

Acute effects of calcium carbonate, calcium citrate and potassium citrate on markers of calcium and bone metabolism in young women

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Both K and Ca supplementation may have beneficial effects on bone through separate mechanisms. K in the form of citrate or bicarbonate affects bone by neutralising the acid load caused by a high protein intake or a low intake of alkalisng foods, i.e. fruits and vegetables. Ca is known to decrease serum parathyroid hormone (S-PTH) concentration and bone resorption. We compared the effects of calcium carbonate, calcium citrate and potassium citrate on markers of Ca and bone metabolism in young women. Twelve healthy women aged 22–30 years were randomised into four controlled 24 h study sessions, each subject serving as her own control. At the beginning of each session, subjects received a single dose of calcium carbonate, calcium citrate, potassium citrate or a placebo in randomised order. The diet during each session was identical, containing 300 mg Ca. Both the calcium carbonate and calcium citrate supplement contained 1000 mg Ca; the potassium citrate supplement contained 2250 mg K. Markers of Ca and bone metabolism were followed. Potassium citrate decreased the bone resorption marker (N-terminal telopeptide of type I collagen) and increased Ca retention relative to the control session. Both Ca supplements decreased S-PTH concentration. Ca supplements also decreased bone resorption relative to the control session, but this was significant only for calcium carbonate. No differences in bone formation marker (bone-specific alkaline phosphatase) were seen among the study sessions. The results suggest that potassium citrate has a positive effect on the resorption marker despite low Ca intake. Both Ca supplements were absorbed well and decreased S-PTH efficiently.

Calcium: Potassium: Acid–base homeostasis: Bone metabolism

A typical Western diet is characterised by suboptimal Ca intake^(1–5), excessive protein intake, and low intake of K-rich, bicarbonate-rich foods (i.e. fruits and vegetables)⁽⁶⁾. Several reports on the importance of adequate Ca intake for bone have been published^(7–9). Ca inhibits parathyroid hormone (PTH) secretion and prevents bone resorption. Recently, interest in the significance of acid–base homeostasis in bone health has grown⁽⁶⁾. An imbalance between intakes of protein and K-rich, bicarbonate-rich foods results in chronic, low-grade metabolic acidosis due to non-carbonic acids being metabolised from sulfuric amino acids. Studies related to metabolic acidosis have shown that a small reduction in extracellular pH leads to increased osteoclastic activity, indicating an increase in bone resorption⁽¹⁰⁾. K and organic anions are metabolised to alkaline compounds, hence, neutralising the acid load caused by a high protein intake⁽¹¹⁾. An increase in both Ca and K in the Western diet is likely to have a beneficial effect on bone through different mechanisms.

Potential ways to increase Ca intake are the use of Ca supplements and fortification of foods. Calcium carbonate and calcium citrate are the most common forms of Ca supplementation⁽¹²⁾. Unlike calcium carbonate, calcium citrate provides an alkaline load in addition to Ca since the citrate anion is metabolised to bicarbonate. Calcium citrate may also be absorbed better than calcium carbonate, as shown in fasting

individuals^(13,14) and in patients suffering from gastric achlorhydria⁽¹⁴⁾, but also in healthy postmenopausal women when taken with a meal⁽¹⁵⁾. However, some studies have found no difference in absorbability between calcium carbonate and calcium citrate^(12,16). Based on a 12-week cross-over study with postmenopausal women, calcium citrate may inhibit bone resorption more efficiently than calcium carbonate, despite similar decreases in serum PTH with both Ca preparations⁽¹⁷⁾.

Potassium bicarbonate administration reduces urinary Ca excretion⁽¹⁸⁾. Supplementation with potassium citrate or potassium bicarbonate has also been observed to reduce markers of bone resorption^(19–21) and increase bone mineral density⁽²⁰⁾ in postmenopausal women with low bone density. According to Jehle *et al.*⁽²⁰⁾ this effect is independent of reported skeletal effects of K. Combined treatment with potassium citrate and calcium citrate inhibits bone resorption and increases Ca absorption relative to either placebo or calcium citrate or potassium citrate treatment alone⁽²²⁾. In cross-sectional studies, an association between better bone health and fruit and vegetable consumption – an index of higher intake of K and bicarbonate – has been observed^(23–25).

