrations and reductions in PTH concentrations will translate into greater suppression of bone turnover. However, few have compared the long-term effects of different Ca preparations on markers of bone turnover. Despite the differences that we observed in the concentrations of ionised Ca, phosphate and PTH between the MCH and citrate–carbonate groups, their effects on CTX and PINP concentrations were the same, acutely and after 3 months of treatment. Consistently, in longer trials, MCH has been as effective as calcium carbonate in slowing bone loss\(^{(42–44)}\). These findings suggest that the acute effects of Ca preparations on serum Ca concentrations might be dissociated from their longer-term effects on bone turnover.

Phosphate concentration was increased in the MCH group at 4 h compared with the control and citrate–carbonate groups. Participants allocated to the MCH treatment would have received an additional 0.5 g phosphate (based on a Ca:phosphate ratio in bone of 1:5) compared with those allocated to the other treatment groups. As higher concentrations of serum phosphate and the Ca–phosphate product have been associated with increased CVD risk in the general population\(^{(10,45–47)}\), this suggests that MCH might not provide a safer form of supplemental Ca.

A weakness of the present study was the size of the dose of Ca studied. As in previous similar trials\(^{(5,6,24,26)}\), we examined...
the effects of 1 g Ca to maximise the differences between the preparations. However, 1 g/d of supplemental Ca would commonly be taken in two doses of 0·5–0·6 g, and daily changes in serum Ca concentrations may be smaller but possibly of a greater duration than that reported here. Most trials in the meta-analysis of Ca and cardiovascular events (27) administered 1 g/d of Ca in two divided doses, so any increase in cardiovascular risk may be related to such a dosing schedule.

In summary, conventional calcium citrate and carbonate supplements raised serum Ca concentrations for at least 8 h, and this effect was not diminished with continuous use. MCH produced a smaller increase in ionised Ca concentrations, and a marginally smaller reduction in PTH concentrations, but had equivalent effects on bone turnover to the conventional Ca supplements. However, elevated concentrations of serum phosphate and the Ca–phosphate product after the MCH treatment suggest that it may not provide a safer form of supplemental Ca. Consuming Ca through dietary sources is currently the safest way for people to achieve their recommended Ca intake. For those unable to consume adequate Ca through diet alone, future research should aim at identifying the forms of supplemental Ca that release Ca into the blood slowly. The findings of the present study suggest that Ca preparations with smaller effects on serum Ca concentrations may still retain comparable efficacy in suppressing bone turnover.

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The authors’ contributions are as follows: S. M. B. and I. R. R. formulated the research question and designed the study; S. M. B., A. S., L. H., M. E. H., O. A., B. M. and A. M. H. carried out the study; G. D. G., S. M. B. and I. R. R. analysed the data and S. M. B. and I. R. R. drafted the manuscript, which was critically revised by the co-authors.

None of the authors has any conflict of interest to declare.

References

Calcium supplements and serum calcium


