Altered Renal Calcium Handling in Hypercalcemia of Malignancy

Katherine R. Tuttle, Robert T. Kunau, Nigel Loveridge, and Gregory R. Mundy

ABSTRACT

It has been controversial whether increased renal tubular calcium reabsorption contributes to hypercalcemia in patients with malignancies. Moreover, whether this abnormality is associated with volume depletion, a parathyroid hormone-like effect, or other mechanisms has not been clarified. Eight consecutive patients with hypercalcemia due to a variety of tumor types were studied in detail. The glomerular filtration rate (iothalamate clearance) was reduced in all patients (0.98 ± 0.10 (mean ± SE) mL/s/1.73 m²; P < 0.001) compared with normal controls (N = 9) (1.93 ± 0.08 mL/s/1.73 m²), but it was similar to that in controls matched for renal insufficiency (N = 6) (1.15 ± 0.05 mL/s/1.73 m²). During hypercalcemia produced by calcium infusion, urinary calcium excretion (millimoles of calcium per liter of glomerular filtrate) was increased in controls with renal insufficiency compared to those with normal renal function (P = 0.028). In all patients with hypercalcemia of malignancy, urinary calcium excretion was decreased compared with controls with renal insufficiency, but it was low in only five of eight patients compared with normal controls. Extracellular fluid volume (iothalamate volume of distribution) was not decreased in any patient, and urinary cAMP and/or plasma parathyroid hormone-like bioactivity were increased in six of eight patients. After treatment with an inhibitor of bone resorption, aminopropylidene 1,1 diphosphonate, abnormal renal calcium handling was not detected if the serum calcium normalized. It was concluded that increased renal tubular calcium reabsorption was consistently present in patients with hypercalcemia of malignancy compared with controls matched for renal insufficiency, but the proportion with the abnormality was underestimated if normal controls were used. Because volume depletion was not observed and parathyroid hormone-like activity was not always demonstrated, hypercalcemia per se or other humoral factors may alter renal calcium handling.

Key Words: Renal tubular calcium reabsorption, urinary calcium excretion, glomerular filtration rate, extracellular fluid volume, parathyroid hormone-like effect

Hypercalcemia of malignancy (HCM) is an important cause of morbidity and mortality among patients with many common types of cancer. Despite the heterogeneity of tumors associated with HCM, enhanced bone resorption is generally a dominant feature of the syndrome (1–6). Because the kidney is the major excretory route for calcium, it could inappropriately retain the large calcium load resulting from accelerated bone resorption (2,7–12). This could occur because of enhanced proximal tubular reabsorption due to volume depletion or a distal tubular effect related to a parathyroid hormone (PTH)-like factor (7–11,13–15). In addition, patients with HCM often have renal insufficiency (1–3) and this could affect renal calcium handling. These are important issues because if renal mechanisms play a role in producing hypercalcemia, they should influence the choice of optimal medical therapy.

Because patients with HCM are often quite ill and rigorous physiologic evaluations are difficult, a major problem in previous studies has been the inability to accurately assess glomerular filtration rate (GFR) and extracellular fluid volume (ECFV). Renal insufficiency may be present despite normal serum creatinine values, and ECFV is impossible to estimate reliably by clinical criteria in these chronically ill patients.

We studied in detail eight consecutive patients with HCM. GFR and ECFV were measured by iothalamate clearance and volume of distribution, respectively. Because all of our HCM patients had moderate renal...
insufficiency, the relationships between serum-ionized calcium and urinary calcium excretion (CaE) were compared with controls matched for renal insufficiency, as well as with subjects with normal renal function. Evidence of PTH-like activity was assessed by measuring urinary cAMP excretion, the tubular maximum for phosphorus reabsorption (TmPO4), and plasma PTH-like biological activity. After the baseline studies, the HCM patients were treated by volume expansion for 2 days to investigate its effects on the serum calcium concentration and CaE. The patients were subsequently placed on a sodium restriction for 2 days to return the volume status to baseline. The sodium intake was then allowed to be ad libitum, and they were treated with aminopropyldened 1,1 diphosphonate (APD), a potent inhibitor of bone resorption, to determine how correction of hypercalcemia would influence renal calcium handling.

