Hypercalcaemia in rheumatoid arthritis revisited

Stuart H Ralston, William D Fraser, Janusz Jankowski, Ian M Richards, Robert A Cowan, Hilary A Capell, Roger D Sturrock

Abstract
The prevalence and mechanisms of hypercalcaemia were studied in a series of patients attending a regional referral centre for rheumatic diseases. In a prospective study one case of hypercalcaemia due to primary hyperparathyroidism was found in 251 consecutive patients who were screened over a three month period. In a retrospective study of 39 patients who had been discovered to be hypercalcaemic during the preceding 12 months known cases of hypercalcaemia were found in 38 (97%) cases. Primary hyperparathyroidism was the most common cause (n=24; 62%), followed by thiazide treatment in five (13%), cancer in three (8%), immobility in three (8%), vitamin D toxicity in two (5%), and chronic liver disease in one (3%). In one case the diagnosis remained unclear after full investigation.

This study shows that the causes of hypercalcaemia in rheumatological patients are similar to those in the general population. These observations contrast with previous reports, which suggested that hypercalcaemia may be a complication of rheumatoid arthritis itself.

In the 1970s Kennedy and his colleagues presented data to suggest that hypercalcaemia and other biochemical abnormalities suggestive of parathyroid overactivity were a common feature of rheumatoid arthritis.1 2 Detailed investigation of these patients showed low serum immunoreactive parathyroid hormone (PTH) values,3 leading the authors to suggest that the hypercalcaemia might have been due to systemic release of a non-PTH bone resorbing factor as part of the disease process.2 In support of this hypothesis further studies showed significant bone resorbing activity in the serum samples of hypercalcaemic but not normocalcaemic patients with rheumatoid arthritis (RA).4

Although hypercalcaemia in RA has rarely been described in association with increased extrarenal synthesis of 1,25-dihydroxyvitamin D,5 the high prevalence of hypercalcaemia found by Kennedy1 2 has not been confirmed by other workers.5 6 Accordingly, the nature of the putative bone resorbing factor responsible for the hypercalcaemia in Kennedy's patients has remained unclear.

In view of these conflicting reports we have reassessed both the prevalence and mechanisms of hypercalcaemia in a consecutive series of patients attending a regional referral centre for rheumatic diseases.

Patients and methods
Two groups of patients were investigated: a consecutive series of 41 subjects who had been found to be hypercalcaemic (serum albumin adjusted calcium >2.70 mmol/l) on routine biochemical testing during clinic attendances over a 12 month period (January 1987–January 1988) and a series of 251 consecutive patients who were prospectively screened during clinic attendances and hospital admissions over a three month period (June–September 1988).

All patients were interviewed and a drug history taken. Blood and second voided urine samples were obtained after an overnight fast. Routine biochemical and haematological measurements were made by standard automated techniques.

Serum total calcium was adjusted for albumin concentration (reference range 2.00–2.60 mmol/l).7 Serum ionised calcium was measured by a Radiometer ICAl analyser (reference range 1.14–1.29 mmol/l). Serum immunoreactive PTH was measured by a double antibody radioimmunoassay, which employs the antisera Wellcome AS 211/238 (reference range from undetectable to 600 ng/l). Urinary cyclic adenosine monophosphate (cAMP) was measured after appropriate dilution by radioimmunoassay.8 Plasma cAMP was measured by radioimmunoassay using a kit (Amersham International, UK). Urinary hydroxyproline was measured using a kit (Hypronostic—Organon Ltd, Netherlands). Serum vitamin D metabolites, 25-hydroxyvitamin D (reference range 15–100 nmol/l) and 1,25-dihydroxyvitamin D (reference range 20–100 pmol/l), were measured by competitive protein binding and radio-receptor assays respectively.8

Derived variables, which were calculated from fasting urine and serum measurements, included urinary calcium/creatinine ratio (reference range <0.50 mmol/mmol), hydroxyproline/creatinine ratio (reference range <30), renal tubular threshold for phosphate reabsorption (reference range 0.80–1.35 mmol/l glomerular filtrate (GF)),10 and nephrogenous cAMP excretion (urinary cAMP (mmol/l) divided by urinary creatinine (mmol/l)) multiplied by serum creatinine (mmol/l) minus plasma cAMP (nmol/l) (reference range 8–28 nmol/l GF).

Statistical methods used were the Mann-Whitney test and Spearman's rank correlation coefficient.

