BIOCHEMICAL CHANGES IN ADULT NIGERIANS WITH PULMONARY TUBERCULOSIS IN KANO-NIGERIA

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ABSTRACT

Background:- Pulmonary tuberculosis is one of the re-emerging diseases often associated with poverty and HIV/AIDS especially in sub saharan Africa. Hypercalcaemia is known to be associated with chronic granulomatous diseases such as tuberculosis, sarcoidosis and lymphoma. Reports of changes in biochemical parameters in patients with TB have been reported elsewhere.

AIM:- This study was aimed at assessing changes in some biochemical parameters in patients with pulmonary tuberculosis.

Subjects and Methods:- Fifty seven TB patients confirmed by culture and/or sputum smear were recruited consecutively over a period of twenty months. Serum calcium, inorganic phosphate, transaminases, proteins, urea, electrolytes and creatinine were assayed using Express plus chemistry autoanalyzer and fp 20 flame photometer. 50 male and 7 female subjects were recruited from among staff and students of the hospital as controls.

Results:-The mean corrected calcium level was 2.54±0.02mmol/l,albumin 24.0±1.27g/L, aspartate aminotransferase 47.6±3.0U/l, alanine aminotransferase 26±1.6Ul, sodium 135±0.8 mmol/l and bicarbonate 20±0.82mmol/l. Statistically significant difference ($p<0.001$) was observed in some parameters when compared with the control subjects. The change in potassium level was also statistically significant ($p<0.01$)

This study has confirmed that Pt and PTB may have significant reduction in ca++ albumin; hyponatraemis .

Conclusion: Hypercalcaemia was observed in 26% of patients. After Calcium concentration was corrected for albumin. Hypoalbuminaemia

and hyponatraemia were also observed in this study.

INTRODUCTION

Tuberculosis is an ancient disease with a lineage that can be traced to the early history of mankind[1]. Advances in science led to its near eradication until recently. WHO in 1993 declared tuberculosis (TB) to be a global emergency and the report stated that TB epidemic was growing unabated especially in sub-saharan Africa[2]. TB is an increasing problem world-wide in terms of disease burden which is closely associated with HIV/AIDS and poverty[3-4]. Most haematological and biochemical abnormalities associated with TB have been reported elsewhere[5–8]. Hypercalcaemia is known to be associated with chronic granulomatous diseases such as tuberculosis, sarcoidosis, lymphoma etc.[8] The reported incidences of hypercalcaemia in active TB differ from one country to another due to differences in vitamin D, calcium intake and amount of sunlight exposure[9]. The incidence of hypercalcaemia in TB is 15% in Hong Kong,16% in India, 25% in Greece, 28% in the United states of America and 51% in Australia[10-11]. Most cases of hypercalcaemia with tuberculosis are asymptomatic or mild. Active tuberculosis is more likely to be associated with hypercalcaemia[8.] This study therefore assesses changes in electrolytes, proteins and liver enzymes in adults with pulmonary tuberculosis in a tertiary teaching Hospital.

SUBJECTS AND METHODS

Fifty seven consecutive TB patients confirmed by sputum culture and/or Ziehl Neelson stain technique were selected for the study over a period of twenty months. Suspected TB patients whose sputum specimens were not confirmed as stated above were excluded. Informed consent was obtained from every patient before blood specimen was collected. Fifty subjects, twenty five males and twenty five females were recruited from among the staff and students of the hospital and were used as controls. Five milliliters of venous blood was collected without stasis into plain tubes and were allowed to clot at room temperature. Sera were obtained after centrifugation at 3000 rpm for 10 minutes. Serum calcium, inorganic phosphorus, urea, creatinine, liver enzymes and proteins were analyzed by Express Plus chemistry auto analyzer supplied by Chiron diagnostics, USA. Sodium and potassium were analyzed using fP 20 flame photometer (by SEAC, Sri–Italy). While chloride and bicarbonate were determined by titrometric method.

Student's t- test was used to compare the mean values and level of significance was set at $p<0.05$.

RESULTS

The study group comprised of thirty nine males and eighteen females. Their mean age was 35.9$\pm$ 3.9years while the mean age of the fifty control subjects was 33 $\pm$2.6years.The mean calcium level in the study group corrected for albumin

was 2.54 ± 0.02mmol/l and that of the control subjects was 2.21 ± 0.04 mmol/l. The difference in the means was statistically significant ($p<0.001$). Forty two (73%) of the subjects had calcium value within reference range of normal, while fifteen (26.3%) had values above the upper limit of norma. The mean values of total protein and albumin of the study group were 64.6 ± 2.5g/L and 24.0 ± 1.27g/L respectively. Statistically significant difference ($p<0.001$) were observed when compared with the control subjects. The mean activities of aspartate amino transferase, alanine amino transferase and alkaline phosphatase were 47.6 ± 13.0 IU/L, 26 ± 9.6lU/L and 104 ± 16.5 IU/L respectively. Statistically significant difference ($p<0.001$) was observed for AST and ALT compared with the means of the control subjects. The mean values of total and direct bilirubin were 24.6 ± 6.4Umol/L and 7.9±4.4 Umol/L respectively. There were no statistically significant differences ($p>0.10$,$p>0.50$) observed when compared with the control subjects. The mean values of Sodium, potassium, Chloride and bicarbonate of the patients were 135 ± 0.82mmo/l, 3.32±0.4mmol/l, 99 ± 0.83mmol/l and 20±0.02 mmol/l respectively. Statistically significant differences were observed for Sodium ($p<0.001$), Potassium ($p<0.01$) and bicarbonate ($p<0.001$) when compared with the control subjects (table 1).