METHODS

The study was approved by the University of Texas Health Science Center Institutional Review Board, and written informed consent was obtained from each participant. All procedures were performed on the Frederic C. Bartten General Clinical Research Center (GCRC) at the Audie L. Murphy Memorial Veterans’ Administration Hospital.

Subjects

Eight patients (seven males and one female) with HCM due to a variety of tumor types were recruited from the University of Texas Health Science Center clinics and hospitals. The malignancies were documented by history, physical examination, medical record review, report of pathologic specimen evaluation, and radiologic studies. The total serum calcium corrected for the serum albumin concentration exceeded 2.6 mmol/L (10.4 mg/100 mL) on a screening blood chemistry evaluation. The mean age of the HCM patients was 58 (range, 36 to 67) yr. The presence or absence of skeletal metastases was assessed on the basis of radionuclide bone scans (Table 1). Five patients were admitted directly from the clinic to the GCRC. The other three patients had been hospitalized and had received i.v. fluids during the preceding 2 wk, but they were not studied until after it had been stopped and their body weights were not above the admission values. For at least 1 month before entry into the study, treatment for the underlying malignancy had not been altered and no patient had received specific therapy for hypercalcemia. None of the patients had been treated with drugs known to affect calcium metabolism (diuretics, prednisone, calcium supplements, vitamin D).

TABLE 1. Tumor types and bone involvement in patients with hypercalcemia of malignancy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor Type</th>
<th>Bone Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pancreatic islet cell carcinoma</td>
<td>+</td>
</tr>
<tr>
<td>2 △</td>
<td>Renal cell carcinoma</td>
<td>+</td>
</tr>
<tr>
<td>3 x</td>
<td>Large cell lung cancer</td>
<td>+</td>
</tr>
<tr>
<td>4 +</td>
<td>Multiple myeloma</td>
<td>+</td>
</tr>
<tr>
<td>5 ▽</td>
<td>Squamous cell carcinoma of the cervix</td>
<td>-</td>
</tr>
<tr>
<td>6 ○</td>
<td>Squamous cell carcinoma of the head and neck</td>
<td>-</td>
</tr>
<tr>
<td>7 +</td>
<td>Squamous cell carcinoma of the lung</td>
<td>-</td>
</tr>
<tr>
<td>8 □</td>
<td>Squamous cell carcinoma of the lung</td>
<td>+</td>
</tr>
</tbody>
</table>

Symbols are used to identify individual patients in the figures.

Nine healthy subjects (five males and four females) who were similar in age to the HCM group (mean, 53 yr; range, 35 to 64 yr) comprised the normal control group. No subject was taking any type of medication.

Six subjects (five males and one female) who were matched to the HCM patients for renal insufficiency and age (mean, 61 yr; range, 44 to 64 yr) were studied. They were selected on the basis of modestly elevated serum creatinine values (110 to 180 μmol/L) which had been stable on at least three occasions in the preceding 3 months. The causes of renal insufficiency included hypertension (N = 3), obstructive uropathy (N = 1), urinary tract infection and hypertension (N = 1), and unknown (N = 1). No subject had been treated with drugs known to affect calcium metabolism (diuretics, prednisone, calcium supplements, vitamin D).

Study Design

HCM Patients. On day 1 of admission to the GCRC, baseline blood samples for measurement of ionized calcium, magnesium, phosphorus, routine chemistries, PTH, and PTH-like biological activity were obtained. A baseline 24-h urine sample was also collected for determination of calcium, sodium, chloride, creatinine, phosphorus, and cAMP. The diet was allowed to be ad libitum for collection of the baseline data.

Body weight was measured on admission and daily thereafter. Vital signs were determined every 8 h during the hospitalization. Serum-ionized calcium, routine electrolytes, and creatinine were measured daily throughout the study.