Whether the positive effect of an alkali administration persists with moderate protein consumption is unknown⁽²⁶⁾. It is also unclear whether an alkali load has a beneficial impact on bone when the diet is not acidogenic. Further,

Abbreviations: NTx, N-terminal telopeptide of type I collagen; PTH, parathyroid hormone; S-iCa, serum ionised Ca.

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calcium carbonate and calcium citrate may have different effects on Ca and bone metabolism. In the present short-term intervention study, we compared the effects of calcium carbonate with those of calcium citrate, and examined the influence of the citrate salts potassium citrate and calcium citrate on markers of Ca and bone metabolism in healthy young women.

Subjects and methods

Twelve healthy female volunteers aged 20–30 years participated in four separate 24 h sessions, with each subject serving as her own control. The sessions were attended at intervals of 7 d. Subjects had no medications or illnesses known to affect Ca or bone metabolism. Eight of the subjects used oral contraceptives. The basic characteristics of participants are shown in Table 1. Before coming to the research unit, the subjects fasted overnight.

Subjects received a single dose of calcium carbonate, calcium citrate or potassium citrate mixed in a berry jelly with their breakfast. Calcium carbonate and calcium citrate doses contained 1000 mg Ca. Calcium citrate and potassium citrate supplements contained equal amounts, 3145 mg, of citrate. Potassium citrate doses contained 2250 mg K. The intakes of selected nutrients during the study sessions are presented in Table 2. The order of the sessions was randomised.

The meals served during each study session were identical, providing 300 mg Ca, 800 mg P, and 3300 mg K per d, by calculation. No additional meals or snacks were allowed, but tap water was provided *ad libitum*. Meals were served at 08.00, 12.00, 14.00, 16.00 and 20.00 hours. For estimation of habitual Ca, P and energy intakes, the volunteers kept a 4 d food record before the beginning of the experiment.

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Committee of the Department of Public Health and Epidemiology in the hospital district of Helsinki and Uusimaa. Written informed consent was obtained from all subjects.

Sampling

Blood samples were taken anaerobically at 08.00, 10.00, 12.00 and 16.00 hours, and again at 08.00 hours on the following

Table 1. Basic characteristics of subjects (*n* 12)
(Mean values and ranges)

Variable	Mean	Range
Age (years)	25	22–30
Weight (kg)	63.8	49–75
Height (cm)	168	156–178
BMI (kg/m ²)	22.6	17.0–28.8
Habitual dietary K intake (mg/d)	3634	2450–5180
Habitual dietary Ca intake (mg/d)	1268	728–2358
Habitual dietary P intake (mg/d)	1680	917–3018
Habitual dietary protein intake (g/d)	85.6	44–177
Habitual energy intake (kJ/d)	8800	6800–13 900

Table 2. Dietary intakes of selected nutrients from meals during the study sessions

Variable	Intake (per d)
Energy (kJ)	9300
Protein (g/kg)	0.8
Ca (mg)	323
P (mg)	812
K (mg)	3300
Fibre (g)	27

morning. Blood samples were taken immediately before meals. Serum was separated from blood and stored at –20°C until analysed. The 24 h urine collections were obtained from 08.00 hours on the study day to 08.00 hours the following morning.

Laboratory methods

Serum ionised Ca (S-iCa) and K concentrations were analysed from anaerobically handled serum samples with an ion selective analyser (Microlyte 6; Thermo Electron, Vantaa, Finland) within 90 min of sample collection. The intra-assay CV for S-iCa was 1.6%. In the other measurements, all samples from the same individual were analysed in the same assay in a randomised order. Serum phosphate and creatinine concentrations and excretions of urinary Ca, phosphate and creatinine were measured spectrometrically with an autoanalyser (Konelab 20; Thermo Electron). The intra- and inter-assay CV of these analyses were 1.7 and 2.4%, respectively. Serum intact PTH concentration was measured by an immunoenzymometric assay using Octeia[®] Intact PTH Kits (Immunodiagnostic Systems Limited, Boldon Colliery, Tyne and Wear, UK). The intra- and inter-assay CV were 2.9 and 5.1%, respectively. Serum bone-specific alkaline phosphatase concentration was determined by an enzyme immunoassay (Metra[™] BAP EIA Kit; Quidel Corp., San Diego, CA, USA). Intra- and inter-assay CV were 4.4 and 10.4%, respectively. The excretion of urinary N-terminal telopeptide of type I collagen (NTx) was analysed by an ELISA using Osteomark[®] NTx Test Kits (Ostex International, Inc., Seattle, WA, USA). The intra- and inter-assay CV were 4.3 and 6.9%, respectively.

