Effect of calcium supplementation on blood pressure in patients with secondary hyperparathyroidism

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ABSTRACT. The aim was to study the effect of calcium supplementation 477 mg twice daily on BP in patients with secondary hyperparathyroidism during an intervention study (6 weeks) and after 954 mg during a short study (3 h). The intervention study was a placebo-controlled, double-blind, cross-over, while the short study gave a placebo and calcium in random order on separate days. The participants were obtained from an epidemiological survey in Tromsø 1994-1995 that included more than 27,000 subjects. The re-examination was performed in 2000/2001 at the University Hospital of North Norway, Norway. There were 18 subjects with secondary hyperparathyroidism and 28 control subjects in the intervention study while there were 14 cases and 8 control subjects in the short study. The results showed that in the subjects with secondary hyperparathyroidism after calcium supplementation in the intervention study there was an increase in serum calcium from 2.28±0.09 to 2.36±0.06 mmol/l (mean±SD) and a decrease in serum PTH from 8.6±1.6 to 6.5±2.4 pmol/l. However, there was no significant difference in either systolic or diastolic BP between calcium supplementation and placebo (138.3±21.0 vs 135.9±17.0 mm Hg and 80.9±11.1 vs 78.9±9.5 mm Hg, respectively). Similar results were seen in the control group. In the short study, serum calcium increased and serum PTH decreased after oral calcium, but the BP did not differ as compared to when placebo was given. To conclude, in the present setting we did not find any effect on BP by calcium supplementation in subjects with moderate secondary hyperparathyroidism. (J. Endocrinol. Invest. 26: 35-41, 2003) ©2003, Editrice Kurtis

INTRODUCTION

There has been a considerable interest in the association between calcium intake and BP (1-6). In most epidemiological studies, an inverse relation has been found but the difference in BP between those with the highest and those with the lowest calcium intake has only been a few mm Hg (7). Furthermore, in intervention studies the effect of calcium supplementation has been marginal, and a reduction of no more than 2 mm Hg for the systolic and one mm Hg for the diastolic BP was found in recent meta-analyses (8, 9). However, in those studies the calcium supplementation was given regardless of the subjects’ calcium status.

In a recent epidemiological study from Tromsø, we found that females with elevated parathyroid hormone (PTH) levels, and thus probably in calcium deficit, have a systolic BP 20 mm higher than those with normal PTH levels (10). The present study was therefore undertaken to examine whether calcium supplementation in subjects with elevated PTH levels would have a more profound effect on the BP than in those with normal PTH levels. If so, this could have considerable clinical implications as approximately 16% of those above the age of sixty and with systolic BP above 160 mm Hg have elevated serum PTH levels (10).

When calcium is given intravenously there is a prompt increase in BP (11), which is in apparent contrast to the suggested effect of oral supplementation. This could be due either to different routes of administration or be a time effect, as intravenous studies usually only last a few hours whereas intervention studies go on for weeks or months. To examine whether there are short-term effects of oral calcium supplementation, in a second study, we followed BP in subjects with elevated and normal PTH levels for three h after intake of calcium.
The identical looking placebo capsules contained lactose. That was an open study. Calcium was given as three capsules added. The study was double-blind, except for the last 12 weeks the latter period one tablet of vitamin D containing 400 IU was diagnosed in another two. Eight subjects reclined further follow-up and 8 subjects were too old or considered too ill to be included in the present study. The remaining 28 subjects were invited to participate. 34 subjects with normal serum PTH and calcium levels in the Tromsø study 1994/1995 were invited as a control group. Subjects with too much concomitant disease, serum creatinine above 130 µmol/l, systolic BP above 180 mmHg or diastolic BP above 105 mmHg, were not included. Intake of calcium and vitamin D supplementation and intake of cod liver oil was stopped 8 weeks before the study. All other medication was continued unchanged. The subjects were randomized to calcium or placebo for 6 weeks, followed by 4 weeks with placebo, then 6 weeks with placebo or calcium, and finally 12 weeks with calcium. During the latter period one tablet of vitamin D containing 400 IU was added. The study was double-blind, except for the last 12 weeks that was an open study. Calcium was given as three capsules twice daily, each containing 400 mg calcium carbonate (159 mg Ca²⁺). The identical looking placebo capsules contained lactose. BP was measured on two consecutive days or not more than three days apart at the start of the study and after 6, 10, and 16 weeks, and on one day after 12, 20, and 28 weeks with an automatic device (Propaq 104 S/W version 6.0; Protocol systems, Beaverton, Oregon, USA). The subjects were seated for 15 min, and three recordings were made at 2-min intervals. The mean value of the 2 last measurements was used. When the BP was measured on 2 days (at start of the study and after 6, 10, and 16 weeks) the mean value of the results from the 2 days was used. Routine blood samples were drawn at the start of the study and analyzed with the use of Hitachi 917 with reagents from Boehringer-Mannheim. Blood samples for serum calcium and PTH were also drawn after 6, 10, 16 and 28 weeks. PTH was measured by an Immulite intact PTH assay (Diagnostic Products Corp), reference range 1.1–6.8 pmol/l, intra-assay and inter-assay coefficient of variation 4% and 7%, respectively, 24-h urine samples for measurement of calcium excretion were collected at the start of the study and after 6, 16, and 28 weeks. The subjects were not asked to fast but were examined at the same time of day at each visit. Height and weight were measured while the subjects wore light clothing and no shoes, and the BMI was calculated (kg/m²). The study drugs were dispensed at start of the study and after 6, 10, 16 and 28 weeks. Unused drugs were counted and compliance calculated.

