# A 20 year follow up of a renal stone former patient with primary hyperparathyroidism

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Primary hyperparathyroidism is perhaps the most common definite disease causing calcium stone formation being present in up 5-10% of calcium renal stone formers.
The enlargement of a single gland with the characteristics of an adenoma or the hyperplasia of all four glands cause excessive secretion of parathyroid hormone which produces hypercalcemia and consequently hypercalciuria because of the increased filtered load of calcium. Hypercalciuria and increased phosphate excretion tend to promote calcium stone formation by raising the urinary calcium phosphate activity product.
Clinical diagnosis of hyperparathyroidism begins with documenting persistently elevated levels of serum calcium, but in some cases the elevation may be small.
We describe a patient with recurrent renal stone formation presenting with hypercalciuria and serum calcium at the upper limit of the normal range who refused neck exploration and thereafter was followed up for 20 years.

## Case report

A 54-year-old women was admitted to our institution in October 1983 with an history of left lumbar pain.
Medical history revealed previous spontaneous passage of 11 urinary calcium stones during the preceding 27 years without known biochemical or hormonal abnormalities. The age at stone onset was 27 year, the time to recurrence after the first renal stone was 3 year.
Intravenous pielography (IVP) showed a 1 cm radiopaque stone of the left pelvic junction with hydronephrosis and the patient underwent surgical pyelolithotomy.
One month after stone removal a blood sample was taken and a 24 h urine urine sample was collected for determination of potassium, sodium, calcium, phosphate, urate, oxalate and creatinine (Table I). Urinary volume and pH were recorded and urinary oxalate was measured in the urine. An oral calcium load test was performed as follow. A serum sample was taken and urine was collected on fasting from 7 A.M. to 9 A.M. An oral load of 1 gr of calcium was then given as calcium lactogluconate and calcium carbonate.Urine was collected from 9 A.M. to 1 P.M. with a serum sample taken at 1 P.M. Calcium,inorganic phosphate and creatinine were measured on each serum and urine sample.Urinary calcium excretion was expressed as calcium to creatinine ratio. Fasting and after load serum concentrations of calcium were respectively 9.2 and 10.8 mg/dl, while fasting and after load calcium to creatinine ratio were respectively 0.05 and 0.21 suggesting the diagnosis of absorptive hypercalciuria.
Serum PTH was in the normal range, sonography and scintigraphy of parathyroid were not able to show any enlargement of parathyroid glands.
On this basis we deferred neck exploration and placed the patient on thiazides treatment in order to "unmask" a latent hyperparathyroidism, but unfortunately the patient was lost at follow up.
After some years we recalled systematically our patients in order to obtain information on stone recurrence.The patient replied to our invitation and she presented for a follow up visit (Tables II and III).
She had developed hypertension being on treatment with propanolol and she had been treated for pancreatitis owing to persistently elevated levels of serum amylase whereas stone disease had not recurred.The serum level of parathyroid hormone was now in the upper range of normal values but scintigraphy was still negative for parathyroid enlargement.
Thereafter blood and 24 urine determinations were repeated every 6 months till now.
Since November 1999, progressively elevated parathyroid hormone levels were shown, ranging between 208 and 501 ng/ml.
On September 2002 an aortic aneurysm involving the celiac trunk was diagnosed.
The patient refused any further surgical treatment.
Actually she is on treatment with propanolol (40 mg) and ramipril (5 mg).
A recent measurement of bone density at femur neck and lumbar spine showed a marked decrease of mineral content.

Table I - Serum levels and urinary risk factors for stone disease at first visit.

| Serum | | | Urine | | 24-h Urine | | |
|---|---|---|---|---|---|---|---|
| K | mEq/L | | mEq/l | 21 | | | |
| Na | mEq/L | | mEq/L | 95 | | | |
| Ca | mg/dl | 10.1 | mg/dl | 12.6 | CaT | mg/day | 226 |
| $PO_4$ | mg/dl | 2.4 | mg/dl | 21 | $PO_4$T | mg/day | 378 |
| UA | mg/dl | | mg/dl | 34 | UAT | mg/day | 612 |
| Cr | mg/dl | 1.4 | mg/dl | 80 | | | |
| Ox | | | mg/dl | 2.2 | OxT | mg/day | 39.6* |
| Vol | | | ml | 1800 | Ca/Cr | | 0.157 |
| pH | | | | 5.5 | | | |

* Colorimetric Hodgkinson-Williams method.

