SHORT COMMUNICATION

Effect of increasing calcium intake on urinary sodium excretion in normotensive subjects

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Summary

1. Eight normotensive subjects were studied in a randomized crossover trial of a high calcium diet (1800 mg of calcium/day) for a week against a low calcium diet (200 mg of calcium/day) for a further week.

2. The subjects were placed on a diet containing 200 mg of calcium/day throughout the study and the high calcium diet was achieved by supplementing the low calcium diet with calcium glubionate and galactogluconate. Sodium and potassium intake were kept constant throughout the study.

3. Twenty-four hour urinary sodium, potassium, calcium and phosphate were measured daily.

4. In spite of a highly significant increase in calcium excretion from the low to the high calcium diet ($P < 0.0001$), there was no increase in sodium or change in potassium excretion with the increased calcium intake. A transient but significant fall in urinary sodium excretion was observed up to the fourth day of the high calcium diet ($P = 0.021$). Twenty-four hour urinary phosphate excretion fell significantly on the high calcium diet ($P < 0.0001$). Body weight, blood pressure, plasma renin activity, aldosterone, plasma creatinine and serum ionized calcium did not change.

5. These results suggest that a short-term increase in calcium intake in normotensive subjects does not increase urinary sodium and potassium excretion.

Key words: oral calcium supplementation, urinary sodium excretion.

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Introduction

It has been known for many years that there is a close relationship between urinary sodium and urinary calcium excretion [1–6] and that an increase in sodium intake leads to an increase in calcium excretion in man [7–9], but none of these studies has investigated the effect of changing calcium intake on sodium excretion in man. An early study in rats [10] has suggested that oral calcium loading may induce an osmotic diuresis and a recent review has emphasized that an initial natriuresis can be observed during the first week of dietary calcium supplementation in rats [11]. In view also of recent claims that an increase in calcium intake could lower high blood pressure [12], we decided to look at the possible effect of a high calcium compared with a low calcium intake on the urinary sodium and potassium excretion in healthy normotensive subjects.

Experimental

Subjects and methods

Eight normotensive healthy volunteers, whose supine diastolic pressure was <80 mmHg on at least two different occasions, were included in the study. None of them was receiving medication or was taking the oral contraceptive pill before or during the period of the study. There were six males and two females, all white. Mean age was 27 years (range 20–43 years). The experimental protocol was fully explained to the subjects and their informed consent was obtained. After 1 week run-in observation period, subjects were entered into a randomized crossover study of a high calcium diet (approximately 1800 mg or 45 mmol of ele-

mental calcium/day) for 1 week against a low calcium diet (approximately 200 mg or 5 mmol of elemental calcium/day) for a further week. The high calcium diet was achieved by supplementing the low calcium diet with calcium glubionate and galactogluconate elixir (Calcium Sandoz 75 ml/day; 325 mg or 8.1 mmol of elemental calcium/15 ml); all food and drink was provided by the metabolic kitchen, and dietary calcium intake was kept constant at 200 mg/day, sodium at 150 mmol/day and potassium at 80 mmol/day. Throughout the study all subjects were studied as outpatients and allowed to go about their normal activities, although vigorous exercise was not allowed. Five subjects were given the low calcium diet first and the other three received the high calcium diet first. Subjects were weighed daily, in the morning, wearing indoor clothing and without shoes. Twenty-four hour urine collections were obtained daily throughout the study for volume, sodium, potassium, calcium and phosphate measurements; sodium, potassium and calcium were measured by atomic absorption spectrophotometry. At the end of each dietary period, blood pressure was measured with standardized procedure [13] and blood was taken for measurement of urea, creatinine, plasma sodium, potassium, phosphate, albumin, protein, total and serum ionized calcium, pH, plasma renin activity and aldosterone. Blood samples were taken without stasis after the subject had been sitting upright for 10 min between 10.00 hours and 12.00 hours. Plasma renin activity and aldosterone were measured by radioimmunoassay [14, 15]. For serum ionized calcium 10 ml of blood was taken anaerobically in plain glass tubes. Serum ionized calcium was measured with a Kone microlyte ion selective electrode analyser; pH of the same sample was measured with a Corning pH meter.

