

THE PREVALENCE OF HYPERCALCAEMIA IN PULMONARY AND MILIARY TUBERCULOSIS – A LONGITUDINAL STUDY

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ABSTRACT

We studied the prevalence of hypercalcaemia in 34 Chinese patients with pulmonary (n=32) or miliary (n=2) tuberculosis. None of these subjects were given vitamin D or calcium supplements. Plasma calcium levels were measured at presentation and at 1- to 2-monthly intervals after treatment. During the 6-month study period, two patients (6%) developed hypercalcaemia (plasma calcium greater than 2.51 mmol/l), as compared to figures of 16% to 28% in the United States and India. By correcting the plasma calcium to a normal albumin, five (15%) of our patients were hypercalcaemic, as compared to a figure of 48% in Greece. Apart from variations in methodology, discrepancies in the reported prevalence of hypercalcaemia in tuberculosis may be due to differences in sun exposure, and vitamin D and calcium intake.

Keywords: hypercalcaemia, tuberculosis, calcium intake

SINGAPORE MED J 1994; Vol 35: 613-615

INTRODUCTION

Hypercalcaemia may occur in active pulmonary tuberculosis (TB), but the exact prevalence is not known. Longitudinal studies from the United States⁽¹⁾ and India⁽²⁾ suggested that 16% to 48% of TB patients may develop hypercalcaemia. Similar study from Greece⁽³⁾ reported a figure of 48% by correcting the serum calcium to a normal albumin. However, patients from the earlier studies^(1,2) were also given vitamin D supplements, both of which might increase the risk of hypercalcaemia. In contrast, hypercalcaemia is relatively uncommon amongst TB patients in the UK^(4,5), Hong Kong^(6,7) and Nigeria⁽⁸⁾.

Since the occurrence of hypercalcaemia in TB is in part related to the dietary calcium intake^(6,7,9), it will be of great interests to study its prevalence amongst Chinese patients living in Hong Kong in whom the average intake is below 500 mg per day⁽¹⁰⁾.

SUBJECTS AND METHODS

Consecutive Chinese patients who presented to the respiratory physicians at the Prince of Wales Hospital, Shatin, Hong Kong from August 1991 to September 1992 with sputum smear (n=17) and/or culture (n=15) positive pulmonary TB or miliary TB (n=2) were included in the study. None of these patients received

calcium and vitamin D supplements either before or during chemotherapy. None of these patients had acquired immune deficiency syndrome (AIDS). One patient with concurrent hypoparathyroidism requiring calcitriol was excluded.

At entry, before treatment commenced, a chest radiograph was taken for the assessment of the extent of disease which was graded 1 to 6 according to the number of one-sixths of the lung field affected⁽¹¹⁾. Blood was sent before and one, two, four and six months after treatment for measurements of calcium, albumin and creatinine. Standard treatment for these patients was with isoniazid, rifampicin given daily for 6 months together with pyrazinamide in the first two months.

Plasma calcium, albumin and creatinine were measured in a multi-channel analyser. Plasma calcium was corrected for a change in albumin concentration using the formula of Payne et al⁽¹²⁾.

All the data are expressed as mean \pm SD. The effect of treatment on plasma albumin and calcium concentrations was assessed by Student's paired t test. Correlation coefficients between variables were determined by simple regression analysis.

RESULTS

There were 19 men and 15 women with a mean \pm SD age of 61.4 \pm 18.4 years (range 16 to 82 years). The radiographic extent of disease in these patients was grade 1 in 9, grade 2 in 11, grade 3 in 4, grade 5 in 3 and grade 6 in 5. Before treatment, there was a significant relationship between the extent of disease and the albumin adjusted plasma calcium ($r=0.41$, $p<0.02$) and plasma albumin ($r=-0.62$, $p<0.001$) levels.

The effect of treatment on plasma calcium and albumin adjusted plasma calcium levels is shown in Fig 1. After six months of treatment, there was a significant increase in plasma calcium (2.23 ± 0.14 to 2.30 ± 0.09 mmol/l, $p<0.02$) and albumin (37.4 ± 6.0 to 41.4 ± 4.2 g/l, $p<0.001$) concentrations. However, albumin adjusted plasma calcium levels did not change (2.29 ± 0.19 vs 2.27 ± 0.11 mmol/l, $p>0.5$).