Statistical analysis

Data were expressed as mean values with their standard errors. For serum variables, the area under the curve for the difference from the morning fasting value was calculated. To exclude the effect of the first fasting sample, the Δ values of the 0 h sample to the 24 h sample were used in the analyses. The results of urinary Ca, urinary phosphate and urinary NTx were corrected for urinary creatinine excretion before statistical analyses. Non-normal distributions were normalised by logarithmic transformations. ANOVA with repeated measures was used to compare the study sessions. If the sphericity assumption was violated, a Huynh–Feldt adjustment was applied. Contrast analysis was used for pairwise comparisons between the study sessions. Analyses were

conducted with the SPSS 12.0 statistical package (SPSS Inc., Chicago, IL, USA) in a Windows environment. We regarded $P < 0.10$ as a trend and $P < 0.05$ as a statistically significant difference.

Results

Serum ionised calcium

The S-iCa concentrations differed between the study sessions ($P = 0.0001$; ANOVA) (Fig. 1). Both calcium carbonate ($P = 0.001$) and calcium citrate ($P = 0.0001$) increased S-iCa concentration as compared with the control session. The difference in S-iCa between the calcium carbonate and calcium citrate sessions was not significant ($P = 0.300$). Potassium citrate had no effect on S-iCa concentration relative to the control session ($P = 0.337$).

Urinary calcium

Differences were found in urinary Ca excretion between the study sessions ($P = 0.0001$; ANOVA) (Fig. 1). Urinary Ca

excretion was higher during the calcium carbonate ($P = 0.0001$) and calcium citrate ($P = 0.0001$) sessions, but lower during the potassium citrate ($P = 0.004$) session than during the control session. During both Ca supplement sessions, urinary Ca excretion was also higher than in the potassium citrate session ($P = 0.0001$). Urinary Ca excretions did not differ between the calcium carbonate and calcium citrate sessions ($P = 0.173$).

Serum phosphate and urinary phosphate

Serum phosphate concentrations differed between the study sessions ($P = 0.0001$; ANOVA) (Fig. 2). Calcium citrate ($P = 0.050$) and calcium carbonate ($P = 0.071$) tended to increase serum phosphate compared with the control session. Potassium citrate decreased the serum phosphate concentration ($P = 0.012$). Urinary phosphate excretions also differed between the study sessions ($P = 0.003$; ANOVA) (Fig. 2). Calcium citrate ($P = 0.001$) and calcium carbonate ($P = 0.002$) decreased urinary phosphate relative to the control session. In addition, calcium citrate tended to decrease urinary phosphate compared with the potassium citrate session ($P = 0.077$). The difference between the control and potassium citrate sessions was not significant ($P = 0.131$).