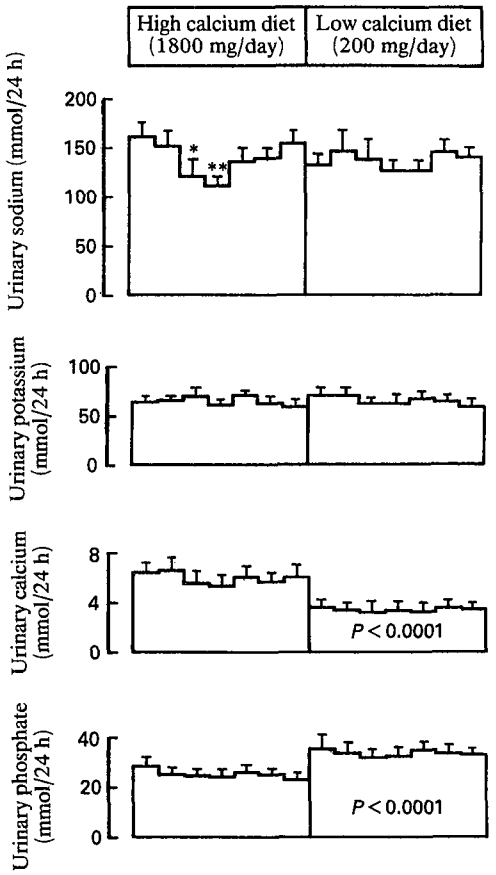

FIG. 1. Average daily urinary sodium, potassium, calcium and phosphate excretion (±SEM) in eight normotensive subjects on a high calcium diet for 1 week and on a low calcium diet for a further week. Significance between dietary periods by analysis of variance. *$P < 0.05$; **$P < 0.001$ vs first day.

Statistical analysis

All results are reported as means ± SEM (95% confidence limits). Statistical analysis was performed using the University of London computer and the North Western Universities' SPSS. For the urinary measurements, the results within each dietary period and between diets were tested for significance by using analysis of variance [16]. If this was significant ($P < 0.05$) comparisons between days were made by two-tailed Student's *t*-test for paired observations. The study had a power of 90% to detect a change in urinary sodium excretion between periods of 24 mmol/24 h at the 5% level of significance [17].

Results (Fig. 1)

Average mean daily urinary calcium excretion increased from 3.48 ± 0.21 (3.0–3.9) mmol/24 h on the low calcium diet to 5.96 ± 0.30 (5.4–6.5) mmol/24 h during the high calcium diet ($F = 46.4$; $P < 0.0001$). Average mean daily urinary sodium excretion was 136.9 ± 5.0 (126.8–147.0) mmol/24 h on the low calcium diet and 135.5 ± 5.1 (125.2–145.8) mmol/24 h during calcium supplementation; no detectable change was observed in sodium excretion between the two dietary periods. During the high calcium diet, however, a significant decrease in urinary sodium excretion was observed ($F = 2.77$; $P = 0.021$); by the third ($P < 0.05$) and fourth ($P < 0.001$) day of the high calcium diet the values were significantly lower when compared with the first day, but these changes were not significant compared with the equivalent day on the low calcium diet. No change in sodium excretion was observed during the low calcium diet. Like sodium

excretion, average mean daily urinary potassium excretion did not change between the two periods (high calcium diet 63.7 ± 2.0 vs low calcium diet 64.5 ± 2.1 mmol/24 h). Average mean daily urinary phosphate excretion was 32.9 ± 1.2 (30.6–35.3) mmol/24 h on the low calcium diet and fell significantly to 25.4 ± 1.0 (23.4–27.4) mmol/24 h on the high calcium diet ($F = 23.7$; $P < 0.0001$). No change was observed in average mean daily urinary volume and body weight throughout the study; blood pressure did not change significantly between periods (high calcium diet 113/69 ± 5/3 vs low calcium diet 114/68 ± 3/3 mmHg). Other variables measured showed no significant change between the low and high calcium diets. All subjects who entered the trial completed it without any adverse effects.

