Influence of urinary sodium excretion on the clinical assessment of renal tubular calcium reabsorption in hypercalcaemic man

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SUMMARY The relation between urinary sodium excretion (NaE) and renal tubular calcium reabsorption (TmCa/GFR) was assessed in patients with hypercalcaemia associated with malignancy and primary hyperparathyroidism. On acute saline loading of seven normally hydrated patients with primary hyperparathyroidism and five patients with malignancy, raised values of TmCa/GFR were reduced to normal in most cases, in association with increases in NaE. The reduction in TmCa/GFR, which occurred, may have been due to a reduction in proximal tubular calcium reabsorption associated with sodium: this would have obscured the effect of humorally mediated increases in distal tubular calcium reabsorption, which are stimulated either by parathyroid hormone or by a putative humoral mediator in hypercalcaemia of malignancy.

In patients who were normally hydrated NaE and TmCa/GFR were not significantly correlated. When data were included from patients who were dehydrated and from those undergoing acute saline loading, significant inverse correlations between NaE and TmCa/GFR were observed both in primary hyperparathyroidism (r = -0.49; p < 0.02) and malignancy (r = -0.60; p < 0.001). In clinical practice changes in TmCa/GFR associated with sodium seem to be of minor importance under normal circumstances, but they become evident at the upper and lower extremes of urinary sodium excretion. In clinical studies of renal calcium handling urinary sodium excretion must also be assessed, as interpreting TmCa/GFR data is difficult in states of excessive sodium loading or depletion.

We recently suggested that in some patients with hypercalcaemia associated with malignancy a humoral mediator is released which possesses a "PTH like" effect on renal tubular calcium reabsorption.1 These findings differ from those of previous workers who have generally considered that the humoral substance causing such hypercalcaemia may be distinguished from parathyroid hormone by its lack of effect on renal calcium handling.2-5 In these earlier studies renal tubular calcium reabsorption was often found to be increased before sodium repletion, but was subsequently reduced to normal, and this feature was interpreted as evidence against a renal tubular action of the putative humoral mediator that causes hypercalcaemia.4 5

In our study1 and in another recent study6 the renal tubular reabsorption of calcium remained increased after rehydration, suggesting that changes in renal calcium handling may indeed have been caused by the action of such a humoral mediator. The reasons for the discrepancies between these studies are at present unclear but they may relate to differences in the degree of sodium repletion. In some studies tubular calcium reabsorption was measured after sodium repletion with intravenous sodium chloride solution 0.9% (saline) 2 litres daily,1 6 whereas in other studies much larger quantities of saline (up to 4 litres daily) were infused,4 5 or rehydration procedures were not specified.3

It is well recognised that in normocalcaemic man and in experimental animals sodium and calcium excretion are related7-10; and that variations in sodium excretion also cause variations in calcium excretion.10 In view of these factors the present study was undertaken to determine whether changes in urinary sodium excretion as a result of saline infusions affect the clinical assessment of renal tubular calcium
reabsorption. The studies in patients with hypercalcaemia of malignancy were compared with similar data on primary hyperparathyroidism, in which a humorally mediated increase in renal tubular calcium reabsorption is known to exist.11,12

Patients and methods

TWO GROUPS OF PATIENTS STUDIED
Primary hyperparathyroidism

This group comprised 31 consecutive patients, diagnosed as suffering from primary hyperparathyroidism: serum calcium (mean (SEM) = 2·89 (0·02) mmol/l) (11·56 mg/100 ml (0·08 mg/100 ml)) with raised or inappropriately detectable serum immunoreactive parathyroid hormone values in the absence of another identifiable cause of hypercalcaemia. In 20 of these subjects the diagnosis was subsequently confirmed by surgical exploration of the neck. One of the above patients had presented with hypercalcaemia and severe dehydration. The remaining 30 were considered to be normally hydrated on clinical and biochemical grounds at the time of study, and as such were documented to have hypercalcaemia and stable renal function (as judged by serum creatinine values) for some weeks or months before the study. Serum creatinine values were within the normal range in most cases as 81·8 (5·9) µmol/l (0·89 (0·06) mg/100 ml) (reference range 50–130 µmol/l (0·55–1·43 mg/100 ml)). Two subjects with renal stone disease had raised serum creatinine values, however, at 230 and 150 µmol/l (2·53 and 1·65 mg/100 ml), respectively. Serum albumin values were within the reference range in most cases (39·2 (1·15) g/l) (reference range 33–55 g/l). In seven patients from this group further studies were performed during saline infusions.