At 8:00 a.m. on day 2, GFR and ECFV were measured by determining the clearance and volume of
distribution, respectively, of $^{[25]}$Hoiothalamate (Isotex Diagnostics, Friendswood, TX). $^{[25]}$Hoiothalamate was given as a single i.v. injection of 30 mCi, and plasma samples were obtained at 1, 2, 4, 6, 8, 10, 20, 40, 60, 80, 100, 120, and 140 min. The disappearance of plasma radioactivity as a function of time was used to calculate GFR, and volume of distribution as was previously described (16,17). After completion of this procedure, the patients received an i.v. infusion of normal saline (6 to 8 L) and were placed on a high-sodium diet (250 mmol daily) during the next 2 days. On day 4, the $^{[25]}$Hoiothalamate study was repeated. The patients were then placed on a reduced sodium intake (60 to 70 mmol daily) for 2 days. On day 6, the $^{[25]}$Hoiothalamate study was repeated again. From day 6 onward, the sodium intake was ad libitum.

Treatment of hypercalcemia with APD (Ciba-Geigy, Summit, NJ) began on day 6. The patients received APD (15 mg) i.v. daily for 4 days (days 6 to 9). When the serum-ionized calcium reached its nadir and was stable for 2 consecutive days, blood samples for determination of magnesium, phosphorus, and routine chemistries were obtained. Twenty-four-hour urine samples for measurement of calcium, sodium, chloride, creatinine, and phosphorus were also collected. The $^{[25]}$Hoiothalamate study was repeated between days 10 and 12 depending on the response to APD in individual patients.

Control Subjects

The subjects with normal renal function and those with renal insufficiency were studied in the GCRC on two different occasions within a 10-day period. First, GFR and ECFV were determined with the $^{[25]}$Hoiothalamate procedure. Second, in order to determine the relationship between serum-ionized calcium and CaE under hypercalcemic conditions, calcium gluconate (total elemental calcium, 250 mmol [1,000 mg]) was infused i.v. over 4 h. Serum for measurement of ionized calcium, sodium, and creatinine and timed urine collections for determination of calcium, sodium, and creatinine were obtained at baseline and every 30 to 60 min during the calcium infusion. Blood samples for PTH, PTH-like biological activity, and routine chemistries were obtained before the calcium infusion. Twenty-four-hour urine samples were collected the day before the study for determination of calcium, sodium, chloride, creatinine, phosphorus, and cAMP.

Analytical Methods

Serum-ionized calcium and total urinary calcium were measured with a Nova 7 total/ionized calcium analyzer (Nova Corp., Waltham, MA). In our laboratory, measurements of total urinary calcium by atomic absorption spectrophotometry (model IL-157, Instrumentation Laboratory, Inc., Wilmington, MA) and the Nova calcium analyzer are virtually identical ($y = 1.06x + 8.8; r = 0.98; N = 40$). Urinary sodium was determined by flame photometry (Model Klina; Beckman Instruments, Fullerton, CA). $^{[25]}$Hoiothalamate was counted by a Minaxi Auto-Gamma 5000 Series Counter (Packard Instrument Company, Laguna Hills, CA). Plasma PTH was measured as the intact molecule by IRMA (Incstar, Stillwater, MN). Urinary cAMP was measured by RIA at Nichols Institute Reference Laboratories (San Juan Capistrano, CA). The following were measured in the clinical laboratory at the Audie L. Murphy Memorial Veterans' Administration Hospital: serum chemistries, urinary creatinine, and phosphorus by the Technicon, SMAII autoanalyzer (Technicon Corporation, Tarrytown, NY), and magnesium by the Hitachi 704 automatic analyzer (Boehringer-Mannheim Biochemicals, Indianapolis, IN). PTH-like biological activity in the plasma was assessed by a renal cytochemical bioassay as described previously (18,19). Briefly, segments of guinea pig kidney were maintained in non-proliferative organ culture for 5 h before exposure to various concentrations of synthetic PTH-related protein (PTHrP 1-34) or to dilution (usually $1/50, 1/500$, and $1/5,000$) of the sample being assayed. After chilling, sectioning, and reacting for glucose 6-phosphate dehydrogenase activity, enzyme activity was measured in the distal convoluted tubules by microdensitometry (Vickers Instruments, York, United Kingdom). In this assay system, PTHrP 1-34 is equipotent on a molar basis with both intact PTH and the 1-34 fragment. The $T_{m}PO_{4}$ was calculated by the nomogram of Walton and Bijvoet (20). CaE and urinary cAMP were expressed as the urine concentrations of calcium and cAMP divided by the ratio of urine-total plasma creatinine concentrations.

