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Serum calcium levels in patients with active pulmonary tuberculosis

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Summary

One hundred and two consecutively diagnosed pulmonary tuberculosis patients were recruited and followed up to ascertain the occurrence of hypercalcaemia before and during treatment with the modified short course antituberculosis therapy. Forty-five patients had hypocalcaemia at presentation, four of whom had hypoalbuminaemia. All those with hypocalcaemia had moderate to extensive radiographic disease on enrolment with BMI of less than 20. On commencement of treatment with the modified short course therapy, two of those with extensive cavitary radiographic disease developed transient asymptomatic hypercalcaemia. Although the hypoalbuminaemia and the hypocalcaemia seem to be related to the extent of radiographic disease and the poor nutritional status of the patients at presentation, no specific cause for the transient hypercalcaemia was found.

Résumé

Cent deux patients, consecutivement diagnostiqué de tuberculose pulmonaire, ont été recrutés et suivent jusqua la certitude de la presence de l'hypercalcemie, avant et pendant le traitement, par la modification de la therapy antituberculeux. Quarante cinq patients ont présenté une hypocalcemie a leur arrivée, parmis lesquels quatre avaient une hypoalbunaemie. Tout ceux qui avaient l'hypocalcemie, ont eu une maladie radioactive moderé à extensive, à leur enrolment avec une BMI de moins de 20. Au debut du traitement par la modific ation du court modele therapeutique, deux des patients qui ont présenté une maladie radiographique cavitaire extensive, ont développé une hypercalcemie assymptomatique passagère. Quoique l'hypoalbuminaemie et l'hypercalcemie semblent être lies au degrée de maladie radiographizue, et du mauvais status nutritionel des patients a leur premiere presentation, aucune cause specifique de l'hypercalcemie passagère n'a été trouvés.

Introduction

The occurrence of hypercalcaemia in some granulomatous disease has been reported by various workers [1-4]. Allthough earlier studies of serum calcium in pulmonary tuberculosis found a high incidence of hypocalcaemia, more recent studies in patients with active pulmonary tuberculosis however reported high incidence of hypercalcaemia in these patients (5-11]. This was mostly attributed by some workers to be due to supplemental vitamin D added to the antituberculosis therapy [5-7). Other workers however, attribute these findings to severity of the disease on chest radiograph [9] and extra-renal synthesis of 1,25 dihydroxy cholecalciferol [12,13] while no attributable factor has been found by other workers [10].

We studied a cohort of newly diagnosed pulmonary tuberculosis patients to ascertain the occurrence or otherwise of hypercalcaemia in this group.

Methods

One hundred and ten male and female consecutively diagnosed pulmonary tuberculosis patients (sputum smear (Ziel-Neelson method), with or without radiographic findings suggestive of tuberculosis, seen at the Jericho Government Chest Hospital, Ibadan, were enrolled into the study. Uncooperative patients, those with history of renal disease, poor clinical state necessitating additional life support, extra-pulmonary tuberculosis, previous or present clinical or laboratory evidence of other granulomatous diseases, default from treatment for more than four weeks, pregnancy or history of previous antituberculosis therapy or drug reaction to any antituberculosis drug excluded the patient from the study.

Verbal consent was obtained from each of the enrolled patients after due explanation of the aims and nature of the study. Pre-treatment early morning sputum sample smear for tubercle bacilli, chest X-ray (postero-anterior) and venous blood sample for serum albumin and calcium were obtained from each patient. Venous blood samples were obtained on a monthly basis and chest radiograph taken again after six months of treatment.

They were all started on anti-tuberculosis therapy with an initial four drug-regimen: Streptomycin (alternate day intramuscular injection), daily oral isoniazid, rifampicin and pyrazinamide for two months followed by six months daily isoniazid and thiacetazone therapy (modified short course therapy).

The results were analyzed using simple frequency tables, chi-square test and probability values. A P-value < 0.05 was considered as significant.

Serum calcium was corrected for hypoalbuminaemia using the following formular [15]:

Adjusted calcium = total calcium - (0.91972 x albumin) + 3.7042.

Results

Six patients defaulted, one died and another developed Steven Johnson syndrome. One hundred and two patients completed the study (59 males and 43 females) aged between 16 and 80 years.