Of the 34 patients included in this study, two had plasma calcium (five had albumin adjusted plasma calcium) levels above the reference range of this laboratory (2.13 – 2.51 mmol/l) either before or during anti-TB chemotherapy (Fig 2). Subject 1 with a history of systemic lupus erythematosus and lupus nephritis developed miliary TB and symptomatic hypercalcaemia (albumin adjusted plasma calcium level 3.01 mmol/l)⁽¹³⁾. He was treated with a course of prednisolone, intra-nasal calcitonin and anti-

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TB chemotherapy. His plasma calcium and renal function returned to normal three weeks later. Subject 2 with grade 5 disease was mildly hypercalcaemic before and during anti-TB chemotherapy with albumin adjusted plasma calcium levels of 2.71 to 2.78 mmol/l. Subjects 3, 4 and 5 with grades 3, 6 and 3 disease and albumin adjusted plasma calcium of 2.59, 2.53 and 2.61 mmol/l respectively developed transient hypercalcaemia either before (subject 3) or during treatment (subjects 4 and 5). All 34 patients completely recovered after a full course of anti-TB chemotherapy.

Fig 1 – Plasma calcium and albumin adjusted plasma calcium levels in 34 Chinese patients with tuberculosis. Both individual values and means (—) are shown.

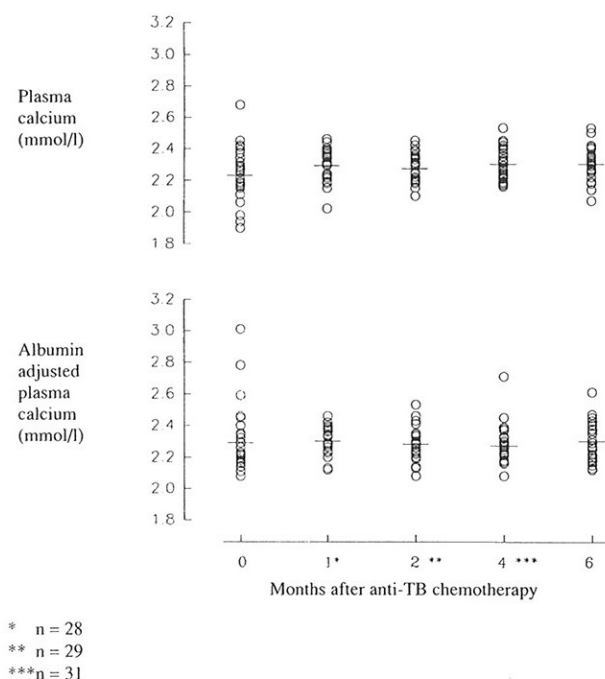
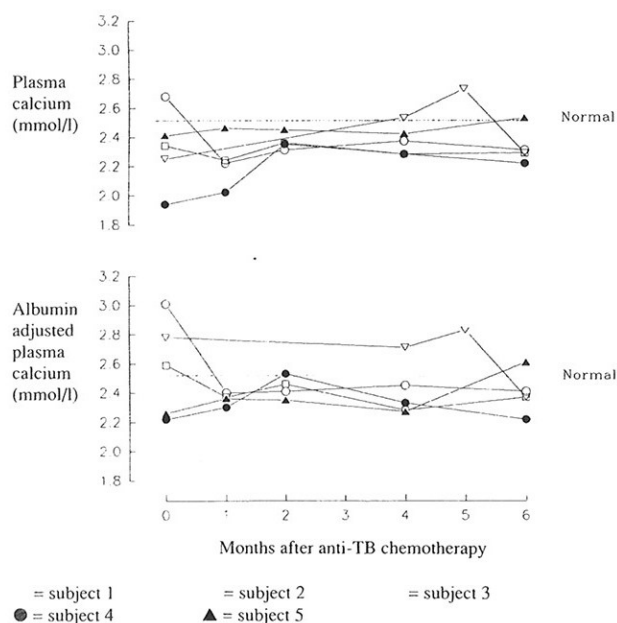


Fig 2 – Two tuberculous patients with plasma calcium (five with albumin adjusted plasma calcium) levels transiently greater than 2.51 mmol/l.