Data Analysis

Comparisons were made by paired t test within the HCM group. Comparisons between the HCM group and the control groups were made by analysis of variance. In the HCM group, serial GFR measurements and effects of varying the sodium intake on body weight and ECFV were assessed by repeated measures analysis of variance. Exponential curve fits were performed for the relationships between serum-ionized calcium and CaE; the difference between the renal insufficiency controls and the normal controls was assessed by analysis of covariance. All data are expressed as mean ± SE. Significance for all statistical tests was defined as $P < 0.05$. Statistical calculations were done with the CLINFO (GCRC Branch, National Institutes of Health, Bethesda, MD) and SAS (Statistical Analysis Systems, Cary, NC) software systems.
RESULTS

Laboratory Values and Blood Pressure Measurements

The serum-ionized calcium at the baseline evaluation (1.95 ± 0.10 mmol/L) was significantly greater than that after APD treatment (1.40 ± 0.07 mmol/L) in the HCM patients (Table 2). In addition, there was a significant decrement in the serum-ionized calcium (0.18 ± 0.07 mmol/L) and an increment in the CaE (2.8 ± 0.4 mmol/day) after the period of i.v. fluid administration. The serum bicarbonate concentrations in the normal controls (26 ± 1 mEq/L) and the renal insufficiency controls (27 ± 1 mEq/L) were similar to that in the HCM patients at baseline (26 ± 1 mEq/L). After APD treatment, however, the serum bicarbonate concentrations in the normal controls (26 ± 1 mEq/L) and the renal insufficiency controls (27 ± 1 mEq/L) were similar to that in the HCM patients at baseline (26 ± 1 mEq/L). After APD treatment, however, the serum bicarbonate concentration was reduced (23 ± 1 mEq/L). After APD treatment, however, the serum bicarbonate concentration was reduced (23 ± 1 mEq/L). The phosphorus concentrations in both serum and urine declined significantly after APD therapy in the HCM patients. The serum albumin concentrations in the normal controls (43 ± 1 g/L) and the renal insufficiency controls (42 ± 2 g/L) were greater than those in the HCM patients at baseline (34 ± 2 g/L) and after APD treatment (32 ± 2 g/L). The systolic blood pressure, but not the diastolic blood pressure, declined significantly after the serum calcium was reduced.

GFR

The GFR was reduced in all patients with HCM at the baseline evaluation (0.98 ± 0.10 mL/s [59 ± 6 mL/min]·1.73 m²; P < 0.001) compared with the normal subjects (1.93 ± 0.08 mL/s [116 ± 5 mL/min]·1.73 m²), but it was similar to that of renal insufficiency controls (1.15 ± 0.05 mL/s [69 ± 3 mL/min]·1.73 m²) (Table 3). Although there was a trend for the GFR to rise (1.17 ± 0.08 mL/s [70 ± 5 mL/min]·1.73 m²) after volume expansion, the change did not achieve statistical significance and the GFR remained significantly lower than that in the normal subjects. The GFR returned to baseline (1.02 ± 0.08 mL/s [60 ± 5 mL/min]·1.73 m²) after 2 days on the reduced sodium intake. There was no significant change in the GFR after APD treatment (1.03 ± 0.05 mL/s [62 ± 3 mL/min]·1.73 m²).

Serum-Ionized Calcium and CaE

A curvilinear relationship between serum-ionized calcium and CaE (y = 0.2247 x -1.2938; r = 0.85; P < 0.05) (Figure 1a) was observed in the normal subjects. The relationship is similar to that of total serum calcium and CaE as originally described by Peacock et al. (21). The CaE was increased relative to the serum-ionized calcium in the renal insufficiency controls compared with the normal controls (p = 0.028). When the values from the renal insufficiency controls were plotted with the line describing the normal relationship (Figure 1b), most points fell to the left of the curve. A curvilinear relationship (y = 0.0421 x ^-1.3123; r = 0.75; p < 0.05) was maintained in the renal insufficiency controls, but the curve was shifted leftward.

