Urinary cyclic adenosine monophosphate discriminates subsets of patients with osteoporosis[1]

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To assess the biologic activity of the parathyroid hormone in osteoporosis, 32 patients with radiologic and clinical evidence of this disease were studied. Measurements of urinary cyclic adenosine monophosphate (cAMP), serum calcitriol (1,25 dihydroxyvitamin D), calcium, phosphorus, albumin, creatinine, and estimated glomerular filtration were obtained. The high cAMP group averaged 5.68 μmol cAMP/g (SEM, 0.35) and the low cAMP group, 2.89 μmol cAMP/g (SEM, 0.22) of creatinine. Mean urinary calcium levels were lower ($P < 0.05$) in the high cAMP group (120 ± 16 versus 288 ± 54 mg/d). Seventy percent of the values from the high cAMP group were below 150 mg/d and averaged 88 mg (range, 36–127). About 70% of the patients with the low cAMP values excreted 368 mg daily (range, 170–700). Although both groups had similar levels of serum calcitriol, almost 70% of the patients had values below the reference limit for the mean; more than 80% of this group were excreting less than 150 mg of calcium daily. Because urinary cAMP levels of patients form a separate distribution from those of young normals, patients can be divided into groups with low or high cAMP values displaying different patterns of calcium excretion. Increased levels of cAMP may represent enhanced parathyroid gland secretory activity due to a deficiency of dietary calcium or to poor absorption from inadequate production of vitamin D.

Index terms: Osteoporosis · Parathyroid hormones, analysis

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Although several studies have investigated the concentration of immunologically reactive parathyroid hormone in the serum of elderly patients with osteoporosis, results have been inconsistent. Different investigators have found normal, increased, and decreased serum levels of this hor-

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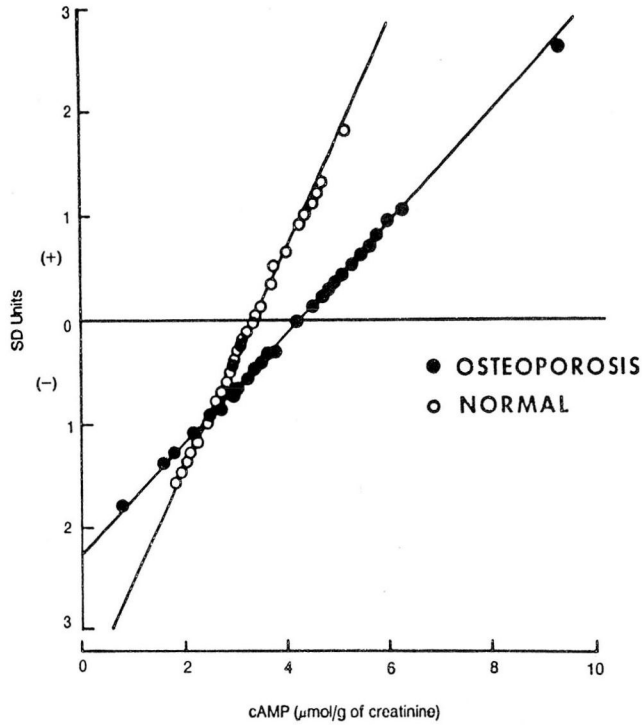

Fig. 1. Plot of urinary cAMP versus a standard score. The standard score (i.e., z = SD units = [urinary cAMP value − mean]/SD) of each value in the reference and osteoporotic group is plotted. Both populations follow a Gaussian distribution. The range of the patients' urinary cAMP data is much larger than that for the reference population. The nonparametric Kolmogrov-Smirnov two-sample test showed that the distributions were different ($P < 0.01$). Mean population values are shown at the "0" SD-unit line (3.3 and 4.3 for the normals and patients, respectively).

mone.[1–3] This disparity is due in part to the heterogeneity of patients with this disease and the lack of suitable age- and sex-matched controls, as well as due to the complexity of parathyroid hormone metabolism and its serum measurements.[4,5]

Table. Serum chemical values in the high and low cAMP groups

Test	High*	Low*
Calcium (mg/dL)	9.3 ± 0.5 (15)	9.2 ± 0.3 (17)
Phosphorus (mg/dL)	3.4 ± 0.4 (15)	3.3 ± 0.5 (17)
Albumin (mg/dL)	4.2 ± 0.3 (15)	4.2 ± 0.3 (14)
Creatinine (mg/dL)	1.0 ± 0.2 (15)	1.1 ± 0.2 (15)
Alkaline phosphatase (IV/L)	96 ± 36 (15)	86 ± 22 (17)
Glomerular filtration rate (mL/min/1.73 m^2)	82 ± 4 (15)	86 ± 7 (16)

* Values expressed as mean ± SD (number of observations).