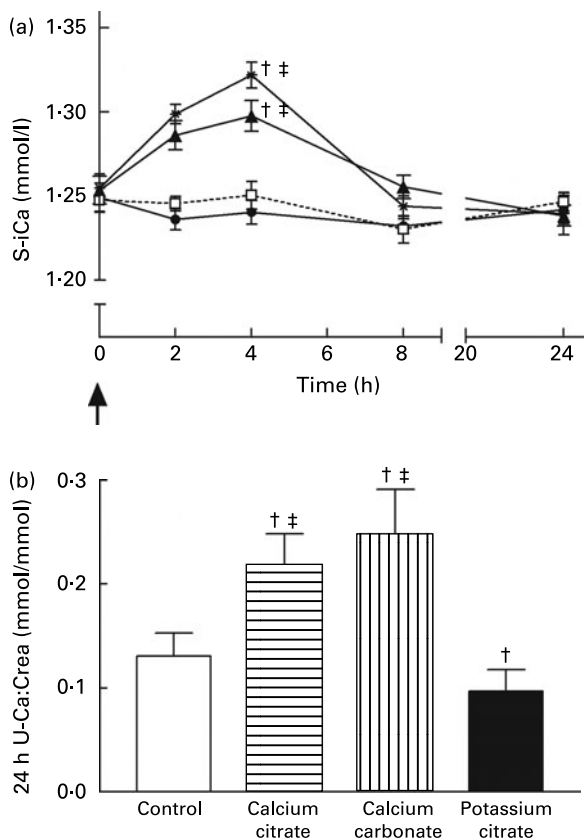


Fig. 1. (a) Changes in serum ionised Ca (S-iCa) concentration during the four study sessions: control (□); calcium citrate (▲); calcium carbonate (*); potassium citrate (●). †, Supplement administration time. (b) 24 h Urinary excretion of Ca (urinary Ca:creatinine ratio; U-Ca:Crea) during the four study sessions. Values are means, with their standard errors represented by vertical bars. The supplements affected area under the curve values of S-iCa ($P = 0.0001$; ANOVA) and 24 h U-Ca:Crea ($P = 0.0001$; ANOVA). † Mean value was significantly different from that of the control session ($P < 0.05$). ‡ Mean value was significantly different from that of the potassium citrate session ($P < 0.05$).

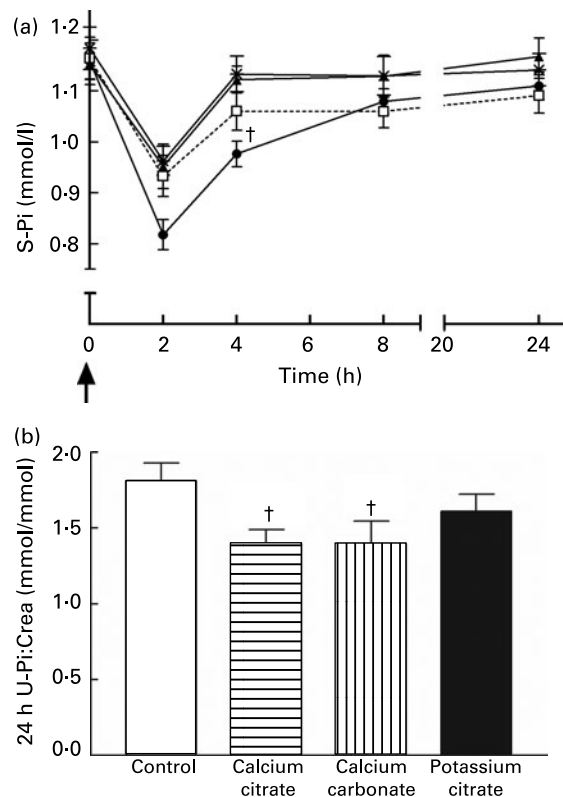


Fig. 2. (a) Changes in serum phosphate (S-Pi) concentration during the four study sessions: control (□); calcium citrate (▲); calcium carbonate (*); potassium citrate (●). †, Supplement administration time. (b) 24 h Urinary excretion of Pi (urinary Pi:creatinine ratio; U-Pi:Crea) during the four study sessions. Values are means, with their standard errors represented by vertical bars. The supplements affected area under the curve values of S-Pi ($P = 0.0001$; ANOVA) and 24 h U-Pi:Crea ($P = 0.003$; ANOVA). † Mean value was significantly different from that of the control session ($P < 0.05$).