Table 2 shows the descriptive characteristics of study subjects on the basis of abnormal calcium, sodium and albumin. The mean calcium level of the fifteen (26.3%) of the patients was above the upper limit of reference range of control subjects. Eighteen (31.6%) of them had mean sodium level below the lower limit of reference range while fifty seven (100%) of the study population had mean albumin level below the lower limit of the reference range. All the parameters when compared with the control subjects were statistically significant $p<0.001$).

Table 1: Biochemical parameters in TB and Control subjects

Parameters	**TB Patients**	**Controls**	**p-value**
Age(Years)	35.9 ± 3.9	33 ± 2.6	
No. of Males	39	25	
No. of Females	18	25	
Total (subjects)	57	50	
Calcium (Corrected)	2.54 ± 0.02 *	2.21 ± 0.04	p<0.001(mmol/l)
Inorganic Phosphate (mmol/l)	0.98±0.20	0.96±0.82	p>0.50
Total Protein (g/L)	64.6± 2.5	65.2 ± 1.1	p>0.50

Albumin (g/L)	24.0 ±1.27	43.2 ± 1.2	p<0.001
Aspartate aminotransferase (U/L)	47.6±3.0	20.6±6.2	p<0.001
Alanine aminotransferase (U/L)	26±1.6	12.7±1.9	p<0.001
Alkaline phosphatase (U/L)	104± 16,5	86.2±9.8	p>0.10
Total bilirubin (Umol/l)	24.6 ± 6.4	16.6 ± 8.2	p>0.10
Direct bilirubin (Umol/l)	7.9 ± 4.4	7.2 ± 4,4	p>0.50
Sodium (mmol/l)	135 ± 0.82	138 ± 0.76	p<0.001
Potassium(mmol/l)	3.32 ± 0.14	3.7 ± 0.26	p<0.01
Chloride (mmol/l)	99 ± 0.83	100 ± 0.26	p<0.005
Bicarbonate (mmol/l)	20 ± 0.82	26 ± 0.76	p<0.001
Urea (mmol/l)	5.98 ± 0.81	6.2 ± 0.81	p>0.10
Creatinine (Umol/l)	110 ± 19.3	108 ± 12.1	p>0.50

Table 2: Descriptive characteristics of study patients on the basis of abnormal calcium, sodium and albumin

Variable	Calcium	Sodium	Albumin
No of patients	15	18	57
No of males	10	10	39
No of females	5	8	18
Percent of total Subject	26.3	31.6	100
Mean value	2.67± 0.04	132±0.5	24.0±1.27
P-value	p<0.001	p<0.001	p<0.001

DISCUSSION

There was no ”absolute” hypercalcaemia in the study population but when the serum calcium level was corrected for albumin, statistically significant difference (P<0.001) was observed compared to the control subjects. The result is consistent with those of other workers.[7-8,13] It was reported that tuberculosis can affect calcium metabolism mainly through enhanced production of active vitamin D in the region

where there is much sunlight [13]. The observed hypercalcaemia was attributed to increased level of active vitamin D even in the presence of reduced calcium intake in the diet. The 1,25 dihydroxyl cholecalciferol ($1,25(OH)_2D_3$) synthesized in T lymphocyte participates in cellular immunity and plays an important role in the immune reaction against mycobacteria. The vitamin D_3 synthesized in T lymphocytes reinforces macrophages to kill mycobacteria without affecting calcium metabolism. However, large amounts of $1,25(OH)_2D_3$ production could lead to hypercalcaemia[9]. Identical serum calcium level when compared with control subjects was however observed by some authors in the temperate regions where the sunlight exposure is not sufficient[14-15]. The calcium content of the body depends on the balance between intestinal absorption and losses through the faeces and urine. Protein – bound calcium consists of about 40-45% of total body calcium. Any change in the circulatory albumin will lead to changes in plasma calcium concentration. However, the concentration of calcium will be kept within normal limit by other factors such as parathyroid hormone (PTH), renal clearance and re-equilibration with protein complexes. $1,25(OH)_2D_3$ was thought to greatly enhance hypercalcaemia in tuberculosis[13-14]. The overall effect of $1,25(OH)_2D_3$ are to increase intestinal absorption of calcium and inorganic phosphate, increase calcium/phosphate resorption from bone as well as promoting the renal retention of calcium and phosphate. The observed hypercalcaemia in 26.3%, hypoalbuminaemia in all the patients was also consistent with recent studies[8,15]

Statistically significant difference ($p<0.001$) was observed for liver transaminases and this again is in agreement with that of Davis et al[9], who reported increased levels of the enzymes in tuberculosis patients. Hyponatraemia was observed in 31.6% in the study group. Hyponatraemia was reported to occur in 22.15% and 50% of patients with tuberculosis elsewhere[15-17]. The causes of this hyponatraemia may be due to increased urinary loss of sodium, a consequence of unregulated antidiuretic hormone release. The release also leads to water retention with natriuresis resulting from secondary extracellular fluid expansion. Anti diuretic hormone-like activity was reported in lung tissue of a tuberculosis patient[18].