Hypercalcaemia of malignancy

This group comprised 36 patients with confirmed malignant disease who had presented with hypercalcaemia: serum calcium (3·21 (0·06) mmol/l) (12·84 (0·24) mg/100 ml) and low or undetectable serum immunoreactive parathyroid hormone values; serum calcium values in this group were significantly higher than in primary hyperparathyroidism (p < 0·01). Twenty seven of these patients were studied after rehydration with 0·9% sodium chloride solution (saline) 2 litres daily, which had been routinely administered over a minimum period of 48 hours before study to correct possible sodium depletion. These patients were recorded as having stable serum creatinine values to within 5 µmol/l (0·05 mg/100 ml) for at least 24 hours before and after the study. Serum creatinine values were normal in most cases and comparable with those in primary hyperparathyroidism (81·9 (4·9) µmol/l (0·90 (0·05) mg/100 ml). Creatinine concentrations were raised in three cases (150, 150, 190 µmol/l (1·65, 1·65, 2·09 mg/100 ml), respectively). Serum albumin values were generally reduced in these patients when compared with those with primary hyperparathyroidism 29·6 (0·78) µmol/l p < 0·01. A further four patients who presented with hypercalcaemia and dehydration were studied before receiving intravenous fluids. The remaining five patients had presented with stable hypercalcaemia and renal function, which had been documented for at least four weeks before the study. These patients were considered to be normally hydrated on clinical and biochemical grounds at the time of study, and hydration was maintained by a high oral fluid intake alone (> 2 litres daily). In these subjects further studies were performed during saline infusions and subsequent administration of antiosteoclastic drugs.

Saline infusion studies

All patients were permitted free oral fluids and received a normal hospital diet throughout the study. In patients with primary hyperparathyroidism infusions of saline were started shortly after collection of the baseline samples on day one and were subsequently continued for 48 hours. The rate of infusion was 500 ml every four hours (450 mmol (450 mEq) sodium chloride daily).

In patients with hypercalcaemia of malignancy saline infusions were started after collection of baseline samples on day minus 3. The rate of infusion was 500 ml four hourly until day minus 1, and subsequently 500 ml six hourly until day plus 3. On day 0 patients were treated with the osteoclast inhibitors; aminohydroxypropylidene diphosphonate (APD) 15 mg daily on days 0–6, or mithramycin 25 µg/kg intravenously on day 0 and day plus 3 (one patient). It is recognised that the hypocalcaemic effect of these drugs principally depends on reducing bone resorption, rather than as the result of changes in renal calcium handling.13,14

Biochemical methods

Biochemical analyses were performed using a multichannel autoanalyser (Technicon) on fasting blood samples and true fasting urine samples, as described previously.1 Total serum calcium was adjusted for albumin concentration to give an “adjusted” calcium value that was used subsequently throughout the study.15 Urinary sodium excretion was expressed as NaE (NaE = urine sodium, divided by urine creatinine, multiplied by serum creatinine mmol/l GF (mEq/l GF)), and as the ratio of sodium clearance to creatinine clearance (ClNa/ClCr = urine sodium divided by urine creatinine, multiplied by serum cre-
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atine, divided by serum sodium). Renal tubular reabsorption of calcium was determined from fasting blood and urine samples using a nomogram to give the notional renal calcium threshold TmCa/GFR.\(^1\)\(^6\)

Calcium excretion was also expressed as the ratio of calcium clearance to creatinine clearance (Cl\(^{Ca}\)/Cl\(^{Cr}\)). Urine calcium divided by urine creatinine, multiplied by serum creatinine, divided by serum calcium). Serum parathyroid hormone was measured using a radioimmunoassay as described previously.\(^1\)

Statistical analysis was carried out using the Wilcoxon test for paired samples, and Spearman’s rank correlation coefficient.

**Results**

In 30 patients with primary hyperparathyroidism who were clinically normally hydrated there was no significant correlation between Na\(_E\) and TmCa/GFR (r = 0.27; p > 0.05). When Na\(_E\) and TmCa/GFR data were included from seven of these patients during saline infusions (two values in each patient (from days 1 and 2) (Fig. 1); total = 14 values) and from an additional patient who was clinically dehydrated (one value), Na\(_E\) and TmCa/GFR were significantly correlated (r = -0.49; p < 0.002) (Fig. 2).

