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Serum Calcium Levels in Newly-diagnosed Patients with Tuberculosis in Hamedan (West of Iran)

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Abstract: To investigate the incidence of hypercalcemia in TB patients and to assess its relationship with TB, a study was conducted in Infectious Diseases Division of Sina Hospital in Hamedan province (west of Iran). During an 18-month period, 65 patients with newly-diagnosed TB (30 males and 35 females), were prospectively evaluated who aged between 15 and 84 years (mean 53.3 years). Age- and sex-matched subjects (82) with chronic obstructive pulmonary disease (27 males and 55 females), aged between 16 and 85 (mean 53.5 years) was selected as a control group. Serum calcium, phosphorus, total protein, albumin and alkaline phosphatase were measured in all subjects. No significant difference was found between the mean albumin-adjusted calcium levels in the TB group (8.79±1.53 mg dL^{-1}) and the control group (8.57±1.12 mg dL^{-1}). Hypercalcemia was found in 11 (16.9 %) of TB patients and 6 (7.3 %) of controls ($\chi^2 = 3.27$, $p = 0.07$, non significant). This study revealed that there is non significant difference association between hypercalcemia and tuberculosis.

Key words: Calcium metabolism disorders, hypercalcemia, tuberculosis

INTRODUCTION

Hypercalcemia has been known to occur in the most granulomatous disorders. Sarcoidosis is the most common granulomatous disease causing hypercalcemia. Tubrculosis (TB) and fungal granulomas are other conditions that are associated with disorders of calcium metabolism. These abnormalities of calcium metabolism are due to dysregulated production of $1,25(OH)_2D_3$ (calcitriol) by activated macrophages trapped in pulmonary alveoli and granulomatous inflammations[1,2]. Calcium metabolism disorders in TB do not always correlate with the serum levels of calcitriol. In some patients, raised serum calcium levels were observed during the early phase of the disease and the peak of calcitriol was seen as many as 9 month later, when the patients was clinically well[3]. Furthermore, corticosteroids added to anti-TB regimen reduce the level of calcium and the concentration of calcitriol[1]. On the other hand, it is known that approximately 40% of total serum calcium is complexed with albumin; however, only the free calcium is the physiologically relevant portion of this mineralion[4]. It is, therefore, essential for the measurement of serum calcium to take the specimen (blood sample) before the initiation of anti-TB treatment and to correct the serum calcium for the serum albumin concentration.
While, some studies from Malaysia and Australia using the albumin-adjusted serum calcium concentration have indicated that up to 51% of TB patients may develop hypercalcemia[5,6], others have reported significantly lower rates[7,8].

Because of the regional variation in the frequency of hypercalcemia in TB, we aimed to ascertain the occurrence of hypercalcemia in an Iranian population with newly diagnosed active TB before the initiation of anti-TB treatment.

MATERIALS AND METHODS

The study was performed at the Sina Hospital (Hamedan, Iran). We prospectively studied 65 consecutively diagnosed TB patients who referred to the Outpatient Department or the Infectious Diseases Unit of the hospital during an 18-month period, between April, 2003 and September, 2004. The diagnosis of TB was based on one of the following criteria in the relevant tissue or specimen: (i) Positive smear of acid-fast bacilli, (ii) Positive culture for *Mycobacterium tuberculosis* and (iii) Presence of necrotic caseous granulomas in biopsy. We also selected 82 age and sex matched patients with Chronic Obstructive Pulmonary Disease (COPD) hospitalized during the study period.

All subjects were evaluated for co-existing calcium metabolism disorders and those with known malignancy, primary hyperparathyroidism, hyperthyroidism, adrenal insufficiency and patients receiving steroids or vitamin D

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were excluded from the analysis. Furthermore, the hypercalcemia patients were thoroughly investigated to exclude other causes of hypercalcemia.

In both groups, fasting venous blood was collected for the measurement of serum calcium, phosphorus, alkaline phosphatase, total protein and albumin using an autoanalyser (Hitachi 704, Japan).

To allow for protein binding of calcium we corrected the plasma calcium concentrations for hypoalbuminemia (according to the formula) using an average correction factor[9]:

$$\text{Corrected Total Ca (mg L}^{-1}) = \text{Total Ca (mg L}^{-1}) + 0.8\ (4\text{-Alb[g dL}^{-1}])$$

Hypercalcemia was defined as an albumin-adjusted serum calcium level greater than 10.5 mg dL^{-1} (the normal range: 8-10.5 mg dL^{-1}).

Statistical Analysis was performed using the student's t-test and chi-square test and a $p \leq 0.05$ was denoted as statistically significant.

RESULTS

Sixty-five patients with TB were enrolled during the study period. They included 30 men (46.1%) and 35 women (53.9%), aged between 15 to 84 years. Forty two subjects (64.6%) from TB patients had pulmonary and twenty-three subjects (35.4%) had extra-pulmonary TB. The controls included 82 age and gender matched patients (27 male, 29 female) with COPD, aged between 16 to 85 years. There was not any significant difference in demographic characteristics of TB patients and control subjects and also between two types of TB patients (Table 1).

