Hypercalcaemia in Greek patients with tuberculosis before the initiation of anti-tuberculosis treatment

A. ROUSSOS*, I. LAGOGIANNI*, A. GONIS†, I. ILIAS*, D. KAZI†, D. PATSOPOULOS* AND N. PHILIPPOU*

*Department of Pulmonary Medicine and †Biochemical Laboratory, Sotiria Chest Diseases Hospital, Athens, Greece

Hypercalcaemia has been known to occur in association with granulomatous diseases. The aim of this study was to ascertain the incidence of hypercalcaemia and determine the prevalence of symptoms associated with it in Greek patients with newly-diagnosed tuberculosis (TB), before the initiation of anti-tuberculosis treatment. We prospectively evaluated all patients with newly-diagnosed TB presenting, either as inpatients or as outpatients, to our hospital, during a 3-year period. We evaluated 88 patients with TB (50 males and 38 females), aged between 23 and 89 years (mean age ± SD: 46 ± 19 years), and 65 age- and sex-matched controls with chronic obstructive pulmonary disease (36 males and 29 females), aged between 28 and 88 years (mean age ± SD: 47 ± 18 years).

Among TB patients, 56 had pulmonary TB, 20 had pleural TB without evidence of pulmonary parenchyma involvement, eight had pulmonary and pleural TB, and four had disseminated disease.

The mean (± SD) albumin–adjusted serum calcium concentration and the mean ionized calcium concentration were significantly higher in the TB group (2.49 ± 0.21 mmol l⁻¹ and 1.27 ± 0.02 mmol l⁻¹ respectively) than in the control group (2.36 ± 0.11 mmol l⁻¹ and 1.19 ± 0.02 mmol l⁻¹, P < 0.05). In the TB group no correlation between type of disease and albumin-adjusted or ionized calcium concentration was seen. Hypercalcaemia was detected in 22 patients with TB (25%) but only three showed symptoms associated with it. We conclude that, although hypercalcaemia is a common laboratory finding among Greek patients with TB before anti-TB chemotherapy, it is usually asymptomatic.

Key words: hypercalcaemia; ionized calcium; tuberculosis.

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Introduction

Many diseases involving granulomatous processes can result in abnormalities of calcium metabolism. Sarcoidosis is the most common granulomatous disease causing hypercalcaemia. Tuberculosis (TB), disseminated coccidiomycosis and histoplasmosis have also been reported to be associated with hypercalcaemia (1).

The incidence of hypercalcaemia in TB patients varies widely between countries. The main reasons are the differences in the vitamin D and calcium intake and the different amount of sun exposure. Another important reason is the various laboratory criteria for the definition of hypercalcaemia. It is known that a component of total serum calcium is complexed with either albumin (40%) or globulins (8%); however, only the free or ionized calcium is the physiologically relevant portion of this mineral ion (2). If the serum calcium is reduced, as often occurs with the anorexia and catabolic wasting that accompany TB, then total serum calcium may be normal, although ionized hypercalcaemia and its resultant symptoms are present. It is, therefore, essential to correct the serum calcium for the serum albumin concentration or, ideally, to measure serum ionized calcium (3). Studies from India and the U.S.A that did not use correction for patients with hypoalbuminaemia indicated that 16–28% of TB patients may develop hypercalcaemia (4,5). In contrast, studies using the albumin-adjusted serum calcium concentration have reported higher prevalence rates (6,7). As far as we know, the serum ionized calcium concentration has not been used yet for the recognition of hypercalcaemia in TB patients.

In Greece, a previous study on TB patients during the treatment period showed that hypercalcaemia is common,
with an incidence of 48% (8,9). The aim of the present study, which used both the albumin-adjusted and the serum-ionized calcium concentration, was to ascertain the incidence of hypercalcaemia and to determine the prevalence of symptoms associated with it in Greek patients with newly-diagnosed TB, before anti-TB therapy.

Methods

The present study was conducted at the Ninth Department of Pulmonary Medicine, in ‘Sotiria’ Chest Diseases Hospital (Athens, Greece). Following a predefined protocol, between 1 March, 1997 and 31 March, 2000 we prospectively studied 88 consecutive patients with newly-diagnosed TB. Only patients with a proven bacteriologically and/or histologically diagnosis were included in the study.

The diagnosis of TB was based on one or more of the following criteria in the relevant tissue or specimen: (1) positive smear of acid-fast bacilli, (2) positive culture for Mycobacterium tuberculosis and (3) presence of necrotic caseous granulomas in biopsy. Patients with known calcium metabolism disorders, such as primary and metastatic neoplastic disease, primary hyperparathyroidism, milk alkali syndrome, adrenal insufficiency, hyperthyroidism and patients receiving steroids or vitamin D supplements were excluded from the analysis. Moreover, hypercalcaemic patients had undergone thorough investigation to exclude other causes of hypercalcaemia. Our control subjects included 65 age- and sex-matched patients with chronic obstructive pulmonary disease (COPD) hospitalized during the study period. Those with co-existing disorders known to affect calcium metabolism were not included.