In 27 patients with hypercalcaemia of malignancy studied during infusion of saline 2 litres daily Na\(_E\) and TmCa/GFR were not significantly correlated (r = -0.16; p > 0.05). When Na\(_E\) and TmCa/GFR data were included from the five normally hydrated patients with hypercalcaemia associated with malignancy during saline infusions of 3 litres daily (one value in each patient from day minus 1 (Fig. 1); total = five values), and from the four patients who were clinically dehydrated (four values), there was a significant correlation (r = -0.60; p < 0.001) (Fig. 3).

In hyperparathyroid patients two values were included during saline infusions compared with only one in patients with hypercalcaemia of malignancy. The reason for this was simply because two measurements were made in hyperparathyroid patients during saline infusions (3 litres) daily compared with only one in the group with malignancy.

In the 12 patients undergoing further studies during saline infusion Na\(_E\) and TmCa/GFR were not significantly correlated before infusion of saline was started, either in primary hyperparathyroidism (n = 7, r = -0.23, p > 0.05), or in malignancy (n = 5, r = -0.17; p > 0.05). Similarly, renal sodium clearance (Cl\(^{Na}\)/Cl\(^{Cr}\)) and calcium clearance (Cl\(^{Ca}\)/Cl\(^{Cr}\)) did not correlate at this stage in either group (n = 7, r = 0.20, p > 0.05; n = 5, r = 0.15, p > 0.05).

Fig. 1 shows the response of serum calcium, Na\(_E\), and TmCa/GFR during saline infusion in primary hyperparathyroidism and malignancy. In primary hyperparathyroidism rises in Na\(_E\) and falls in TmCa/GFR and serum calcium were observed during infusion of saline (days 1 and 2). These changes reversed after saline infusions were stopped and most of the above variables had returned towards their basal values by days 3 and 4. There was a highly significant inverse correlation between Na\(_E\) and TmCa/GFR values during days 0–3 of the study (28 pairs of observations r = -0.72; p < 0.001) and a positive correlation between (Cl\(^{Na}\)/Cl\(^{Cr}\)) and (Cl\(^{Ca}\)/Cl\(^{Cr}\)) (r = 0.73; p < 0.001). (Fig. 4). Serum creatinine values were not significantly affected by the saline infusions, however, (mean (SEM) serum creatinine was 73.5 (7.4) μmol/l (0.80 (0.08) mg/100 ml) v 72.1 (7.6) μmol/l (0.79 (0.08) mg/100 ml) v 73.5 (8.1) μmol/l (0.80 (0.09) mg/100 ml) on days 0, 2, and 4, respectively.

![Fig. 1 Response of serum calcium urinary Na\(_E\) and TmCa/GFR in normally hydrated patients undergoing saline infusion. (Significant change from initial values: \*p 0.05; \*\*p 0.02.](http://jcp.bmj.com/ on August 15, 2017 - Published by group.bmj.com)
In hypercalcaemia of malignancy a similar pattern of response was observed: significant rises in $N_a^E$ and falls in TmCa/GFR were observed on day minus 1, by which time patients had received 6 litres of saline and were continuing to receive saline infusions at the rate of 500 ml/4 hours. On the day of antiosteoclast treatment $N_a^E$ had tended to fall and TmCa/GFR rise, as the rate of saline infusion was reduced to 500 ml/6 hours. Following antihypercalcaemic treatment further falls in $N_a^E$ and rises in TmCa/GFR occurred as saline infusions were withdrawn. During the initial phase of saline infusion (days minus 3, minus 1, 0) there was a significant inverse correlation between $N_a^E$ and TmCa/GFR (15 pairs of observations ($r = -0.70; p < 0.01$), and a positive correlation between ($C^{Na^+_c} / C^{Cr}$) and ($C^{Ca^+_c} / C^{Cr}$) ($r = 0.77; p < 0.005$) (Fig. 4). There was, in addition, a significant inverse correlation between $N_a^E$ and TmCa/GFR and a positive correlation between ($C^{Na^+_c} / C^{Cr}$) and ($C^{Ca^+_c} / C^{Cr}$) when data were included from days plus 2, plus 4, and plus 6, after antiosteoclast treatment (30 pairs of observations, $r = 0.74; p < 0.001$); ($r = 0.73; p < 0.001$), respectively (Fig. 4). As in the case of primary hyperparathyroidism serum creatinine values did not change significantly during the saline infusions: mean serum creatinine = 86 (14-4) $\mu$mol/l (0-94 (0-15) mg/100 ml) v 84 (14-6) $\mu$mol/l (0-92 (0-15) mg/100 ml) v 79 (15-9) $\mu$mol/l (0-86 (0-17) mg/100 ml) v 76 (9-1) $\mu$mol/l (0-83 (0-10) mg/100 ml) on days minus 3, minus 1, 0 and plus 6, respectively.