To overcome the problem of the immunoassay for parathyroid hormone, we employed the measurement of urinary cyclic adenosine monophosphate (cAMP) to study the hormonal secretion of the parathyroid gland. In general, the plasma concentration of this nucleotide is constant so that fluctuations in urinary output reflect the renal production that is stimulated by parathyroid hormone.[6,7] Due to this unique relationship, the measurement is a useful indicator of primary or secondary hyperparathyroidism. We measured urinary cAMP and other chemical indexes of calcium metabolism. In patients with osteoporosis, our data showed a unique distribution of cAMP values that allowed identification of two subgroups with either high or low values.

Materials and methods

Thirty-two patients (29 women, 3 men; average age, 68 years) were studied. Each had radiologic evidence of osteopenia and one or more vertebral compression fractures. No patient had a disorder of the gastrointestinal tract, kidneys, or endocrine glands as assessed by routine laboratory evaluation, history, and physical examination. Calcitriol (1,25-dihydroxyvitamin D) was measured with a commercial assay that had a population mean of 50 pg/mL (SEM, 2) with interassay and intraassay coefficients of variation of 10.1% and 11.1%, respectively. The radioimmunoassay technique was used to measure urinary cAMP in aliquots of either 24-hour or two-hour specimens. The reference mean was 3.3 μmol/g of creatinine (N = 41; range, 1.3–5.3). The interassay coefficients of variation were 11.6% and 10.0%, and the intraassay coefficients were 7.4% and 5.7% for two control specimens. Urinary calcium was assessed by atomic absorption spectrophotometry, and routine serum chemistries were performed by automated techniques. The glomerular filtration rate was estimated based on the method described by Rowe et al.[8] Statistical evaluations were performed with the SAS-biostatistical package on a VAX-Digital System Computer.

Results

The mean cAMP value of the patients was significantly greater than that of the reference population. However, the distribution of values was distinctly different (*Fig. 1*) ($P < 0.01$, non-

parametric Kolmogorov-Smirnov two-sample test). Because there was an age disparity in the reference and patient groups, bias might be introduced by a direct comparison. Therefore, we analyzed the data by dividing patients in two groups with urinary values above (high) or below (low) the population mean. The mean values for the high and low groups were 5.68 μmol/g (SEM, 0.35) and 2.89 μmol/g (SEM, 0.22) of creatinine, respectively. Serum chemical values and estimated renal function were similar, but alkaline phosphatase tended to be greater ($P < 0.05$) in the former group (*Table*). The mean urinary calcium value was lower ($P < 0.05$) in the high cAMP group (120 mg/d) and higher in the low cAMP group (288 mg/d) (*Fig. 2*). Seventy percent of all the patients with urinary values less than 150 mg had greater cAMP values (χ^2 analysis, $0.05 > P > 0.01$). These patients excreted, on the average, 88 mg daily (range, 36–127). About 70% of the patients with lower cyclic values were excreting more than 150 mg/d and averaged 370 mg (range, 170–700).

Serum calcitriol was similar in both subgroups and was within two standard deviations of the population or reference mean (*Fig. 3*). However, 67% of all patients had values below the reference mean (i.e., 44 pg/mL) and more than 80% of these patients were excreting less than 150 mg of calcium daily (χ^2 analysis, $P < 0.05$). Although a greater proportion of patients with low calcitriol levels had high cAMP values and vice versa, these proportions were not statistically significant ($P < 0.10$).

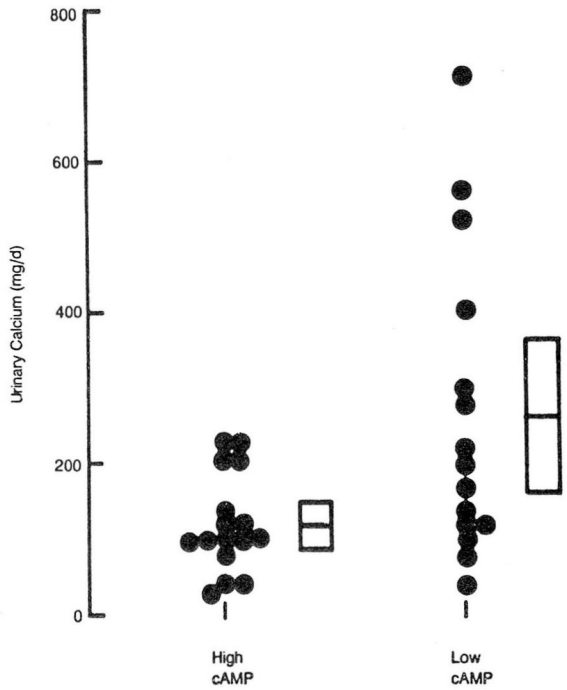

Fig. 2. Urinary calcium in the high and low cAMP groups. There was a statistical difference ($P < 0.05$) in the urinary calcium values in both groups. The mean of the high cAMP group was 120 mg/d (SEM, 16) and for the low cAMP, 288 mg/d (SEM, 54).