At the baseline evaluation, the CaE in the HCM patients was always lower than expected for the

<table>
<thead>
<tr>
<th>TABLE 2. Laboratory values and blood pressure measurements in normal controls, renal insufficiency controls, and patients with HCM at baseline and after APD treatment</th>
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</thead>
<tbody>
<tr>
<td>Normal Controls</td>
</tr>
<tr>
<td>(N = 9)</td>
</tr>
<tr>
<td>Serum-ionized calcium (mmol/L)</td>
</tr>
<tr>
<td>Serum bicarbonate (mmol/L)</td>
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<tr>
<td>Serum magnesium (mmol/L)</td>
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<tr>
<td>Serum phosphorus (mmol/L)</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
</tr>
<tr>
<td>Urinary phosphorus (mmol/day)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
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</tbody>
</table>

* All data are expressed as mean ± SE.
* P < 0.05 versus normal controls.
* P < 0.05 versus renal insufficiency controls.
* P < 0.01 versus patients with HCM baseline.
Figure 1. The relationship between serum-ionized calcium, and CaE in (a) normal controls (○) and (b) renal insufficiency (RI) controls (●). CaE was increased relative to the serum-ionized calcium in the renal insufficiency controls compared with the normal controls (P = 0.028). Therefore, the curvilinear relationship was shifted leftward in the renal insufficiency controls.

Figure 2. The relationship between serum-ionized calcium and CaE in patients with HCM at baseline (a) and after treatment with APD (b) compared with renal insufficiency controls (●). To identify individual patients, different symbols have been used as described in Table 1.

Table 3. GFR, ECFV, urinary sodium excretion (UNaV), and urinary chloride excretion (UCl V) in normal controls, renal insufficiency controls, and patients with HCM at baseline and after APD treatment

<table>
<thead>
<tr>
<th></th>
<th>Normal Controls (N = 9)</th>
<th>Renal insufficiency controls (N = 6)</th>
<th>Patients with HCM (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (mL/s · 1.73 m²)</td>
<td>1.93 ± 0.08</td>
<td>1.15 ± 0.05b</td>
<td>0.98 ± 0.10b</td>
</tr>
<tr>
<td>ECFV (% body weight)</td>
<td>21 ± 1</td>
<td>20 ± 1</td>
<td>24 ± 1c</td>
</tr>
<tr>
<td>UNaV (mmol/day)</td>
<td>145 ± 14</td>
<td>141 ± 22</td>
<td>121 ± 23</td>
</tr>
<tr>
<td>UCl V (mmol/day)</td>
<td>109 ± 16</td>
<td>116 ± 25</td>
<td>117 ± 18</td>
</tr>
</tbody>
</table>

a All data are expressed as mean ± SE.
b P < 0.001 versus normal controls.
c P < 0.05 versus renal insufficiency controls.

serum-ionized calcium when compared with the controls matched for renal insufficiency (Figure 2a). There was not a single point of overlap between the groups, and all points fell outside the 95% confidence limits of the line, indicating that renal tubular calcium reabsorption was increased in all HCM patients. When the HCM patients were compared with the normal subjects, only five of eight values were outside the 95% confidence limits of the line describing...
the normal relationship. When the serum-ionized calcium normalized after APD treatment, the HCM patients could not be distinguished statistically from the renal insufficiency controls (Figure 2b), although CaE appeared to remain very low in patients 2, 4, and 6. In the two patients who remained hypercalcemic despite APD treatment, however, a significant reduction in CaE persisted.