Table II - Serum levels in the follow up visits

| | | 7/3/94 | 3/10/94 | 10/4/95 | 6/11/95 | 13/5/96 |
|---|---|---|---|---|---|---|
| K | mEq/L | 3.8 | 3.9 | 3.8 | 4.1 | 4.0 |
| Na | mEq/L | 147 | 145 | 146 | 145 | 141 |
| Ca | mg/dl | 9.96 | 10.0 | 9.80 | 10.2 | 10.9 |
| $PO_4$ | mg/dl | 1.9 | 2.3 | 2.2 | 2.0 | 2.6 |
| UA | mg/dl | 3.4 | 4.4 | 5.7 | 4.7 | 6.[illegible] |
| Cr | mg/dl | 0.83 | 0.92 | 1.0 | 1.0 | 1.18 |
| | | 16/12/97 | 15/6/98 | Nov 2000 | Apr 2001 | May 2003 |
| K | mEq/L | 4.1 | 4.0 | | | |
| Na | mEq/L | 141 | 142 | | | |
| Ca | mg/dl | 11.0 | 11.0 | 12.39 | 11.83 | 11.48 |
| $PO_4$ | mg/dl | 2.78 | 2.40 | | | |
| UA | mg/dl | 6.0 | 7.0 | | | |
| Cr | mg/dl | 1.1 | 0.8 | | | |

Table III - Urinary risk factors for stone disease in the follow up visits.

| | | 7/3/94 | 3/10/94 | 10/4/95 | 6/11/95 | 13/5/96 |
|---|---|---|---|---|---|---|
| Vol | ml | 1150 | 1550 | 1[illegible]50 | 1450 | 1650 |
| PH | | 5.6 | 6.4 | 5.[illegible] | 6.7 | 6.0 |
| K | mEq/L | 29 | 29 | 41 | 31 | 26 |
| Na | mEq/L | 76 | 81 | [illegible]6 | 70 | 90 |
| Ca | mg/dl | 12.5 | 13.3 | 5.8 | 3.36 | 2.0 |
| $PO_4$ | mg/dl | 32 | 31 | 53 | 25 | 25 |
| UA | mg/dl | 32 | 17 | 39 | 16 | 14 |
| Ox | mg/dl | 1.55 | 1.7 | 4.1 | 1.3 | 1.17 |
| Cit | mg/dl | 2.07 | 1.46 | 4.7 | 10.8 | 5.3 |
| Mg | mg/dl | 4.81 | 6.[illegible] | 7.47 | 4.51 | 4.81 |
| Cr | mg/dl | 57 | 40 | 83 | 34.5 | 40 |
| CaT | mg/day | 143 | 206 | 43 | 48 | 33 |
| $PO_4T$ | mg/day | 368 | 480 | 397 | 362 | 412 |
| UAT | mg/day | 368 | 263 | 292 | 232 | 231 |
| OxT | mg/day | 17.[illegible] | 26.3 | 30.7 | 18.8 | 19.3 |
| CitT | mg/day | 23.8 | 7.1 | 35.2 | 156 | 87 |
| MgT | mg/day | 55 | 97 | 55 | 65 | 79 |
| | | 1[illegible]12/97 | 15/6/98 | | | |
| Vol | ml | 1300 | 1400 | | | |
| PH | | 5.8 | 5.8 | | | |
| K | mEq/L | 31 | 33 | | | |
| Na | mEq/L | 77 | 108 | | | |
| Ca | mg/dl | 2.2 | 2.3 | | | |
| PO | mg/dl | 32.8 | 24.8 | | | |
| UA | mg/dl | 16 | 23 | | | |
| C[illegible] | mg/dl | 1.28 | 1.82 | | | |
| Cit | mg/dl | 3.68 | 9.0 | | | |
| M[illegible]g | mg/dl | 6.2 | | | | |
| Cr | mg/dl | 46 | 50 | | | |
| CaT | mg/day | 28 | 32 | | | |
| $PO_4T$ | mg/day | 426 | 347 | | | |
| UAT | mg/day | 208 | 322 | | | |
| OxT | mg/day | 16.6 | 25,4 | | | |
| CitT | mg/day | 48 | 126 | | | |
| MgT | mg/day | 80 | | | | |

**Discussion**

PTH stimulates renal tubular calcium reabsorption (1), therefore is difficult to explain how an exaggerated secretion of PTH could lead to hypercalciuria with normal serum calcium values (normocalcemic hyperparathyroidism).
On the contrary this finding could be explained as a consequence of a primitive tendency to renal calcium leak with secondary elevation of parathyroid secretion and anatomical hyperplasia of the parathyroid glands (secondary hyperparathyroidism).
An alternative explanation for the existence of normocalcemic hyperparathyroidism is that phosphate depletion provoked by elevated PTH may cause a reduction of renal calcium reabsorption before the increase of serum calcium (2).
In the present patient we demonstrated the progressive change of the biochemical and clinical presentation from a renal disease characterized by hypercalciuria and recurrent calcium stone formation to a bone disease with low urinary excretion of calcium and progressively higher calcium and PTH levels.
Probably this change has been enhanced from the "unmasking" effect by thiazide administration (3,4) and from the effect on calcium metabolism of estrogenic deprivation after menopause. In this case the normal values of PTH in the early period of observation can be explained by the problem connected with the routine determination of serum PTH in the early eighties. In fact N-terminal assay was often not able to disclose elevated levels of PTH in mild primary hyperparathyroidism.
Unfortunately we were not able to evaluate citrate excretion at the first observation, although the acidic value of urine on fasting should be enough to exclude a pre-existent renal tubular acidosis.
On the other hand the low citrate excretion observed in hyperparathyroid patients have been attributed to a depressed bicarbonate reclamation due to chronic phosphate depletion rather than to a direct effect of parathyroid hormone (5,6).

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