Conclusion:- Increased levels of corrected calcium, decreased albumin and electrolyte imbalance were observed in tuberculosis patients. Increased vitamin D synthesis by alveolar macrophages has been postulated to be responsible. The attending physicians must be reminded that anti TB medications are known to cause remission in calcium levels after 18-20 months of treatment.

Hypercalcaemia was observed in 26.3% of patients after the calcium concentration was corrected for albumin. Hypoalbuminaemia and hyponatraemia were also observed in this study. Increased vitamin D synthesis by the alveolar

macrophages has been postulated to be responsible for the hypercalcaemia.

Key words:- Tuberculosis, hypercalcaemia, albumin, transaminases

REFERENCES:

1. Farer L.S Mycobacterium tuberculosis: Bacteriology, epidemiology and treatment In: Principle and Practice of Infectious Diseases (eds Mandell G.L,Douglas R.G Barrett J.E) A Wiley medical publication 1979:1905-1925
2 Rariglone M C Dye C, Schmidt S, Kochi A. Assessment of worldwide tuberculosis control. Lancet 1997; 350: 624 – 629.
3. Subhash H.S, Ashwin I. Mukundan U, et al. Drug resistant tuberculosis in diabetes mellitus: a retrospective study from South India. Trop. Doc. 2003; 33 : 154 – 156.
4. Ghuhen M, Active TB detection. African Health 2004; 10:3.
5. Stockman J.A. Haematologicalc Manifestations of Systemic diseases, In: Nathan DG, Oski FA (eds) Heamatology of infancy and childhood. Saunders, Philadelphia, 1987:1632 - 1675.
6. Wessels G, Schaaf H.S, Beyers N, Gie R.P, Nel E and Donald P.R. Haematological Abnormalities in children with Tuberculosis. J. Trop Paed. 1999; 45 : 307 – 310.
7. Clan T.Y, Poon P, Pany J. et al. A study of calcium and vitamin D metabolism in Chinese patients with pulmonary tuberculosis J. Trop. Med. Hyg. 1994; 97(1):26-30.
8. Lind. J. and Ljunghall. S. Hypercalcaemia in Pulmonary tuberculosis. Ups. J. Med. Sci 1990; 95 (2): 157 – 160.
9. Eun Seok Kang, Mi Young Do ,So Young Park et al. Hypercalcaemia in Hepatic tuberculosis: A case Report in Korea. Am. J. Trop. Med. Hyg. 2005; 72(4): 368- 369.
10. Rousses A. Lagogianni I . Gonis A et al. Hypercalcaemia in Greece patients with tuberculosis before the initiation of anti tuberculosis treatment. Respir. Med. 2001;95:187-190
11. Abbasi A.A ChemparilJ.K Farah S. Muller B.F Arnstein A.R Hypercalcaemia in active pulmonary tuberculosis. Ann.Intern. Med. 1979;90:324-328
12. Sharma S.C Serum calcium in pulmonary tuberculosis. Postgrad.Med.J 1981; 57:694-694
13. Davies P.D Church HA Brown. RC Woodhead J.S Raised Serum calcium in tuberculosis patients in Africa. Eur. J. Respir Dis 1987; 71 (5) : 341 - 344.
14. Davis PD, Brown RC, Woodhead JS. Serum concentration of vitamin D

Metabolites in untreated tuberculosis. Thorax 1985; 40 (3) : 187 – 190.

15. Chan T.Y Chan CH, Shek CC, Davis PD Hypercalcaemia in active pulmonary tuberculosis and its occurrence in relation to the radiographic extent of disease. Southeast Asian J. Trop. Med. Public Health 1992; 23 (4): 702 – 704.
16. Abal A.T Jayakrishman B, Parwer S et al. Demographic pattern and clinical characteristics of patients with smear positive pulmonary tuberculosis in Kuwait. J. Med. Prin. Pract. 2005; 4:306-312
17. Steigbigel R.T. Mycobacterium tuberculosis, clinical manifestation in: Principles and practice of infections diseases (eds G.L Mandell, RG Douglas, J.E Bannett). A Wiley Medical Publication, 1979: 1925 – 1942.
18. Vorherr H, Massy S, Faller R. Antidiuretic Principle in tuberculous lung tissue of a patient with pulmonary tuberculosis and hyponatraemia. Ann Intern. Med. 1970; 72 : 383.