Discussion

The association between urinary sodium and calcium excretion has been extensively investigated [1–6] and the effects of extreme variations in sodium intake on calcium excretion have also been studied [7–9]. Urinary calcium excretion increases with increasing sodium excretion; this dependence of calcium excretion on sodium excretion and, therefore, on sodium intake has been related to a certain degree of competition for common transport pathways for reabsorption in the proximal tubule and in the loop of Henle [3, 8], though in the distal tubule different reabsorptive mechanisms probably exist for each ion [3, 18]. The concept that there may be different mechanisms for the reabsorption of calcium and sodium in the distal tubule is supported by the observation that chronic mineralocorticoid administration induces an increase in urinary calcium excretion without increase in urinary sodium excretion [19, 20], whereas thiazide diuretics cause natriuresis without increase in urinary excretion of calcium [21, 22]. Alternatively, therefore, it has been suggested that increases in calcium excretion with increases in sodium excretion could be related to changes in extracellular volume and not to the urinary sodium excretion itself [19, 20].

However, our results clearly demonstrate that, at least in the short term, large increases in calcium intake cause no increase in sodium excretion. Indeed there was, if anything, a transient reduction in sodium excretion maximum on the fourth day of supplementation without affecting the overall sodium excretion over the whole week. If a common transport pathway is the major factor responsible for the relationship between sodium and calcium excretion, the lack of any detectable increase in sodium excretion on the high calcium diet may be due to the different molar ratio of these two ions at the tubular site which may have possibly caused very small and undetectable changes in sodium excretion in relation to calcium excretion. Alternatively, a reduced reabsorption of sodium at the proximal site (where mechanisms are shared with calcium) could be compensated by greater sodium reabsorption at more distal sites (where mechanisms are independent) resulting in no overall change in urinary sodium excretion despite an increase in urinary calcium.

We also found no effect of increasing calcium intake on potassium excretion. One recent report has suggested that changes in potassium excretion caused by increases in sodium intake could possibly be modified by differences in calcium intake [9], but there was no evidence that changes in calcium intake *per se* would directly affect potassium excretion.

With the increase in calcium intake, we found a significant decrease in urinary phosphate excretion, whereas it rose on the low calcium diet. This pattern in phosphate excretion has been found previously and shown to be, at least in part, dependent on the dietary intake of calcium [23]. The mechanism for the fall in phosphate excretion on a high calcium diet could either be due to a decreased intestinal absorption of phosphate [24, 25], or to suppression of the parathyroid hormone secretion which, in turn, would lead to increased tubular phosphate absorption and thus decreased phosphate excretion [26, 27], or to a combination of both.

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References

1. Walser, M. (1961) Calcium clearance as a function of sodium clearance in the dog. *American Journal of Physiology*, **200**, 1099–1104.
2. King, J.S., Jackson, R. & Ashe, B. (1964) Relation of sodium intake to urinary calcium excretion. *Investigative Urology*, **1**, 555–560.
3. Antoniou, L.D., Eisner, G.M., Slotkoff, L.M. & Lilienfield, L.S. (1969) Relationship between sodium and calcium transport in the kidney. *Journal of Laboratory and Clinical Medicine*, **74**, 410–420.
4. Modlin, M. (1966) The interrelation of urinary calcium and sodium intake in normal adults. *Investigative Urology*, **4**, 180–189.
5. Phillips, M.J. & Cooke, J.N.C. (1967) Relation between urinary calcium and sodium in patients with idiopathic hypercalciuria. *Lancet*, **i**, 1354–1357.
6. Goulding, A. (1981) Fasting urinary sodium/creatinine in relation to calcium/creatinine and hydroxyproline/creatinine in a general population of women. *New Zealand Medical Journal*, **93**, 294–297.