**ECFV and Urinary Sodium Excretion**

The ECFV was 24 ± 1% of body weight in the patients with HCM at the baseline study and after APD treatment. These values did not differ significantly from that in the normal controls (21 ± 1% of body weight), but they were slightly greater than that in the renal insufficiency controls (20 ± 1% of body weight). The ECFV in the HCM patients increased significantly to 30 ± 3% of body weight after volume expansion and declined to 25 ± 2% of body weight, a value not significantly different from the baseline measurement, after 2 days of sodium restriction. The changes in body weight under the conditions of volume expansion, sodium restriction, and *ad libitum* sodium intake paralleled those of ECFV. It was 60.8 ± 4.5 kg at baseline, 65.3 ± 4.3 kg after volume expansion (*p* < 0.05 versus the baseline measurement), 61.8 ± 4.3 kg after 2 days of sodium restriction, and 60.5 ± 4.6 kg after APD treatment. The urinary sodium excretion was similar in the HCM patients at baseline and after APD treatment, and it did not differ significantly from the values in the control groups. Likewise, urinary chloride excretion was comparable in all of the groups.

**Evaluation of a PTH-like Effect**

Urinary cAMP was elevated in six of eight patients with HCM (Figure 3a), and the TmPO₄ was reduced (i.e., greater than 2 SD below the normal mean) in the same six of eight patients. Plasma PTH-like biological activity was measured in six of our HCM patients. Technical difficulties with specimen handling precluded measurements in patients 1 and 3. In four subjects who had increased urinary cAMP, PTH-like biological activity was increased (Figure 3b), whereas in two subjects without elevated urinary cAMP, including the patient with multiple myeloma, the concentration was less than 0.2 pmol/L. The plasma PTH concentration was suppressed in all of the HCM patients (1.8 ± 0.4 pmol/L; *p* < 0.05) compared with the renal insufficiency controls (5.5 ± 0.4 pmol/L) and the normal controls (3.0 ± 0.3 pmol/L).

**DISCUSSION**

Our study demonstrates that increased renal tubular calcium reabsorption is a common feature of HCM associated with a variety of tumor types. This was readily apparent when the relationships between serum-ionized calcium and CaE were compared with controls matched for renal insufficiency. Because we studied control subjects who had structural renal diseases similar to those common in patients with malignancies (obstruction, urinary tract infections, past hypertension, chemotherapeutic agents and other drugs), alterations in renal calcium handling should be related to the presence of the malignancy rather than differences in intrinsic renal disease. We are not aware of other studies that have accurately measured GFR with markers such as iothalamate or that have specifically controlled for renal function in HCM. This is an important issue because serum creatinine and creatinine clearance do not reliably reflect GFR, particularly in the setting of renal insufficiency (22) such as that observed in the HCM patients. Our data confirm a previous report (23) which showed that the amount of calcium excreted per unit of glomerular filtrate was increased in moderate renal insufficiency. When the HCM patients were compared with subjects who had significantly greater GFR values, the proportion with altered renal calcium handling was underestimated. Because prior
studies of renal calcium handling in HCM have not used controls matched for renal function, they may have overlooked the renal contribution to hypercalcemia in a number of patients.

ECFV also has an important influence on renal calcium handling. It has previously been assumed, but not proven, that the syndrome of HCM is associated with volume depletion, possibly related to hypercalcemia-induced natriuresis, vomiting, poor fluid intake, or other factors (1-4,24,25). Because volume depletion increases proximal tubular reabsorption of fluid and solutes, this led to the hypothesis that it is a major cause of increased renal tubular calcium reabsorption in HCM (7,14,15). However, ECFV has not been directly measured previously and cannot be reliably estimated by clinical criteria in severely ill patients such as those with HCM. We evaluated ECFV directly by determining the iothalamate volume of distribution and indirectly by assessing the urinary sodium excretion.