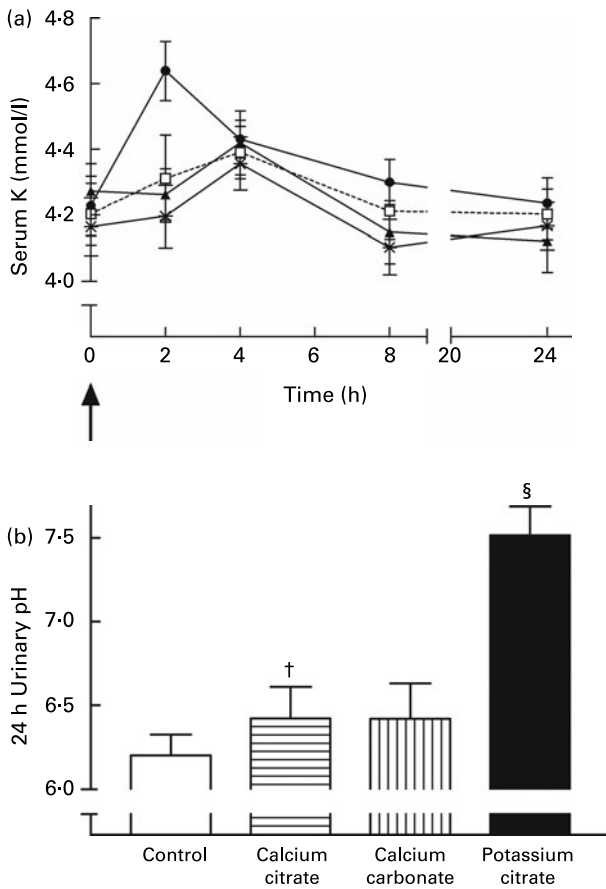


Fig. 3. (a) Changes in serum K concentration during the four study sessions: control (□); calcium citrate (▲); calcium carbonate (*); potassium citrate (●). †, Supplement administration time. (b) 24 h Urinary pH during the four study sessions. Values are means, with their standard errors represented by vertical bars. The supplements tended to affect area under the curve values of serum K ($P=0.068$; ANOVA) and affected urinary pH ($P=0.0001$; ANOVA). † Mean value was significantly different from that of the control session ($P<0.05$). § Mean value was significantly different from those of all the other sessions ($P<0.05$).

Serum potassium

The area under the curve values of serum K tended to differ between the study sessions, but did not reach statistical significance ($P=0.068$; ANOVA) (Fig. 3). However, when comparing the serum K results at 10.00 hours (2 h after ingesting the supplements or the placebo), differences were observed ($P=0.001$; ANOVA). At the same point, serum K was higher at 10.00 hours in the potassium citrate session than in the control ($P=0.016$), calcium citrate ($P=0.007$) or calcium carbonate ($P=0.001$) sessions. At other sampling times, serum K values did not differ.

Urinary pH

The supplements affected urinary pH ($P=0.0001$; ANOVA) (Fig. 3). Urinary pH was greater in the potassium citrate session than in all other sessions ($P=0.0001$). Moreover, in the calcium citrate session, urinary pH was higher than in the control session ($P=0.049$). No difference was observed in urinary pH values between the calcium carbonate and control sessions ($P=0.214$).

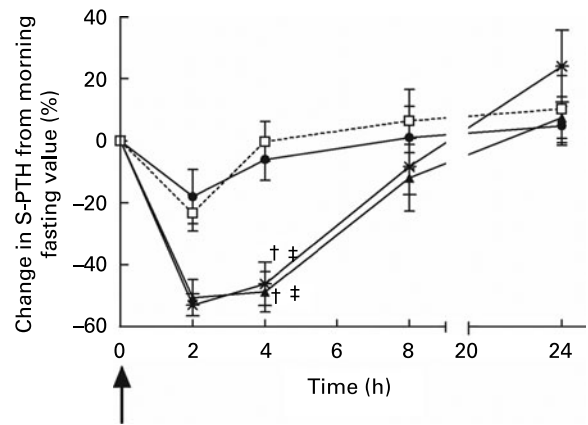


Fig. 4. Changes in serum parathyroid hormone (S-PTH) concentration from the morning fasting value during the four study sessions: control (□); calcium citrate (▲); calcium carbonate (*); potassium citrate (●). †, Supplement administration time. Values are means, with their standard errors represented by vertical bars. The supplements affected area under the curve values of S-PTH ($P=0.002$; ANOVA). † Mean value was significantly different from that of the control session ($P<0.05$). ‡ Mean value was significantly different from that of the potassium citrate session ($P<0.05$).