Results
Forty one hypercalcaemic patients were identified by retrospective analysis of biochemical
Hypercalcaemia in rheumatoid arthritis

Relevant clinical and biochemical details of the patients with hypercalcaemia.* Values are given as means (SEM)

<table>
<thead>
<tr>
<th>Primary hyperparathyroidism</th>
<th>Thyroid</th>
<th>Malignancy</th>
<th>Immobilisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>24</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>% Of total</td>
<td>62</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 (2-4)</td>
<td>60 (2-7)</td>
<td>65 (1-2)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>2/22</td>
<td>1/4</td>
<td>2/1</td>
</tr>
<tr>
<td>Serum calcium (adjusted) (mmol/l)</td>
<td>2.75 (0-42)</td>
<td>2.70 (0)</td>
<td>2.85 (0-10)</td>
</tr>
<tr>
<td>Serum calcium (ionised) (mmol/l)</td>
<td>1.38 (0-91)</td>
<td>1.34 (0)</td>
<td>NM4</td>
</tr>
<tr>
<td>Plasma parathyroid hormone (ng/l)</td>
<td>632 (85)</td>
<td>UD</td>
<td>UD</td>
</tr>
<tr>
<td>Serum creatinine (umol/l)</td>
<td>95 (77)</td>
<td>95 (5-0)</td>
<td>93 (4-3)</td>
</tr>
<tr>
<td>Rheumatological diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>15</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>5J</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Details of the remaining four hypercalcaemic patients are recorded in the text ('Results' section).
†Ionised calcium was measured on only one patient in each group.
‡NM—not measured; UD=undetectable.
§Serum creatinine values were 80 and 85 umol/l in two patients with Reiter's syndrome and 950 umol/l in one patient with pseudogout/serpentine arthritis who had longstanding chronic renal failure.
¶Reiter's syndrome (one); gout (one); primary Raynaud's disease (one); soft tissue rheumatism (one); polymyalgia rheumatica (one).
††Reiter's syndrome (two); pseudogout + serpentine arthritis (one).

records from approximately 5000 patients who attended the centre between January 1987 and January 1988. Sufficient clinical and biochemical data were available for 39 of these patients, either from the initial clinic visit or on reinvestigation, to confirm or exclude known causes of hypercalcaemia. The table shows the relevant clinical and biochemical details for the major diagnostic categories. The most common cause of hypercalcaemia was primary hyperparathyroidism, followed by thiazide treatment, malignancy, and immobilisation. Not shown in the table are two cases of mild hypercalcaemia (serum adjusted calcium 2.80, 2.95 mmol/l) due to vitamin D intoxication (rheumatological diagnoses—osteomalacia and osteoporosis) and one case of mild hypercalcaemia (serum adjusted calcium 2.75 mmol/l, PTH undetectable) associated with chronic liver disease11 (rheumatological diagnosis pseudogout, seronegative erosive RA). In one further patient no known cause could be found for the hypercalcaemia. This was a woman aged 64 with seropositive RA who was euthyroid and had mild stable hypercalcaemia (2.75–2.85 mmol/l) of two years' duration. Plasma immunoreactive PTH values were undetectable on a number of occasions. Other relevant investigations were serum creatinine 110 mmol/l, renal tubular threshold for phosphate reabsorption 0.94 mmol/l GF, nephrogenous cAMP 26 mmol/l GF, urinary calcium/creatinine ratio 0.36, serum 25-hydroxyvitamin D 9 nmol/l, serum 1,25-dihydroxyvitamin D <5 pmol/l.

In all cases the hypercalcaemia was mild and complications were few; two patients with biochemical evidence of primary hyperparathyroidism had a previous history of renal stone disease and one other had hypertension. Only one of the patients with primary hyperparathyroidism had been referred for parathyroidectomy—a man of 34 who was asymptomatic with serum calcium values of 3.00–3.10 mmol/l.