**Discussion**

We found a close correlation between urinary sodium excretion and renal tubular calcium reabsorption during acute sodium loading in normally hydrated patients with primary hyperparathyroidism and hypercalcaemia of malignancy. These findings concur with previous data: in various experimental circumstances proximal renal tubular reabsorption of calcium has been shown to be correlated with that of sodium.\(^6\)\(^-\)\(^9\) None the less other data have suggested that, in general, proximal renal tubular calcium reabsorption is relatively stable and is a function of the filtered calcium load,\(^1\) whereas changes in overall tubular calcium reabsorption are determined mainly...
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by the effects of parathyroid hormone on the distal tubule.\(^{12}\) Unfortunately, only the net tubular reabsorption of calcium can be determined in clinical practice. Changes in this measurement reflect the sum of changes in both proximal and distal tubular reabsorptive processes, and as such, do not distinguish between their relative contribution to net TmCa/GFR. Interestingly, there was no significant correlation between TmCa/GFR and urinary sodium excretion in normally hydrated patients with primary hyperparathyroidism who were receiving oral fluids, or in patients with hypercalcaemia of malignancy in a steady state of hydration who were receiving moderate quantities of intravenous saline (2 litres daily) (Figs. 2 and 3). This suggests that in these circumstances sodium independent (and possibly humoral) changes in renal tubular reabsorption were of primary importance in determining TmCa/GFR.

In clinically dehydrated patients with both malignancy and primary hyperparathyroidism TmCa/GFR was invariably raised, presumably as the result of increased sodium linked calcium reabsorption in the proximal tubule\(^{11}\) (Figs. 2 and 3). Conversely, under conditions of acute sodium loading with intravenous saline (3 litres daily) there was a positive correlation between the rise in urinary sodium excretion and the fall in TmCa/GFR, suggesting that decreased sodium related calcium reabsorption in the proximal tubule\(^{7-10}\) was a major factor in changing the rate of renal tubular calcium reabsorption. Taken together, these findings suggest that sodium related changes in net renal tubular calcium reabsorption are of relatively minor importance under conditions of normal hydration but become evident at the upper and lower extremes of urinary sodium excretion.

In two previous studies of renal tubular calcium reabsorption in hypercalcaemia associated with malignancy, tubular calcium reabsorption was often raised before saline repletion but was generally reduced to normal afterwards.\(^{4,5}\) These findings were construed as evidence against a renal tubular action of the putative humoral mediator causing hypercalcaemia. Our data suggest that such conclusions are invalid, however, as although reductions in TmCa/GFR were observed during saline infusions in our patients with hypercalcaemia of malignancy, they were also observed in primary hyperparathyroidism, a condition in which a parathyroid hormone mediated rise in renal tubular calcium handling is known to exist.\(^{11,12}\) It is apparent from these data that even moderate degrees of sodium loading can cause clinically important reductions in net renal tubular calcium reabsorption, even in the presence of a humoral mediated increase in distal tubular reabsorption.

It is difficult to put a precise value on the amount of urinary sodium excretion that would be expected to cause clinically important changes in TmCa/GFR from our data. Such effects, however, seem to predominate at the upper and lower extremes of urinary sodium excretion (Na\(_E\) > 5 mmol/l (MEq/l) GF:Na\(_E\) < 0-10 mmol/l (MEq/l) GF). In the studies of hypercalcaemia associated with malignancy cited above\(^4,5\) renal tubular calcium reabsorption was generally assessed at the values of sodium excretion, which were raised, when compared with our normally hydrated patients; thus in one study median Na\(_E\) was 4.9 mmol/l/GF (MEq/lGF) and the other 5.8 mmol/l/GF (MEq/l GF); this suggests that the "normal" TmCa/GFR values observed in some cases may, in fact, have largely been the result of a sodium related reduction in proximal tubular calcium reabsorption and as such did not exclude a concomitant increase in humorally mediated distal tubular calcium reabsorption.

From the clinician's point of view assessment of TmCa/GFR under conditions of normal sodium balance is desirable in hypercalcaemic disorders for diagnostic and therapeutic purposes.\(^{17}\) Our data re-emphasise the importance of measuring sodium excretion in any investigation of renal tubular calcium reabsorption.\(^{10}\) Moreover, we suggest that caution must be exercised in the interpretation of renal tubular calcium reabsorption data in patients who are excessively loaded with or depleted of sodium.

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