Hypocalcaemia was noted in 45 (44.1%) patients four of whom also had hypoalbuminaemia. None of the 102 patients had hypercalcaemia before commencement of therapy (Table 1).

Table 1: Summary of serum calcium and albumin values in 102 patients with PTB during the first six months of therapy

Value	No of patients in months				Range for the values within 6 months
	0	2	4	6	
Calcium *					
< 9mg%+	45	16	1	-	(7.8 -
> 11mg%	-	2	-	-	12.5mg%)
Albumin *					
< 2.5mg%	4	-	-	-	(2.0 - 3.5g%)
> 5.5mg%	-	-	-	-	

* Normal values as obtained in the chemical pathology laboratory of the University College Hospital, Ibadan

\+ Serum calcium values corrected for hypoalbuminaemia [15].

Table 2 shows the radiographic extent of pulmonary tuberculosis (PTB) in the patients studied. Only 12 (11.8%) patients had minimal disease, 38 (37.3%) had moderate disease with 22 of them (57.9%) having cavities. Fifty-two

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patients (51.0%) had severe disease, 37(71.2%) of whom had cavities.

Table 2: Pre-treatment radiographic extent of PTB in 102 patients

CXR grade * (14)	No. of patients	Percentage
Minimal disease	12	11.8
Moderate disease	38	37.3
with cavities	22	57.9
without cavities	16	42.1
Extensive disease	52	51.0
with cavities	37	71.2
without cavities	15	28.9

* Minimal disease Involvement of one radiographic zone
Moderate disease Involvement of two radiographic zones
Extensive disease Involvement of three or more zones or a whole lung

Table 3 shows the distribution of the body mass indices (BMI) in the 102 patients before and at six months of treatment with antituberculosis drugs. At presentation, only 19 (18.6%) of the 102 patients had normal BMI. Six months after therapy with antituberculosis drugs, forty-four (43.1%) of the 102 patients achieved normal BMI while 58 (56.9%) still had BMI below 20 ($P = 0.0002$).

Table 3: Body mass index (BMI) in 102 patients with PTB before and at six months of treatment

	No. with BMI				Overall
	<20 (mean)	20-25 (mean)	>25	Range	mean
Pre-treatment	83 (16.6)	19 (21.0)	-	12.2 - 22.4	17.3
At 6 months	58 (17.8)	44 (21.7)	-	13.6 - 24.6	19.5

$X^2 = 13.227$ $P = 0.0002$

Discussion

While forty-five (44.1%) of the 102 patients were noted to have asymptomatic hypocalcaemia (range 7.3-8.9mg%), no patient had hypercalcaemia on presentation. This agrees with the earlier findings of Kamisky and Davidson [16] who reported low or low-normal serum calcium levels in fifteen of their 47 freshly diagnosed PTB patients. The hypocalcaemia seems likely to be due to anorexia and secondary malnutrition in most of these patients. This was further suggested by the fact that the four patients who had hypoalbuminaemia all had body mass indices below 20 which improved (to normal range) within six months of commencement of therapy.

Although two patients had transient hypercalcaemia while on treatment, no definite cause could be found. While both patients had hypocalcaemia, low BMI and extensive disease on chest radiographs at presentation, other patients did have similar findings without developing any hypercalcaemia while on antituberculosis therapy. None of the patients studied received Vitamin D supplements before or during treatment. The suggestion of some workers [13] that it might be the granulomatous tissue itself that forms an extra renal site for the synthesis of 1,25 dihydroxycholecalciferol would have been reasonable if all the patients with, for instance, extensive radiographic disease had hypercalcaemia before commencement of antituberculosis therapy. Other probable causes of hypercalcaemia such as bone or adrenal involvement in patients with disseminated tuberculosis, acute bone atrophy due to reduced physical activity, impairment of degradation of prostaglandin E (a potent stimulator of bone resorption) abnormal secretion of osteoclast activating factor by lymphocytes or incidental coexistence of other granulomatous diseases could not however be excluded in the two patients that had transient hypercalcaemia.

Conclusion

Hypocalcaemia seems to be commoner in patients with active pulmonary tuberculosis at presentation in developing countries probably because of late presentation and resultant secondary nutritional problems.

Hypercalcaemia although rare and mostly asymptomatic in those on antituberculosis therapy, is still seen though no definite cause was found.

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