HYPERCALCEMIA IN ACTIVE PULMONARY TUBERCULOSIS
AND ITS OCCURRENCE IN RELATION TO THE RADIOGRAPHIC
EXTENT OF DISEASE

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Abstract. The prevalence of hypercalcemia in tuberculosis in Hong Kong and its occurrence in relation
to the radiographic extent of disease were studied in 57 patients with sputum smear (n = 44) and/or culture
positive (n = 13) pulmonary tuberculosis and in five patients with military tuberculosis prior to treatment.
Only one (1.6%) patient had a corrected plasma calcium level above the reference range for our laboratory.
There was a positive relationship between the corrected plasma calcium levels and the radiographic extent
of disease (r = 0.37), p < 0.01). As the occurrence of hypercalcemia in tuberculosis is known to be influ­
enced by the calcium intake, our finding of a low prevalence of "absolute" hypercalcemia in Hong Kong
could be related to the low dietary calcium intake in these subjects.

INTRODUCTION

Hypercalcemia has been known to be associated
with tuberculosis but the reported prevalence varies
widely (Abbasi et al, 1979; Chan et al, 1991; Davies
et al, 1987; Kitrou et al, 1983; Lind and Ljunghall
1990; Need et al, 1980; Shai et al, 1972; Sharma
that its occurrence is related to the intake of vita­
mim D (Abbasi et al, 1979; Shai et al, 1972; Sharma
1981) and calcium (Shai et al, 1972) in these patients.
It is not clear if the radiographic extent of disease
itself is an important determinant as studies so far
have yielded conflicting results (Chan et al, 1991;
Davies et al, 1987; Kitrou et al, 1983; Need et al,
1980).

In Hong Kong, tuberculosis was found to be an important cause of hypercalcemia in the hospital
population (Shek et al, 1990). However, in a recent survey conducted by our group, none of the
24 patients with active pulmonary tuberculosis had "absolute" hypercalcemia (Chan et al, 1991).
We have since extended this prospective study in
order to ascertain the prevalence of hypercalcemia in these patients and its occurrence in relation to
the radiographic extent of disease.

MATERIALS AND METHODS

Consecutive patients presented to the respiratory
physicians at the Prince of Wales Hospital, Shatin,
HYPERCALCEMIA IN PULMONARY TUBERCULOSIS

Table 1

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5/6</th>
<th>p value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=11)</td>
<td>(n=21)</td>
<td>(n=15)</td>
<td>(n=4)</td>
<td>(n=11)</td>
<td></td>
</tr>
<tr>
<td>M : F</td>
<td>8 : 3</td>
<td>15 : 6</td>
<td>9 : 6</td>
<td>4 : 0</td>
<td>9 : 2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.1±3.6</td>
<td>60.0±3.4</td>
<td>61.7±5.5</td>
<td>69.5±5.6</td>
<td>64.6±3.0</td>
</tr>
<tr>
<td>Plasma creatinine (μmol/l)</td>
<td>86.4±6.0</td>
<td>82.0±4.1</td>
<td>77.0±3.8</td>
<td>77.0±9.8</td>
<td>116.7±23.7b</td>
</tr>
<tr>
<td>Plasma albumin (g/l)</td>
<td>39.6±1.9</td>
<td>35.2±1.5*</td>
<td>32.9±1.8**</td>
<td>29.0±3.9*</td>
<td>30.5±2.0**</td>
</tr>
<tr>
<td>Plasma calcium (mmol/l)</td>
<td>2.29±0.04</td>
<td>2.19±0.04</td>
<td>2.14±0.04*</td>
<td>2.08±0.12</td>
<td>2.16±0.06</td>
</tr>
<tr>
<td>Plasma calcium (Adjusted) (mmol/l)</td>
<td>2.30±0.02</td>
<td>2.31±0.02</td>
<td>2.32±0.02</td>
<td>2.36±0.04</td>
<td>2.39±0.03*</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, when compared to patients with grade 1 disease.
* Only one patient had grade 6 disease.
* Including two patients with renal impairment.

These patients had acquired immune deficiency syndrome (AIDS).

Of the 62 patients studied, only one (1.6%) had plasma calcium level above the reference range of this laboratory (2.13 - 2.51 mmol/l). As can be seen in Table 1 and Fig 1, there was a trend for patients with more extensive disease to have a higher adjusted plasma calcium level (r = 0.37, p < 0.01). A negative correlation between the radiographic extent of disease and the plasma albumin level was observed (r = -0.40, p < 0.01).

DISCUSSION

In the present study, we have confirmed our earlier report that "absolute" hypercalcemia was uncommon among patients with active pulmonary tuberculosis in Hong Kong. In comparison, both cross-sectional (Ling and Ljunghall 1990) and longitudinal (Abbasi et al, 1979; Kitrou et al, 1983; Need et al, 1980; Sharma 1981) studies from other countries have generally reported a much higher prevalence of 15.5 to 48%.

One likely explanation for this observed difference in the prevalence of hypercalcemia is the low calcium intake in our patients (Chan et al, 1991). It has been demonstrated by others (Felsenfeld et al, 1986; Shai et al, 1972) that hypercalcemia in tuberculous patients occurs after the administration of vitamin D and/or calcium supplements, and disappears when these are removed from the diet. It therefore appears likely that a low dietary calcium
intake of 300 to 500 mg per day in Hong Kong (Pun et al, 1989) might help to prevent hypercalcaemia from occurring.

The mechanism for hypercalcaemia in tuberculosis is now thought to be extra-renal synthesis of 1,25(OH)₂D₃ (Felsenfeld et al, 1986; Gkonos et al, 1984; Peces and Alvares, 1987) resulting in increased gastrointestinal absorption of calcium. Recently, it has been shown that 1,25(OH)₂D₃ may be produced by inflammatory cells obtained by bronchoalveolar lavage in a patient with pulmonary tuberculosis (Cadranel et al, 1988). So it was anticipated that increased hydroxylation of 25(OH)₂D₃ by the granulomata would occur in the presence of more extensive disease and there would be a correlation between the plasma calcium levels and the extent of disease.

Like others (Kitrou et al, 1983; Need et al, 1980), we were able to demonstrate a positive relationship between the radiographic extent of disease and the adjusted plasma calcium levels. However, it should be pointed out that this apparent relationship between the two variables could merely reflect the limitations of the calcium adjustment formula used; the formula becomes increasingly unreliable as the deviation of plasma albumin from normal becomes greater. Therefore, measurements of ionized calcium and calcium regulating hormones (parathroid hormone and calcitriol) would be needed to determine whether or not the level of plasma calcium is related to disease severity.

A reduction in plasma albumin is a consistent finding in patients with tuberculosis (Chan et al, 1991; Davies et al, 1987; Kitrou et al, 1983). In the present study, it appeared to a better correlate with disease severity than plasma calcium level. It is likely to be a result of generalized debility caused by disease (Chan et al, 1991; Davies et al, 1987).

In summary, we confirmed the low prevalence of hypercalcaemia in patients with pulmonary tuberculosis in Hong Kong. It is likely that the low dietary calcium intakes in our patients have prevented hypercalcaemia from occurring. There was a positive although weak correlation between the plasma calcium levels and the radiographic extent of disease in these patients.

REFERENCES