Urinary 3',5'-cyclic adenosine monophosphate in relation to serum and urinary calcium in acromegaly and primary hyperparathyroidism

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Abstract. A comparison of the interrelations between serum and urinary calcium values and the urinary excretion of cAMP in acromegaly (No. of subjects: 26), patients with primary hyperparathyroidism (n = 18) and control subjects (n = 42) is presented. The cAMP excretion was greatest in primary hyperparathyroidism, but acromegalics also exhibited higher values for this parameter than controls. A positive correlation was found between serum calcium values and cAMP in primary hyperparathyroidism, while acromegalics showed no correlation between these parameters. In controls there was a negative correlation between serum calcium and cAMP. Serum calcium levels corrected for variations in total protein concentrations were elevated both in acromegaly and primary hyperparathyroidism, mostly in the latter.

Acromegalics and patients with primary hyperparathyroidism exhibited an increase in 24 h calcium excretion. While there was a negative relationship between urinary calcium excretion and cAMP in acromegaly, a positive correlation between these parameters was found in primary hyperparathyroidism. Controls showed a negative correlation between urinary calcium values and cAMP. It is concluded that the role of the parathyroids in the regulation of calcium metabolism in acromegaly is different from that of both normal controls and primary hyperparathyroidism. It is postulated that an active form of Vitamin D plays a major role in the regulation of calcium metabolism in acromegaly.

Acromegaly is associated with an abnormal and seemingly conflicting regulation of the calcium/phosphate metabolism (Nadarajah et al. 1968; Corvillain & Abramow 1972; Halse & Haugen 1980). We have previously reported on elevated or normal PTH levels concomitant with a moderate but significant increase in serum calcium levels in this disease (Halse & Haugen 1980). Parathyroid hyperactivity has been thought to be the explanation for this relative hypercalcaemia (Brown & Singer 1969). Our results have, however, indicated that some factor other than PTH could be involved in the regulation of calcium metabolism in this disease.

To elucidate this possibility a comparison of calcium (serum and urinary)–urinary 3'5'-cyclic adenosine monophosphate (cAMP) interrelations in acromegaly, primary hyperparathyroidism and control subjects has been performed. The results of this study seems to provide indirect evidence for involvement of an active Vitamin D metabolite in the regulation of the calcium metabolism in acromegaly.

Materials and Methods

The acromegaly group consisted of 26 consecutively admitted patients (11 males and 15 females, mean age ± sd: 46.4 ± 11.0 years). Eighteen acromegalics had received treatment either in the form of radiotherapy or hypophysectomy previously. Of these, six were on continuous medication with bromocriptine. Two patients had received bromocriptine treatment only. The remaining six acromegalics were untreated when investigated. All had active acromegaly defined as elevated fasting.
growth hormone levels which could not be suppressed to values below 5 µg/l serum during an oral glucose tolerance test in addition to symptoms indicating disease activity.

Eighteen patients (6 males and 12 females, mean age ± sd: 56.5 ± 10.0 years) with hypercalcaemia and later operatively verified primary hyperparathyroidism were chosen for comparison.

The control group consisted of 42 subjects (17 males and 25 females, mean age ± sd: 43.9 ± 13.8 years) recruited from healthy volunteers and ambulatory patients hospitalized for coronary heart disease. The latter subjects received no medication except nitroglycerine during the study.

All acromegalics received a collagen free diet during the study. A 2000 cal portion of this diet contains about 1000 mg calcium. Most control subjects received this diet, but two had no dietary restrictions. All hyperparathyroid subjects received an ordinary hospital diet when studied. Estimated calcium intake was of the same order in this group as in the two former.

Urine was sampled for 24 h on two consecutive days in all acromegalics. All control subjects sampled only one 24 h portion of urine. The number of available 24 h urinary calcium values in patients with primary hyperparathyroidism ranged from 1 to 5 (mean 2.4) in the individual patient. The respective number of available cAMP data were 1 to 6 (mean 2.7) estimations. Only four of the patients with primary hyperparathyroidism had estimations of cAMP and calcium on the same urine sample. Since there is no difference between fasting and 24 h values for cAMP/creatinine ratio (Shaw et al. 1977) both types of estimations were used arbitrarily. All available data were included. Fasting blood samples were obtained from all on appropriate days.

Serum and urinary concentrations of Ca (calcium) and creatinine as well as total serum concentrations were determined by standard laboratory methods. Urinary cAMP was determined using a kit (The Radiopharmaceutical Corp., Amersham, England). The urine samples were diluted with distilled water and analysed according to the original description (Tovey et al. 1974). Details regarding assay performance has been reported elsewhere (Halse & Gordeladze 1979; Halse & Haugen 1980). Serum Ca values were corrected for individual variations in serum protein concentrations (Parfitt 1969).