In both study and control groups, venous blood was drawn with minimal venostasis after overnight fasting for the measurement of serum calcium, phosphorus, alkaline phosphatase, BUN, total protein and albumin by a multi-channel automated analyser. To allow for protein binding of calcium, we assumed that 0·025 mmol l\(^{-1}\) of calcium is bound per gram of albumin. Thus, the measured total serum calcium concentration was corrected for serum albumin levels by adding of subtracting 0·025 mmol l\(^{-1}\) of calcium for each 1 g dl\(^{-1}\) of serum albumin short or in excess of 4 g dl\(^{-1}\), respectively. Hypercalcaemia was defined as an albumin-adjusted serum calcium level greater than 2·62 mmol l\(^{-1}\). Furthermore, we measured ionized calcium concentration in arterial blood sample collected into heparinized (20–30 IU ml\(^{-1}\)) glass capillary tubes. Ionized calcium was measured simultaneously at 37°C with a semiautomated ICA1™ analyser. Hypercalcaemia was considered present if the ionized calcium concentration was above the normal range of 1·13–1·32 mmol l\(^{-1}\).

Results are expressed as mean ± 1 standard deviation (sd). Significance of difference between groups was assessed by an unpaired Student’s t-test for continuous variables and \(\chi^2\) test for proportions. Correlation coefficients between variables were determined by simple regression analysis. The Newman–Keuls multiple comparisons test was used to determine whether the type of TB had any effect on serum calcium concentration.

Results

During the study period TB was diagnosed and confirmed in 88 patients aged 46·4 ± 19 years. Fifty were men aged 45·8 ± 18·3 years and 38 were women aged 46·9 ± 19·3 years (male:female ratio 1:3). Table 1 summarizes the distribution of the types of TB and the number of patients with each type. Our control subjects included 65 age- and sex-matched patients with COPD (36 men aged 48·9 ± 17·2 years and 29 women aged 46·4 ± 17·9 years).

The mean serum albumin level among TB patients was 3·1 ± 0·6 g dl\(^{-1}\). Hypoalbuminaemia (serum albumin level <3·5 g dl\(^{-1}\)) was present in 44 patients (50%) at diagnosis, before commencement of anti-TB chemotherapy. The mean albumin-adjusted serum calcium concentration before treatment was 2·49 ± 0·21 mmol l\(^{-1}\) (range: 2·16–3·69 mmol l\(^{-1}\)). The mean ionized calcium concentration in arterial blood was 1·27 ± 0·02 mmol l\(^{-1}\) (range: 1·14–1·41 mmol l\(^{-1}\)). Pretreatment hypercalcaemia was present in 22 patients (25%). In all cases of hypercalcaemia, both albumin-adjusted and ionized calcium concentrations were above the normal range. Age and sex had no effect on the calcium levels.

The mean serum albumin level in the controls was significantly higher than that of the TB patients (3·9 ± 0·5 g dl\(^{-1}\), \(P<0·01\)) while their albumin-adjusted calcium concentration (2·36 ± 0·11 mmol l\(^{-1}\)) and ionized calcium concentration (1·19 ± 0·02 mmol l\(^{-1}\)) were significantly lower (\(P<0·01\) in both cases, Table 2). None of the control patients had hypercalcaemia. The types of TB and the serum calcium levels are also shown in Table 2. The differences in the serum albumin-adjusted calcium concentration among the various types of TB were not statistically significant.

Of the 22 hypercalcaemic TB patients only two (9%) had symptoms associated with high calcium concentration. The first was a 48-year-old man with pulmonary TB who had polyurea, polydypsia and constipation. The albumin-adjusted serum calcium concentration and the ionized calcium concentration were 2·74 mmol l\(^{-1}\) and 1·37 mmol l\(^{-1}\), respectively. As soon as he received fluid hydration, the serum calcium levels came down and the previous symptoms disappeared. The second patient was a 52-year-old woman with disseminated disease, but without

<table>
<thead>
<tr>
<th>Types</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>56</td>
</tr>
<tr>
<td>Pulmonary and tuberculous pleurisy</td>
<td>8</td>
</tr>
<tr>
<td>Pleural without pulmonary involvement</td>
<td>20</td>
</tr>
<tr>
<td>Disseminated</td>
<td>4</td>
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<td>Total</td>
<td>88</td>
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clinical or laboratory evidence of bone involvement, who experienced exactly the same symptoms. The albumin-adjusted serum concentration and the ionized calcium concentration were 2.78 mmol/l and 1.39 mmol/l, respectively. The patient needed a short course of systemic corticosteroids to bring down the serum calcium levels but recovery was complete.