Recognizing the limitations of these techniques (i.e., subtle changes in ECFV not detected by iothalamate volume of distribution and influences other than ECFV on urinary sodium excretion), there was no evidence for overt volume depletion at the baseline evaluation in our HCM patients. Indeed, the ECFV in the HCM patients was increased compared with both control groups, although only the comparison to renal insufficiency controls achieved statistical significance. Because ECFV is related to lean body mass (26) and patients with HCM usually lose weight because of the underlying malignancy, ECFV expressed as a percentage of body weight should be greater. However, it is unlikely that ECFV was inappropriately low in the hypercalcemic patients because there was no change in ECFV, body weight, or urinary sodium excretion after the APD-induced decrease in serum calcium. Although volume depletion does not appear to be a regular feature of chronic hypercalcemia, this does not exclude volume expansion as a valuable treatment modality. By carefully increasing ECFV beyond the euvoletic state, the urinary excretion of calcium can be enhanced and lead to clinically significant decrements in the serum calcium concentration. In our patients, we noted a decline in the serum-ionized calcium of 0.18 ± 0.10 mmol/L after volume expansion alone.

A 141-amino-acid peptide which is homologous to PTH at 8 of the first 13 amino acids has recently been identified (27,28). This PTHrP has many effects similar to those of PTH including stimulation of adenylate cyclase in renal epithelial cells and decreased urinary calcium excretion (CaE) in experimental animals (29,30). However, PTHrP is immunologically distinct from PTH and is not detected by PTH radio-immunoassays (6). In order to assess whether a PTH-like effect was responsible for the increased renal tubular calcium reabsorption, we measured urinary cAMP, TmPO4, and plasma PTH-like biological activity. In six of eight patients, the urinary cAMP was elevated and the TmPO4 was reduced. Similarly, the plasma PTH-like biological activity was increased only in those patients with increased urinary cAMP. The plasma PTH was suppressed in all HCM patients, indicating that primary hyperparathyroidism was not responsible. Because two of our patients, including one with multiple myeloma, had no evidence of increased PTH-like activity, other mechanisms which influence renal calcium handling may exist in some patients. A recent preliminary report showed that chronic administration of interleukin-1β, a bone-resorbing cytokine associated with solid tumors and hematologic malignancies, causes hypercalcemia and increased renal tubular calcium reabsorption in rats (31). In addition, if chronic hypercalcemia per se leads to a sustained increase in renal vascular tone and decreased peritubular hydrostatic pressure, this could enhance reabsorption of fluid and solutes including calcium.

The serum calcium declined in all patients after APD treatment. In the six patients in whom it normalized, CaE could no longer be statistically differentiated from the renal insufficiency controls, although it appeared to be very low in at least three of them. It is difficult to detect small differences in CaE in the lower range. At hypercalcemic levels, the differences are more readily demonstrated, perhaps because of PTH suppression in the control subjects and persistence of the calcium-retaining influence in the HCM patients. If chronic hypercalcemia per se influences renal calcium handling, however, then a reduction in serum calcium could normalize its relationship to CaE. APD is not known to affect renal calcium handling or malignant processes (32), but this cannot be excluded by the study presented here.

In addition to the decrease in serum calcium after APD treatment, there were also significant decrements in serum bicarbonate and phosphorus. The decline in serum bicarbonate probably reflects an APD-induced reduction in release of bone buffers into the circulation. Correction of hypercalcemia also would be expected to decrease renal acid secretion by a direct tubular effect and indirectly because of a rise in PTH (25). The decrease in serum phosphorus was accompanied by a reduction in urinary phosphorus excretion, an effect characteristic of bone resorption inhibition. There also was a reduction in systolic blood pressure, whereas the diastolic blood pressure remained constant after the serum calcium declined. Because increased circulating calcium enhances myocardial contractility (33), it could elevate systolic blood pressure. Indeed, when calcium was infused into normal subjects during hemodynamic monitoring, hypercalcemia caused an increase in systolic blood pressure as a result of increased cardiac output (34).
In summary, renal tubular calcium reabsorption was increased in eight consecutive patients with HCM due to a variety of tumor types. This was readily apparent when the relationships between serum-ionized calcium and CaE were compared with controls matched for renal insufficiency, but the proportion with the abnormality was underestimated if controls with normal renal function were used. Although altered renal calcium handling was not associated with volume depletion, volume expansion is a valuable therapeutic modality. Because a PTH-like effect was often, but not always, present, chronic hypercalcemia per se or other humoral factors may influence renal calcium handling.

ACKNOWLEDGMENTS

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