We have previously demonstrated that large day to day variations occur in the urinary excretion rates for cAMP and Ca (Halse & Gordeladze 1979). Mean values for these parameters as well as the serum values were therefore used in the statistical evaluation of the results. T-test statistics were used for group comparison and linear regression analysis to test correlations between the various parameters in the control group. In the patient groups rank correlation analysis according to Spearman was performed. P was considered significant when < 0.05.

**Results**

Mean values for urinary cAMP expressed as cAMP/creatinine ratio or as a function of GFR (glomerular filtration rate) for patients and controls are shown in Table 1. Acromegalics had higher values for cAMP/creatinine than controls (P < 0.04) but

<table>
<thead>
<tr>
<th>Patients</th>
<th>No.</th>
<th>corr sCa mmol/l</th>
<th>24 h uCa mmol</th>
<th>cAMP/creatinine ratio</th>
<th>cAMP/GFR nmol/100 ml</th>
<th>screat µmol/l</th>
<th>24 h ucreat mmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acro (A)</td>
<td>26</td>
<td>2.49</td>
<td>7.31</td>
<td>415.6</td>
<td>3.05</td>
<td>75.0</td>
<td>13.34</td>
</tr>
<tr>
<td>PHP (B)</td>
<td>18</td>
<td>3.08</td>
<td>7.81</td>
<td>580.1</td>
<td>6.30</td>
<td>106.6</td>
<td>12.56</td>
</tr>
<tr>
<td>Controls (C)</td>
<td>42</td>
<td>2.42</td>
<td>4.90</td>
<td>337.1</td>
<td>2.80</td>
<td>84.2</td>
<td>12.50</td>
</tr>
</tbody>
</table>

Comparison of calcium, cAMP and creatinine data in acromegaly, primary hyperparathyroidism and controls. (corr sCa: serum Ca corrected for total protein concentration, uCa: urinary Ca, cAMP/creatinine ratio, cAMP/GFR: cAMP/100 ml GFR, screat: serum creatinine, ucreat: urinary creatinine, Acro: acromegalis, PHP: primary hyperparathyroidism. The numbers listed are means and sd).
Lack of correlation between corrected serum Ca values and cAMP/creatinine ratio in acromegaly. Line of regression for the same parameters obtained in controls is drawn for comparison ($r = -0.59, P < 0.001$).

Control serum Ca values were significantly elevated in acromegaly as compared with controls ($P < 0.007$) but lower than in primary hyperparathyroidism ($P < 0.001$). The 24 h urinary Ca excretion was about equal in the two patient groups but significantly greater than in controls ($P < 0.006$). While there was no significant difference in 24 h urinary creatinine excretion between the three groups (urinary creatinine values were available in only 16 of the hyperparathyroid patients), significant differences in serum creatinine levels were observed (Table 1).

Controls demonstrated a significant negative correlation between corrected serum Ca and cAMP/creatinine ratio ($r = -0.59, P < 0.001$) or cAMP/GFR ($r = -0.48, P < 0.05$). Acromegals showed no correlation between these parameters (Figs. 1 and 2). Patients with primary hyperparathyroidism demonstrated a positive correlation between corrected serum Ca values and cAMP/creatinine ratio ($R_s = 0.48$, $P \leq 0.05$) or cAMP/GFR ($R_s = 0.60$, $P < 0.02$) (Figs. 3 and 4).

The 24 h urinary Ca excretion was marginally but significantly inversely correlated to cAMP/creatinine ratio ($r = -0.35$, $P < 0.05$) but not to cAMP/GFR in controls. Acromegals displayed a significant negative correlation between 24 h urinary Ca excretion and cAMP/creatinine ratio ($R_s = -0.44$, $P < 0.05$) or cAMP/GFR ($R_s = -0.60$, $P < 0.01$) (Fig. 5). In primary hyperparathyroidism there was a positive correlation between 24 h urinary Ca excretion and cAMP/creatinine ratio ($R_s = 0.52$, $P < 0.05$) but cAMP/GFR did not correlate to this parameter (Fig. 6).

Discussion

The study demonstrates that the regulation of calcium metabolism in acromegaly is different from that found both in normal subjects and in patients with primary hyperparathyroidism.

Our results confirm the existence of an inverse correlation between serum Ca levels and the urinary excretion of cAMP in normal subjects (Madsen et al. 1976; Shaw et al. 1977). Since urinary cAMP is a measure of parathyroid function (Kaminsky et al. 1970; Murak & Pak 1972; Halse &
Positive correlation between corrected serum Ca and cAMP/creatinine ratio in primary hyperparathyroidism ($R_S = 0.48, P \leq 0.05$). The line represents the normal relationship between these parameters.

Positive correlation between corrected serum Ca and cAMP/GFR in primary hyperparathyroidism ($R_S = 0.60, P < 0.02$). The line represents the normal relationship between these parameters.
Negative correlation between 24 h urinary Ca excretion and cAMP/creatinine ratio in acromegaly ($R_s = -0.44, P < 0.05$). Line of regression for the same parameters obtained in controls is drawn for comparison ($r = -0.35, P < 0.05$).