7. Kleeman, C.R., Bohannan, J., Bernstein, D., Ling, S. & Maxwell, M.H. (1964) Effect of variations in sodium intake on calcium excretion in normal humans. *Proceedings of the Society for Experimental Biology and Medicine*, **115**, 29–32.
8. McCarron, D.A., Rankin, L.I., Bennett, W.M., Krutzik, S., McClung, M.R. & Luft, F.C. (1981) Urinary calcium excretion at extremes of sodium intake in normal man. *American Journal of Nephrology*, **1**, 84–90.
9. Castenmiller, J., Mensink, R.P., van der Heijden, L., Kouwenhoven, T., Hautvast, J.G.A.J., de Leeuw, P.W. & Schaafsma, G. (1985) The effect of dietary sodium on urinary calcium and potassium excretion in normotensive men with different calcium intakes. *American Journal of Clinical Nutrition*, **41**, 52–60.
10. Ayachi, S. (1979) Increased dietary calcium lowers blood pressure in the spontaneously hypertensive rat. *Metabolism*, **28**, 1234–1238.
11. Lau, K. & Eby, B. (1985) The role of calcium in genetic hypertension. *Hypertension*, **7**, 657–667.
12. McCarron, D.A. & Morris, C.D. (1985) Blood pressure response to oral calcium in persons with mild to moderate hypertension. *Annals of Internal Medicine*, **103**, 825–831.
13. Cappuccio, F.P., Markandu, N.D., Beynon, G.W., Shore, A.C., Sampson, B. & MacGregor, G.A. (1985) Lack of effect of oral magnesium on high blood pressure: a double blind study. *British Medical Journal*, **291**, 235–238.
14. Roulston, J.E. & MacGregor, G.A. (1978) Measurement of plasma renin activity by radioimmunoassay after prolonged cold storage. *Clinica Chimica Acta*, **88**, 45–48.
15. James, V.H.T. & Wilson, G.A. (1976) Determination of aldosterone in biological fluids. In: *Assay of Drugs and Other Trace Compounds in Biological Fluids — Methodological Developments in Biochemistry*, vol. 5, pp. 149–158. Ed. Reid, E. Elsevier, Amsterdam.
16. Snedecor, G.W. & Cochran, W.G. (1980) *Statistical Methods*, 7th edn. Iowa State University Press, Ames, Iowa.
17. Bulpitt, C.J. (1983) *Randomised Controlled Clinical Trials*, pp. 96–117. Martinus Nijhoff Publishers, The Hague, Boston, London.
18. Rastegar, A., Agus, Z., Connor, T.B. & Goldberg, M. (1972) Renal handling of calcium and phosphate during mineralcorticoid "escape" in man. *Kidney International*, **2**, 279–286.
19. Suki, W.N., Schwettmann, R.S., Rector, F.C., Jr & Seldin, D.W. (1968) Effect of chronic mineralcorticoid administration on calcium excretion in the rat. *American Journal of Physiology*, **215**, 71–74.
20. Massry, S.G., Coburn, J.W., Chapman, L.W. & Kleeman, C.R. (1968) The effect of long-term desoxycorticosterone acetate administration on the renal excretion of calcium and magnesium. *Journal of Laboratory and Clinical Medicine*, **71**, 212–219.
21. Duarte, C.G. & Bland, J.H. (1965) Calcium, phosphorus and uric acid clearances after intravenous administration of chlorothiazide. *Metabolism*, **14**, 211–219.
22. Duarte, C.G. & Bland, J.H. (1965) Changes in metabolism of calcium, phosphorus and uric acid after oral administration of chlorothiazide. *Metabolism*, **14**, 899–903.
23. Robertson, W.G. (1976) Urinary excretion. In: *Calcium, Phosphate and Magnesium Metabolism*, pp. 113–161. Ed. Nordin, B.E.C. Churchill-Livingstone, Edinburgh, London, New York.
24. Clark, I. (1969) Importance of dietary Ca:PO_4 ratios on skeletal, Ca, Mg and PO_4 metabolism. *American Journal of Physiology*, **217**, 865–870.
25. Wilkinson, R. (1976) Absorption of calcium, phosphorus and magnesium. In: *Calcium, Phosphate and Magnesium Metabolism*, pp. 36–112. Ed. Nordin, B.E.C. Churchill-Livingstone, Edinburgh, London, New York.
26. Agus, Z.S., Gardner, L.B., Beck, L.H. & Goldberg, M. (1973) Effects of parathyroid hormone on renal tubular reabsorption of calcium, sodium and phosphate. *American Journal of Physiology*, **224**, 1143–1148.
27. Lau, K., Chen, S. & Eby, B. (1984) Evidence for the role of PO_4 deficiency in antihypertensive action of a high-Ca diet. *American Journal of Physiology*, **246**, H324–H331.