METHODS

Intervention study

Men and women, 50-80-yr-old, with secondary hyperparathyroidism (serum PTH >6.9 pmol/l and serum calcium <2.40 mmol/l) and a corresponding control group with normal serum PTH and calcium levels, were invited to participate. All subjects had previously participated in the Tromsø study 1994/1995. In that study, serum PTH was measured in 1,113 randomly selected subjects and found elevated (PTH >6.9 pmol/l) in 118. Eighty-two subjects from this latter group were re-examined in 1998 and PTH still was elevated in 56 (12). Most of these subjects were considered to have secondary hyperparathyroidism and calcium and/or vitamin D supplementation was recommended. At a second follow-up one year later, the PTH levels were normalized or serum calcium >2.40 mmol/l in 10 subjects, and primary hyperparathyroidism (serum PTH >6.9 pmol/l and serum calcium >2.55 mmol/l) was diagnosed in another two. Eight subjects reclined further follow-up and 8 subjects were too old or considered too ill to be included in the present study. The remaining 28 subjects were invited to participate. 34 subjects with normal serum PTH and calcium levels in the Tromsø study 1994/1995 were invited as a control group. Subjects with serious concomitant disease, serum creatinine above 130 µmol/l, systolic BP above 180 mmHg or diastolic BP above 105 mmHg, were not included. Intake of calcium and vitamin D supplementation and intake of cod liver oil was stopped 8 weeks before the study. All other medication was continued unchanged. The subjects were randomized to calcium or placebo for 6 weeks, followed by 4 weeks with placebo, then 6 weeks with placebo or calcium, and finally 12 weeks with calcium. During the latter period one tablet of vitamin D containing 400 IU was added. The study was double-blind, except for the last 12 weeks that was an open study. Calcium was given as three capsules twice daily, each containing 400 mg calcium carbonate (159 mg Ca²⁺). The identical looking placebo capsules contained lactose. BP was measured on two consecutive days or not more than three days apart at the start of the study and after 6, 10, and 16 weeks, and on one day after 12, 20, and 28 weeks with an automatic device (Propaq 104 S/W version 6.0; Protocol systems, Beaverton, Oregon, USA). The subjects were seated for 15 min, and three recordings were made at 2-min intervals. The mean value of the 2 last measurements was used. When the BP was measured on 2 days (at start of the study and after 6, 10, and 16 weeks) the mean value of the results from the 2 days was used. Routine blood samples were drawn at the start of the study and analyzed with the use of Hitachi 917 with reagents from Boehringer-Mannheim. Blood samples for serum calcium and PTH were also drawn after 6, 10, 16 and 28 weeks. PTH was measured by an Immulite intact PTH assay (Diagnostic Products Corp), reference range 1.1–6.8 pmol/l, intra-assay and inter-assay coefficient of variation 4% and 7%, respectively, 24-h urine samples for measurement of calcium excretion were collected at the start of the study and after 6, 16, and 28 weeks. The subjects were not asked to fast but were examined at the same time of day at each visit. Height and weight were measured while the subjects wore light clothing and no shoes, and the BMI was calculated (kg/m²). The study drugs were dispensed at start of the study and after 6, 10, 16 and 28 weeks. Unused drugs were counted and compliance calculated.

Short study

Subjects that had completed the calcium intervention study were invited to participate. Before inclusion they were without calcium and vitamin D supplementation for at least 4 weeks. Apart from that they continued their regular medication, but medicine for hypertension were not taken the evening before and the morning of the study. The subjects were studied in the morning in the fasting state on two separate days at least one week apart. After resting for 30 min, either 6 capsules containing a total of 2400 mg calcium carbonate (954 mg Ca²⁺) or an equal looking placebo containing lactose were given. The order of calcium or placebo was random, and the study was performed double-blind. The subjects remained seated throughout the study. Blood pressure was measured and blood samples drawn before and 60, 120, and 180 min after taking the calcium or placebo. The measurements were performed as in the intervention study. Both studies were performed at the Clinical Research Unit, University Hospital of Tromsø, Norway.

Statistical analyses

The data were analyzed with all subjects taken together and also separately for those with elevated and those with normal PTH levels. The effects of calcium, placebo, and calcium together with vitamin D on serum calcium, PTH, urinary excretion of calcium, and BP were evaluated within each group with t-test for paired samples. Comparisons between groups were done with t-test for unrelated samples. In most of the analyses the data from those that started with calcium were pooled together with those that first received placebo. When repeated comparisons were performed the Bonferroni correction for repeated analyses was used. p<0.05 was considered statistically significant. Unless otherwise stated the data are presented as mean±SD. The baseline data were tested for normal distribution, and for all parameters both skewness and kurtosis had an absolute value below 1. The data were analyzed with the SPSS statistical package for Windows version 10.0 (SPSS Inc. Chicago, IL, USA).

Ethics

The regional Ethics Committee approved the two studies, and all subjects gave their written informed consent to participate.

RESULTS

Intervention study

The patients were included from April to August 2000. Of the 34 subjects with normal and 28 subjects with elevated PTH levels that were invited to participate, 29 and 21, respectively, were included in the study. Among the 29 with initially normal PTH in 1994/95, 5 had at the start of this study an elevated PTH level and where thus included in the “high” group. Six of those with previously elevated levels now had normal levels and included in the control group. Two subjects in each group dropped out during the study. Accordingly, 28 subjects with normal PTH and 18 subjects with elevated PTH lev-