Fig. 5.

Positive correlation between 24 h urinary Ca excretion and cAMP/creatinine ratio in primary hyperparathyroidism ($R_s = 0.52, P < 0.05$). The line represents the normal relationship between these parameters.

Fig. 6.

Gordeladze 1979) these results support a previous report on the PTH/serum Ca relationship in normal subjects (Purnell et al. 1974).

The inverse correlation between urinary Ca excretion and cAMP found in controls corroborates previous reports by Pak et al. (1974) and Wålinder et al. (1978). Since the 24 h urinary Ca excretion normally reflects the gut absorption of Ca, this finding indicates an inverse relationship between absorbing capacity and parathyroid function. An inverse relationship is already established between parathyroid activity and activation of Vitamin D to 1,25-(OH)$_2$D$_3$ (Garabedian et al. 1974) and the latter hormone is considered to be the sole modulator of intestinal Ca absorption (DeLuca 1974).

In primary hyperparathyroidism the positive correlation found between serum Ca values and the urinary cAMP excretion demonstrates the altered relationship between these parameters in this disease and supports the report by Purnell et al. (1974) on PTH/serum Ca interrelations.

A positive correlation between 24 h urinary Ca excretion and cAMP could be demonstrated in primary hyperparathyroidism. In this disease bone resorption and intestinal hyperabsorption of Ca
are the causes of hypercalciuria. Since bone resorption is PTH mediated, the bone Ca fraction of the total amount of urinary Ca would be positively correlated to the urinary cAMP excretion. The increased absorption of Ca from the gut is probably related to the increased levels for 1,25-(OH)₂D₃ found in this disease (Kaplan et al. 1977). Our data may demonstrate that the normal feed-back between PTH (measured as cAMP) and 1,25-(OH)₂D₃ (expressed as urinary Ca excretion) is not functioning and that the defect is analogous to the one seen between PTH and serum Ca.

Acromegalics had elevated serum Ca levels as compared with controls. The urinary excretion of cAMP was also elevated or normal but there was no correlation between these two parameters. Since acromegalics have normal or elevated levels of PTH (Halse & Haugen 1980) this implies that these patients have either a normal or a hyperparathyroid functioning feed-back system between PTH and serum Ca or that a factor in addition to PTH determines the serum Ca level.

Hypercalciuria, comparable to that found in patients with primary hyperparathyroidism was also found in acromegaly. In contrast to primary hyperparathyroidism there was an inverse relation between 24 h urinary Ca and urinary cAMP. Thus, there seems to be a 'normally' operating feed-back system between PTH and 1,25-(OH)₂D₃ in acromegaly but since the urinary Ca excretion is increased relative to cAMP as compared with controls, the set-point for the feed-back system must be altered.

The hypercalciuria of acromegaly is secondary to hyperabsorption of Ca from the gut (Sigurdsson et al. 1973; Halse & Haugen, 1980). Since visceromegaly is common in acromegaly, the increased absorption may be due to a larger absorbing area. However, indirect evidence points to other explanations. First activation of the 1-hydroxylase, which activates Vitamin D, is one feature of GH actions as shown in hypophysectomized rats (Spanos et al. 1978). Secondly, successful treatment with bromocriptine causes a reduction in urinary Ca excretion after a few months (Eskildsen et al. 1978). Finally, the hypercalciuria which follows GH treatment becomes evident only after a few days of treatment in normal man (Ikkos et al. 1959; Hanna et al. 1961). It is most unlikely that gross anatomical changes are responsible for these changes in urinary Ca excretion.

Acromegalics thus seem to have a regulation of Ca metabolism which is intermediary to that found in normal subjects and in primary hyperparathyroidism. The feed-back system between the parathyroids and intestinal Ca absorption seems to be intact but the set-point is altered. Hyperabsorption of Ca is probably also the cause of the moderate hypercalcaemia we observed. Sigurdsson et al. (1973) found a significant correlation between gut absorption of radioactive Ca and the serum Ca level in acromegalics. The increased turn-over of bone metabolism observed in biopsies from acromegalics (Melsen & Halse, to be published) may also contribute to this relative hypercalcaemia but since osteoporosis is not a feature of acromegaly (Doyle 1967; Riggs et al. 1972; Ikkos et al. 1974) the net contribution of bone Ca to serum Ca would be of little importance.

Increased serum levels of 1,25-(OH)₂D₃ have recently been reported in acromegalics (Brown et al. 1979; Lund et al. 1979). A study of Vitamin D metabolites in our patients is currently under way. The results of the present study may imply that an active form of Vitamin D have leading role in the regulation of Ca metabolism in acromegaly.

References


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