Serum parathyroid hormone

Differences were present in serum PTH concentrations between the study sessions ($P=0.002$; ANOVA) (Fig. 4). Serum PTH decreased in the calcium citrate ($P=0.006$) and calcium carbonate ($P=0.029$) sessions relative to the control session. Serum PTH also decreased in the calcium citrate ($P=0.005$) and calcium carbonate ($P=0.015$) sessions relative to the potassium citrate session. No difference existed between the potassium citrate and control sessions in serum PTH concentrations ($P=0.803$).

Serum bone-specific alkaline phosphatase

No differences were found in serum bone-specific alkaline phosphatase concentrations during the study sessions ($P=0.198$; ANOVA) (Fig. 5 (a)).

Urinary N-terminal telopeptide of type I collagen

Urinary excretion of NTx differed between the study sessions ($P=0.027$; ANOVA) (Fig. 5 (b)). Urinary NTx decreased in the potassium citrate session ($P=0.017$) and calcium carbonate ($P=0.045$) sessions compared with the control session. The difference in urinary NTx between the calcium citrate and control sessions was not significant ($P=0.112$). The results relative to the control session are summarised in Table 3.

Discussion

The present results showed that a single, moderate dose of potassium citrate had a more positive effect on bone resorption than calcium citrate. Potassium citrate decreased Ca excretion and reduced bone resorption acutely in healthy premenopausal women in an experimental setting with a moderate protein intake. Furthermore, potassium citrate had no effect on serum PTH concentration, but affected phosphate metabolism

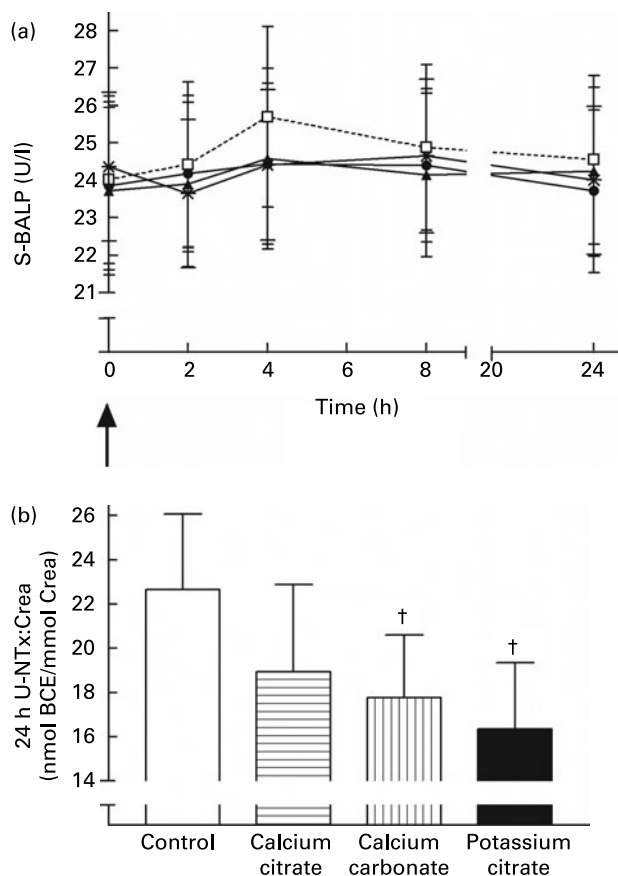


Fig. 5. (a) Changes in serum bone-specific alkaline phosphatase (S-BALP) activity during the four study sessions: control (□); calcium citrate (▲); calcium carbonate (*); potassium citrate (●). †, Supplement administration time. (b) 24 h Urinary excretion of N-terminal telopeptide of type I collagen (U-NTx:creatinine ratio; U-NTx:Crea) during the four study sessions. BCE, bone collagen equivalents. Values are means, with their standard errors represented by vertical bars. The supplements did not affect the area under the curve values of S-BALP ($P=0.198$; ANOVA), but affected 24 h U-NTx:Crea ($P=0.027$; ANOVA). † Mean value was significantly different from that of the control session ($P<0.05$).

by decreasing serum phosphate. Ca supplements decreased bone resorption, although the difference relative to the control session was significant only with calcium carbonate. Both Ca supplements also reduced serum PTH concentration equally efficiently. No significant differences were found between the calcium citrate and calcium carbonate sessions. In addition, none of the supplements affected the marker of bone formation (bone-specific alkaline phosphatase).