In a further prospective study of 251 consecutive patients (RA n=102), seronegative spondyloarthitis (102), osteoarthritis (47) who had been screened over a three month period only one case of hypercalcaemia was found—a woman with seropositive RA, who had biochemical evidence of primary hyperparathyroidism and who had also been identified in the retrospective study. Other biochemical variables, including serum ionised calcium, serum creatinine, serum albumin, serum phosphate, urinary calcium/creatinine ratio, urinary hydroxyproline/creatinine ratio, and renal tubular threshold for phosphate reabsorption, were generally normal and did not differ between diagnostic groups (data not shown). Although mean (SEM) nephrogenous cAMP values were also normal and did not differ significantly in the three diagnostic groups (RA 22.7 (3.5) mmol/l GF; seronegative spondyloarthitis 19.31 (2.4) mmol/l GF; osteoarthritis 12.1 (1.8) mmol/l GF), raised nephrogenous cAMP values were found in 20 patients with RA (range 32.0–117.0 mmol/l GF), 17 with seronegative spondyloarthitis (28.0–214.0 mmol/l GF), and five patients with osteoarthritis (range 28.0–31.0 mmol/l GF). Subgroup analysis showed no significant difference in any of the above variables when patients were stratified according to use of non-steroidal anti-inflammatory drugs, disease modifying agents (that is, gold, salazopyrine, penicillamine, antimalarial drugs), cytotoxic drugs, or steroids (data not shown). When data from all patients were combined significant correlations were observed between the following variables: serum adjusted calcium and ionised calcium (r=0.55, p<0.0001); erythrocyte sedimentation rate (ESR) and serum albumin (r=–0.65, p<0.0001); ESR and serum globulin (r=–0.65, p<0.0001); ESR and urinary hydroxyproline/creatinine ratio (r=0.31, p<0.001); and ESR and serum adjusted calcium (r=0.31, p<0.001).

Discussion
In contrast with Kennedy’s observations,1 2 we found only one case of hypercalcaemia in 102 consecutive patients with RA, and on further investigation this patient was found to have primary hyperparathyroidism. Our observations, in combination with those of Scott et al and Bramble et al,4 suggest that hypercalcaemia is seldom a feature of uncomplicated RA itself and indicate that the high prevalence of hypercalcaemia in Kennedy’s patients was probably due to selection bias in the relatively small number who were studied.

Even if one accepts this to be the case, however, there remains the problem of explain-
ing the mechanism of hypercalcaemia in the 7/50 (14%) of Kennedy’s patients whose serum calcium values remained raised over a six month period. A review of the original data from this study shows that PTH values in the hypercalcaemic patients were generally low to normal, and on this basis primary hyperparathyroidism was excluded. It is now recognised, however, that the poor sensitivity of the PTH assays then available did not permit such an assumption.12

Indeed, the finding of a detectable PTH value under these circumstances may be interpreted as ‘inappropriate’, suggestive of primary hyperparathyroidism.12

In recent years PTH-like biochemical abnormalities have been described in patients with cancer, where the tumour releases a PTH related peptide which binds to the PTH receptor but is not recognised by standard PTH antiserum.13 These patients can be identified biochemically by the findings of hypercalcaemia, increased nephrogenous cAMP excretion (an index of PTH-like bioactivity), and suppressed serum immunoreactive PTH concentrations.13 Biochemical abnormalities similar to these were found in only one hypercalcaemic patient in our study. Although PTH related peptide release would be a plausible explanation for the hypercalcaemia in this patient, primary hyperparathyroidism could not be completely ruled out because of the relative insensitivity of our assay at low PTH concentrations.

We cannot readily explain the raised nephrogenous cAMP values which were noted in many of the normocalcaemic patients with inflammatory and degenerative arthritides, but they seemed to be an isolated abnormality in the absence of other biochemical evidence of PTH-like activity. At present the reason for this is unclear, but stress induced release of PTH (and hence nephrogenous cAMP) is possible.14

As in the general population, the commonest cause of hypercalcaemia in our patients was primary hyperparathyroidism.15 16 Although hypercalcaemia was more commonly associated with RA than other rheumatological conditions, this simply reflects the fact that most (65%) patients attending the centre suffer from this disease. These figures give an approximate prevalence of 24 cases of primary hyperparathyroidism per 3250 patients with RA—that is, 1:135. Although this is more than one order of magnitude higher than that in the pretrial population (approx 1:5000),15 16 high prevalences have also been reported in other selected patient groups, including postmenopausal women (1:500–1:1000)15–17 and hospital outpatients (1:700–1:2000).18 19

In accordance with previous reports15–19 the primary hyperparathyroidism in our patients was mild, asymptomatic, and discovered by routine biochemical screening. The optimal form of management in patients such as these is controversial; some authorities have argued in favour of conservative treatment for asymptomatic patients over the age of 60, whereas others advise a surgical approach because of the beneficial effect on bone density and apparent reduction in the risk of cardiovascular mortality.22 Although theoretically a surgical approach in RA might reduce the risk of osteoporosis associated with the disease itself19 and the primary hyperparathyroidism,22 against this enthusiasm for parathyroidectomy must be weighed the possible increase in perioperative morbidity due to cervical spine involvement in RA. Accordingly, before a policy of routine neck exploration is embarked upon in these patients we suggest that further studies should be undertaken on the natural history of the disease in RA.

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