DISCUSSION

We confirmed our earlier reports^(6,7) that hypercalcaemia was relatively uncommon in patients with active pulmonary TB in Hong Kong. In the present study, two patients (6%) had plasma calcium levels above the reference range, as compared to a prevalence rate of 16% to 28% in the United States⁽¹⁾ and India⁽²⁾. By correcting the plasma calcium to a normal albumin, five (15%) of our patients were hypercalcaemic, as compared to a figure of 48% in Greece⁽³⁾. However, it should be pointed out that the prevalence of hypercalcaemia is expected to be higher if plasma calcium was checked at shorter intervals^(1,3) and, as in the present study, patients were followed up for periods longer than two months^(1,2). The criteria for the diagnosis of hypercalcaemia also differed amongst previous studies (serum calcium > 2.60 mmol/l in the study of Abbasi et al, serum calcium > 2.63 mmol/l in Sharma's study, albumin adjusted serum calcium > 2.75 mmol/l in the study of Kitrou et al).

Extra-renal production of 1,25 (OH)₂D, the metabolically active form of vitamin D, is now believed to play a key role in producing hypercalcaemia in TB. High circulating levels of 1,25 (OH)₂D were reported in anephric patients with TB⁽¹⁴⁻¹⁶⁾, and increased serum levels of 1,25 (OH)₂D have been shown in some patients with TB and hypercalcaemia⁽¹⁴⁻¹⁶⁾. It has been shown that 1,25 (OH)₂D may be produced by cells including cultured alveolar macrophages obtained by bronchoalveolar lavage from a patient with pulmonary TB⁽¹⁷⁾.

Available evidence indicates that the occurrence of hypercalcaemia in TB patients may be related to the intake of vitamin D and calcium, the extent of disease, the amount of sun exposure, the circulating levels of vitamin D and the presence of impaired renal function⁽¹⁸⁾. The vitamin D intake was greater in hypercalcaemic patients than the normocalcaemic group, and there was a positive correlation between vitamin D intake and the degree and duration of hypercalcaemia^(1,2). In patients with hypercalcaemia, the serum calcium returned to normal only when vitamin D and calcium supplements were removed from the diet and the underlying TB was treated^(1,2,9). The importance of calcium intake is also supported by the observation that hypercalcaemia is less common in populations in whom the average calcium intake is below 500 mg per day^(6,7). The fact that hypercalcaemia is less commonly reported in countries located in cold or temperate climate suggests that the amount of sun exposure and the circulating levels of vitamin D may be of importance^(4,5,19). The presence of an abnormal substrate-product relationship between 25 (OH)D and 1,25(OH)₂D in TB suggests that serum 1,25(OH)₂D will be raised if its substrate, 25(OH)D, is plentiful^(7,20). There was a positive relationship between the radiographic extent of disease and the plasma calcium⁽⁶⁾ and the occurrence of hypercalcaemia^(3,21). Those with impaired renal function, which results in decreased renal excretion of calcium during hypercalcaemic states, may be more prone to severe hypercalcaemia^(13,22). Apart from variation in methodology, these various factors may explain the difference in the reported prevalence of hypercalcaemia from different countries.

In agreement with previous reports⁽¹⁻³⁾, hypercalcaemia in TB may occur several months after anti-TB chemotherapy was given (subjects 4 and 5). This finding suggests that the occurrence of hypercalcaemia in TB is not related to the presence of acid-fast bacilli (AFB) in the sputum. It is possible that the extra-renal production of 1,25(OH)₂D is related to the severity of immune and inflammatory response, rather than the number of AFB⁽¹⁶⁾. It will be of great interest to study the relationship between the plasma levels of calcium and 1,25(OH)₂D and some markers of disease and T lymphocyte activities such as serum soluble interleukin-2 receptor⁽²³⁾.

Apart from the disease itself, anti-TB chemotherapy may affect the plasma calcium levels in these patients. Isoniazid and rifampicin, which are essential first-line drugs, may decrease the circulating levels of $1,25(\text{OH})_2\text{D}^{(24)}$ and their use may increase the risk of osteomalacia^(5,19) particularly in patients with dark skin and those with reduced exposure to sunlight.

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