We first discuss the potassium citrate session and its results. The potential renal acid load of the test diet was low

(-27 mEq/d), as calculated by using the algorithm of Remer *et al.*⁽²⁷⁾, i.e. the test diet was alkalisating rather than acidogenic. However, to our knowledge, the effect of an extra alkali load on an alkalisating diet was not previously known. The low potential renal acid load value was due to moderate protein and P intakes. We kept P intake at the recommended level to avoid a possible effect of high P intake on serum PTH⁽²⁸⁾. Because high-P foods are also high in protein, we could not use large amounts of protein-rich foods. Hence, protein intake during study sessions was 48.4 g/d. The subjects' average protein intake/kg body weight during study sessions was normal, 0.8 g/kg on average. The K supplement increased the alkaline load of the study diet relative to all other sessions, as indicated also by increased urinary pH. As citrate intakes during the potassium citrate and calcium citrate sessions were identical, the results for urinary pH suggest that potassium citrate provides a larger alkali load than calcium citrate, i.e. K *per se* has an alkalisating effect, or that more citrate was absorbed from potassium citrate than from calcium citrate.

Dietary K intake (3.3 g) was at the level recommended by the Nordic nutritional recommendations⁽²⁹⁾. In dietary reference intakes, the adequate intake of K for adults is higher, 4.7 g⁽³⁰⁾. During the potassium citrate session, the total K intake (diet + supplement) was 5.55 g. The amount of K supplemented in the present study was smaller than in previous interventions⁽¹⁹⁻²²⁾, suggesting that 2.25 g K is sufficient to increase Ca retention and affect bone resorption. We cannot distinguish whether this effect was due to higher K intake or an increase in dietary alkali load. It is unclear whether the positive effect of K anions on bone metabolism is due to an increased intake of K or buffering through the generation of bicarbonate⁽⁶⁾. By including another K supplement, without an alkalisating anion (i.e. potassium chloride) in the present study, we would have more specific data on this issue. The skeletal benefit of dietary K has been speculated to be dependent on the accompanying bicarbonate-generating anion⁽³¹⁾.

Previous studies have shown that alkali substances affect Ca and bone metabolism through four separate mechanisms: by enhancing reabsorption of Ca in the kidneys^(21,32), by enhancing Ca absorption in the intestine, as shown among patients with distal renal tubular acidosis⁽³³⁾, by inhibiting osteoclastic bone resorption⁽³⁴⁾, and by stimulating osteoblastic bone formation^(21,34). Similarly, neutralisation of dietary acid load without an increase in K intake decreases urinary Ca excretion^(20,35,36).

The decrease in bone resorption during the potassium citrate session is consistent with previous longer-term intervention studies. A decrease in bone resorption due to potassium citrate^(19,20) and potassium bicarbonate⁽²¹⁾ supplementation

Table 3. Summary of the results relative to the control session

	Serum ionised Ca	Urinary Ca	Serum phosphate	Urinary phosphate	Urinary pH	Serum PTH	Serum BALP	Urinary NTx
Potassium citrate	–	↓	↓	–	↑	–	–	↓
Calcium citrate	↑	↑	↑*	↓	↑	↓	–	–
Calcium carbonate	↑	↑	↑*	↓	–	↓	–	↓

PTH, parathyroid hormone; BALP, bone-specific alkaline phosphatase; NTx, N-terminal telopeptide of type I collagen; –, no significance; ↓, decrease; ↑, increase. * 0.05 < P < 0.1.

has been observed in postmenopausal women. Potassium citrate has also been shown to prevent increased bone resorption, as measured by urinary NTx excretion caused by high salt intake in postmenopausal women⁽³⁷⁾. In a cross-sectional study, bone resorption markers were significantly greater in the lowest quartile of K intake than in the other quartiles⁽²⁴⁾. By contrast, in a recent 2-year trial, potassium citrate supplementation did not affect bone turnover⁽³⁸⁾.