**Discussion**

Hypercalcaemia is one of the most common metabolic emergencies, occurring in approximately 0.5% of hospitalized patients. Malignancy is the most common cause of hypercalcaemia, but other diseases, including acute hyperparathyroidism, sarcoidosis and tuberculosis may be heralded by high calcium concentration (10,11).

In this prospective study we found that hypercalcaemia is a common laboratory abnormality among Greek patients with newly-diagnosed TB, before the initiation of antituberculosis chemotherapy. The presence of hypercalcaemia in 25% of our patients is higher than that found in Hong Kong (15%) and in India (16%) (4,12). It is comparable to the incidence rate of 27-5% in Malaysia, but significantly lower than that reported is Australia (51%) (6,7). This is the first study of calcium concentration among Greek TB patients before the commencement of treatment. A previous study during the treatment period showed high rates of hypercalcaemia (48%) (8).

We have also reported that symptoms associated with hypercalcaemia are rare among hypercalcaemic TB patients. The results of our study are consistent with the conclusion of others who have examined the prevalence of symptomatic hypercalcaemia in patients with newly-diagnosed TB. In the largest series (n=318), Chan reported that only two patients with abnormal serum calcium concentration had symptoms related to it (13). Although hypercalcaemia among TB patients is generally mild and asymptomatic it can be severe, as seen in some of our patients and reported by others. Numerous case reports have documented that symptomatic hypercalcaemia can occur in patients with tuberculosis during the active phase of the disease (14–18).

Another common observation in patients with active TB is the low albumin concentration (19,20). Hypoalbuminaemia was present in about two-thirds of our patients at the time of diagnosis. It could have been related to the malnutrition that accompanies TB and hypoalbuminaemia may mask hypercalcaemia. It is known that if the serum albumin is reduced then total serum calcium may be normal even though ionized hypercalcaemia is present. However, in our study, the measurement of both albumin-adjusted and ionized calcium ensures the accurate evaluation of serum calcium abnormalities.

Although hypercalcaemia has been known to be associated with TB since 1972, the exact pathophysiological mechanism remains unclear (21). Involvement of the bone is a possible cause of high calcium concentration (22). Tuberculosis of bone as a cause of hypercalcaemia in one patient is unlikely because clinical and laboratory evidence of bone disease were absent.

Parathyroid hormone (PTH), in association with vitamin D, is the principal regulator of serum calcium concentration. PTH increases delivery of calcium from the skeleton to the extracellular fluid. Additionally, it acts on the kidney to increase tubular reabsorption of calcium and stimulates the renal 1-α-hydroxylase enzyme which is responsible for the 1-α hydroxylation of 25-hydroxycholecalciferol [25(OH)D₃] to 1,25-dihydroxycholecalciferol [1,25(OH)₂D₃]. The active form of vitamin D [1,25 (OH)₂D₃] increases the fractional absorption of calcium from the gut (24).

Overproduction of 1,25(OH)D₃ has been described in sarcoidosis and other granulomatours diseases (25,26). T- lymphocytes (possibly CD8⁺ T-lymphocytes), and alveolar macrophages obtained by bronchoalveolar lavage from patients with pulmonary TB have been shown to produce 1,25(OH)₂D₃. This compound is produced by T-cells plays a critical role in the immune response against mycobacteria as it is an important component of cell-mediated immunity to TB (27,28). The produced vitamin D has only a local effect in enhancing macrophages to kill mycobacteria and does not normally affect calcium metabolism. However, if large quantities of 1,25(OH)₂D₃ are produced, the subsequent ‘overspill’ into the circulation results in hypercalcaemia (29).

A question remains as to why all TB patients do not present with high calcium concentration. The differences in calcium intake could be a first explanation. Another reason lies in the availability of the substrate 25(OH)D₃, which is synthesized from 7-dehydrocholesterol in the skin. Ultraviolet light is essential for this reaction. In tropical climates, where the amount of sun exposure is high, the concentration of 25(OH)D₃ is increased (30). In TB patients, circulating 25(OH)D₃ is used from both kidney and macrophages for the production of the active vitamin D. The result is high incidence of hypercalcaemia among TB patients in countries with abundant sunshine throughout the year, such as Malaysia and Australia (6,7). The relative low amount of sun exposure seems to be the cause of low incidence of hypercalcaemia in TB patients in the U.K. In
Greece, sunlight is plentiful and this may explain the high percentage of hypercalcaemia in our study population.

References