The difference in the serum albumin-adjusted calcium concentration among the TB patients (8.79±1.53) and controls (8.57±1.12) were not statistically significant. Age and sex had no effect on the mean±SD calcium levels. Also, there was not any significant difference between serum calcium levels among two types of TB (Table 2). Similarly, no significant difference was found between the mean±SD serum albumin, phosphorus and alkaline phosphatase concentration of TB patients and controls. Hypercalcemia was found in 11 TB patients (16.9%) and 6 control subjects (7.3%) (χ^2 = 3.27, no significant difference). 17(26.8%) of TB patients and 25(30.5%) of controls were hypocalcemic (χ^2 = 0.33, not significant). None of the patients in both groups had clinical evidence of hypercalcemia or hypocalcemia.

DISCUSSION

Hypercalcemia has been known to be associated with tuberculosis. In some studies it has been reported to occur commonly. It seems that the most studies in which TB was complicated by hypercalcemia were retrospective and therefore the other causes of hypercalcemia could not be excluded. Liam *et al.*[5] in an uncontrolled study have reported the high incidence rate of hypercalcemia (27%) in TB patients in Malaysia. Also a retrospective study from Kuwait indicated the incidence rate of 25.7% in patients with smear-positive pulmonary TB[10].

In the present prospective study, the incidence of hypercalcemia was not significantly different in Iranian patients with TB and controls. Moreover, there was no association between hypercalcemia and types of TB.

Whereas some prospective, controlled studies using the albumin-adjusted serum calcium concentration have

Table 1: Demographic characteristics of patients with tuberculosis and control subjects

	Tuberculosis			
	Pulmonary (n = 42)	Extra-pulmonary (n = 23)	Total (n = 65)	Controls (n = 82)
Gender: n (%)				
Male	20(47.6)	10(43.5)	30(46.1)	27(32.9)
Female	22(52.4)	13(36.5)	35(53.9)	55(67.1)
Age:				
mean (range) year	56.6 (15-84)	48.9(15-74)	53.3(15-84)	53.5(16-85)
Residence: (%)				
Urban	64.3	43.5	61.5	63.5
Rural	35.7	56.5	38.5	36.5

Table 2: Serum albumin, calcium and albumin-adjusted calcium levels in tuberculosis patients and controls

	Tuberculosis			
	Pulmonary (n = 42)	Extra-pulmonary (n = 23)	Total (n = 65)	Controls (n = 82)
Albumin (g dL^{-1})	3.97±0.76	4.32±0.72	4.11±0.77	4.31±0.71
Calcium(g dL^{-1})	8.77±1.44	8.87±1.56	8.8±1.53	8.82±1.12
Albumin-adjusted Calcium (g dL^{-1})	8.80±1.30	8.87±1.58	8.79±1.53	8.57±1.12

reported significantly high incidence rates (25% in Greece[11], 27.5% in Malaysia[5]), others have reported the very low incidence (Tennessee[7], Turkey[12], Nigeria[13]).

On the other hand, the highest incidence rate of hypercalcemia has been reported in dialysis patients with TB. In a recent study in Taiwan, hypercalcemia was detected in about 46% of TB patients with end-stage renal disease[14]. Other investigators have reported the incidence rate of 63% in dialysis patients with TB peritonitis[15]. Sever hypercalcemia has been reported in a patient with chronic renal failure and disseminated TB[16]. We believe that the higher rates of hypercalcemia in dialysis patients with chronic renal failure may be are mainly due to secondary hyperparathyroidism or higher calcium intake[17]. However, other possibilities require further investigation.

Although the mechanism of hypercalcemia in TB has been shown to be due to spontaneous production and abnormal regulation of the vitamin D metabolite by alveolar macrophages and granulomatous tissues, some questions remain as to why all TB patients do not present with hypercalcemia and why the frequency of hypercalcemia in TB patients varies widely between countries. One explanation could be the differences in calcium intake. For example, the low incidence of hypercalcemia reported from Hong Kong could be related to the low dietary calcium intake in this papulation[18].

Another reason may be the differences in vitamin D status related to the amount of sun exposure and the availability of ultraviolet light for vitamin D synthesis in the skin. In tropical climates, where the amount of sun exposure is high, the concentration of 25 $(OH)D_3$ is increased[19]. In TB patients, circulating 25 $(OH)D_3$ is used from both kindly and macrophages for the production of the active vitamin D. The result is high incidence of hypercalcemia among TB patients in countries with abundant sunshine throughout the year, such as Malaysia and Kuwait[5,10]. The relative low amount of sun exposure seems to be the cause of low incidence of hypercalcemia in TB patients in the UK[18]. In this study the relatively high percentage of hypercalcemia (16.9%) in TB patients may be related to high calcium intake in our population.

We concluded that, apart from variations in methodology, discrepancies in the reported incidence of hypercalcemia in TB is probably multifactorial, and may be due to differences in sun exposure, circulating vitamin D levels and calcium intakes in various papulation. The present study suggests that TB itself appears not to be responsible for hypercalcemia.

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