Based on *in vitro* studies, a reduction of extracellular pH increases osteoclastic activity independent of the effect of PTH⁽³⁹⁾. In the present study, the alkaline load was largest during the potassium citrate session, which probably caused the largest increase in extracellular pH, and a further decrease in osteoclastic activity relative to other sessions.

To elaborate on the PTH results during the potassium citrate session, as in previous interventions^(19,20,22,37), potassium citrate had no effect on serum PTH. Possibly, the increase in Ca retention due to potassium citrate was insufficient to produce a decrease in PTH secretion, despite the frequent sampling. Interestingly, a decrease in urinary NTx was seen regardless of low Ca intake (300 mg). S-iCa remained at the same level during the control and potassium citrate sessions, suggesting that potassium citrate did not increase Ca absorption. Based on these results, the direct effect of potassium citrate on osteoclasts can be speculated to be stronger and/or more rapid than its effect on bone through Ca metabolism. Furthermore, as the decrease in urinary NTx was notable, albeit not statistically significant, during the potassium citrate session relative to the Ca supplement sessions, this could imply that potassium citrate reduced bone resorption more rapidly than Ca.

Potassium citrate did not affect the bone formation marker (bone-specific alkaline phosphatase) used here. This may be due to the short duration of the study. Longer administration of K alkali has resulted in an increase in serum osteocalcin concentration^(19,21). In the 12-month study of Jehle *et al.*⁽²⁰⁾, serum bone-specific alkaline phosphatase increased but serum osteocalcin decreased in both the potassium citrate and potassium chloride groups.

Relative to the control session, serum phosphate decreased during the potassium citrate session. The reason for this is unknown, as dietary P intake was exactly the same in all sessions, and P intake was at the recommended level⁽²⁹⁾. Due to the decrease in bone resorption, which was a consequence of the increased extracellular pH, a decrease in the release of P from bone probably also occurred. This may partly explain the decrease in serum phosphate. Urinary phosphate:creatinine ratio was not significantly lower during the potassium citrate session than during the control session. Possibly due to the short duration of the study or the limited number of the subjects, we could not detect a decrease in the urinary phosphate excretion. In longer-term studies, K administration has resulted in a decrease in urinary phosphate excretion^(20,21).

In examining the effects of Ca supplements, both calcium citrate and calcium carbonate supplements were absorbed well, based on S-iCa, and decreased serum PTH efficiently. Calcium carbonate decreased urinary NTx relative to the control session, but during the calcium citrate session the decrease in urinary NTx relative to the control session did not reach statistical significance. However, because no difference in serum PTH between Ca supplement sessions was found, the

small difference in urinary NTx between these sessions was probably coincidental. The present results on serum PTH and urinary NTx are contrary to those recently published by Thomas *et al.*⁽⁴⁰⁾ who found half the dose of calcium citrate to be at least as effective as calcium carbonate in suppressing PTH and C-terminal telopeptide, another marker of bone resorption, in postmenopausal women. The reason for the discrepant results may be in timing of the samples or in the different age group of subjects. However, not all previous studies support calcium citrate as being better absorbed than calcium carbonate^(12,16). The present results indicate that both Ca supplements when taken with a meal are as effective in healthy premenopausal women. The present results support the use of the most common and least expensive form of Ca, calcium carbonate, in this age group. Based on the study of Sakhae *et al.*⁽²²⁾, combined treatment with potassium citrate and calcium citrate probably delivers the best result.

To conclude, potassium citrate supplementation, at least acutely, may decrease urinary Ca excretion and reduce bone resorption even when the diet is not acidogenic, Ca intake is low, and K intake is at recommended level. Furthermore, calcium citrate and calcium carbonate are absorbed effectively and suppress PTH equally well in healthy premenopausal women. The present results await confirmation in a longer-term setting.

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All authors took part in designing the study.

M. E. K. recruited the study subjects and conducted the experimental work. H. J. K. and M. E. K. did the laboratory and statistical analyses. H. J. K. wrote the manuscript, and C. J. E. L.-A. and M. E. K. participated in the critical revision of the paper. C. J. E. L.-A. was the principal investigator supervising the study.

None of the authors have conflicts of interest.

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