Discussion

The measurement of urinary cAMP is an in vivo bioassay for the functional activity of the parathyroid gland and, therefore, obviates the problems associated with the assay for immunologically reactive parathyroid hormone.[6,7] Our observation that the distribution of values in the patient was distinct from the reference group is important because it emphasizes the important principle that comparable populations must be analyzed. It is not surprising that elderly patients had a different distribution of values. Age alone might be the cause of this disparity, as Insogna et al noted.[9] However, other factors, such as renal function which may not be readily apparent from routine serum chemical tests, could have contributed to the distortion in values.[10,11]

By segregating the patients into groups with either high or low values, some observations of potential clinical significance were noted. Routine serum chemical measurements were unable to discriminate these subsets. Yet, in the absence of renal disease, lower urinary calcium excretion implies an inadequate dietary intake or intestinal absorption. The fact that more patients with high cAMP levels had lower urinary calcium suggests that compensatory hyperparathyroidism may exist.

For unclear reasons, aging is accompanied by a decrease in calcium absorption and increase in the quantity of parathyroid hormone.[12–14] In elderly patients with osteoporosis, the general trend is toward lower, but not markedly abnormal, values of serum calcitriol.[14] This tendency was noted in our studies. The low urinary calcium excretion and the low level of serum calcitriol are consistent findings since poor absorption of calcium occurs with low vitamin levels. The interesting observation in our data is that there was a tendency for the patients with the higher cAMP level to have low serum calcitriol levels, too. This

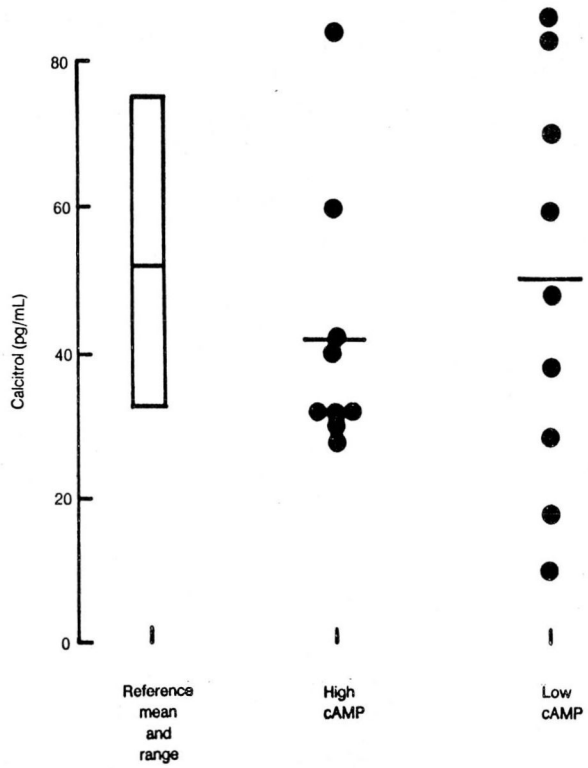

Fig. 3. Serum calcitriol values in the cAMP groups. The reference mean is 50 pg/mL (SEM, 2) (range, 30–75). The mean value for the high cAMP group was 44 pg/mL and for the low cAMP group, 49 pg/mL.

is paradoxical since parathyroid hormone, if increased, should stimulate the production of this vitamin. However, with aging, there may be abnormalities in the production of this metabolite even in the presence of high stimulatory activity by parathyroid hormone. Slovik et al[15] showed that elderly osteoporotic patients are unable to produce increased levels of this metabolite even after being given pharmacologic doses of parathyroid hormone. In a similar fashion, Zerwekh et al[16] showed that some patients do not increase intestinal absorption of calcium even after being given pharmacologic doses of calcifediol (25-hydroxyvitamin D), the precursor of calcitriol.[16] Our subset of patients with a higher cAMP level may well be similar to these patients.

Inadequate dietary calcium is another possible explanation for the higher cAMP values. In the calcium-deficient state, compensatory hyperparathyroidism develops to maintain serum levels of calcium in the presence of inadequate dietary intake. Since we did not obtain detailed dietary histories from our patients, our information to support this notion is speculative. In a few patients, we were able to show that supplementation of the diet with up to 1.5 g of calcium reduced the cAMP level to a normal range and increased urinary calcium output. These patients obviously had adequate absorptive capacity, but due to inadequate dietary intake of calcium, compensatory parathyroid-gland activity ensued and urinary calcium output was lower.[17,18]

In contrast to these findings, there were a number of patients with hypercalcuria. Four patients in the low cAMP group excreted 400 mg or more of calcium daily (mean cAMP value, 1.8 μmol/g of creatinine). This implied that the patients probably hyperabsorbed calcium and had a secondary decrease in parathyroid hormone.

The clinical implications of our findings are twofold. First, some patients with osteoporosis may be in a state of compensatory hyperparathyroidism due to inadequate intake or absorption of calcium. Supplemental calcium in these patients would be an advantageous undertaking to suppress the potential catabolic effects of the hormone on the skeleton. Monitoring cAMP and urinary calcium levels would be a way of assessing the effectiveness of this therapy. Second, there is a subset of patients with lower cAMP levels who may not be helped to any large extent by supplemental dietary calcium. Determinations of specific therapies advantageous for this subgroup are still purely speculative. In either case, the urinary cAMP measure seems to be a useful way of discriminating these two subsets.

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