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Study of calcium metabolism in newly diagnosed pulmonary tuberculosis patients

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Abstract
Background: Tuberculosis is a global infectious health problem. The association between tuberculosis (TB) and hypocalcaemia is well recognized. The reported incidence of hypocalcaemia in TB varies widely between countries, probably because of differences in the vitamin D and calcium intake, the amount of sun exposure, the extent of disease and the criteria for hypercalcaemia.
Objective: The aim is study is To compare serum calcium, phosphorus, vitamin-D and alkaline phosphatase, level in pulmonary tuberculosis patients with normal healthy control
Methodology: A Hospital based Case control study conducted at Department of Tuberculosis and Respiratory medicine, Institute of respiratory diseases SMS Medical College, Jaipur, Rajasthan during the year 2014 – 2015. The present study includes total 164 participants among them 82 adults newly diagnosed pulmonary tuberculosis patients of both genders of age group 18-80 yr (Group A) and 82 age and sex matched healthy control. (Group B). Blood sample was collected from all participants to measure complete blood count (CBC), ESR, S.Calcium, S.Phosphorus, S.alkaline phosphatase and Vitamin D. sputum sample was also collected for AFB detection. Obtained results were analysed statistically to determine the difference of significance by calculating p value.
Results: The Mean level of S.Calcium(mg/dl),S.Phosphorus(mg/dl),S.alkaline phosphatase(U/L) and Vitamin D(ng/ml) in case group is group is 7.74± 2.77, 3.52± 1.07, 118.95±18.95, 19.33± 5.88 while in control group it is 9.27±2.11, 3.92±1.14, 63.16±19.40, 46.23±12.63 Respectively.
Conclusion: In conclusion, serum calcium and phosphorus significantly decreased in pulmonary tuberculosis. While the cationic levels decreased to hypocalcemic range, the decrease in phosphorus was within normophosphatemic range. High prevalence of vitamin D deficiency was found among newly diagnosed TB patients.

Keywords: tuberculosis, calcium, Vit D, phosphorus

Introduction

WHO estimates that there were 9.4 million cases of tuberculosis and 1.8 million deaths from the disease globally in 2008 [1].

Disturbance in calcium metabolism leading to variations in blood calcium concentration can cause a spectrum of clinical features[7]. Serum levels of ionized calcium are maintained in the normal range by inducing increases in the secretion of PTH. PTH acts to increase bone resorption, renal calcium reabsorption, and increases the conversion of 25(OH)D to $1,25(OH)_2D$ in the kidney, thereby increasing gastrointestinal calcium absorption. Every hormone involved in calcium homeostasis, and its activity is stimulated by PTH, estrogen, calcitonin, prolactin, growth hormone, low calcium and low phosphorus [2].

Serum calcium (macronutrient) levels are tightly controlled within a narrow range, usually 8.5–10.5 mg/dl. Serum phosphorus significantly decreased but was within normophosphatemic limits in pulmonary tuberculosis. Chemotherapy for tuberculosis managed to raise serum levels of both the ions, with hypocalcaemia still persisting in majority of patients during treatment but getting resolved in a significant percentage of patients at the end of 6 months of treatment [3]. Results indicate the need for calcium and phosphorus supplements in tuberculosis patients during chemotherapy. The recommended daily allowance (RDA) for phosphorus is 800 mg/day. Phosphorus is the most important mineral constituent of nerve tissue, of both the white matter and the gray matter [4].

Vitamin-D is a hormone present in the human body to manage levels of some essential electrolytes such as calcium and phosphate. Vitamin D is important for bone formation and prevention of bone breakdown (osteoporosis). There is also new evidence that links vitamin D to function of our immune system as well. Even though our bodies can make vitamin D and can also obtain vitamin D from our diet; most adults, especially patients with tuberculosis have low vitamin D levels (are vitamin D deficient) that need to be corrected. Full correction of low vitamin D levels requires 6 weeks or more of weekly vitamin D supplements [5].

Material and Method

Study Design: A Hospital based Case control study conducted at Department of Tuberculosis and Respiratory medicine, Institute of respiratory diseases SMS Medical College, Jaipur, Rajasthan during the year 2014-2015.

Materials and Methods

The present study conducted on 164 adults newly diagnosed pulmonary tuberculosis patients of both genders visiting TB & Chest Hospital of S.M.S. Hospital, Jaipur. The results will be compared with age & sex matched healthy control subjects with no history or symptoms of pulmonary tuberculosis. A written consent will be taken from all subjects or their relatives.

1. Group A (n=82): Normal healthy control.
2. Group B (n=82): Will include newly diagnosed PTB patients

Inclusion criteria
- Diagnosed cases and newly diagnosed cases of Tuberculosis willing to participate were included in the present study
- Age 18-80 years.

Exclusion criteria
- Patients with drug resistant TB (MDR) or extra pulmonary TB
- Patients with significant diabetes, renal, cardiac or neoplasm, HIV
- Patients on drugs that interfere in vitamin-D metabolism like alcohol
- Steroid or calcium preparation
- Hyperparathyroidism or any other endocrine or genetic disorder
- Pregnant or lactating women
- Patients with significant liver disease (abnormally high AST& ALT)
- Previous ART (Antiretroviral) treatment/or HIV positive

Study protocol
This study was affiliated by Institutional Review Board, SMS Medical College, Jaipur. After giving full explanation regarding the study, An inclusion and exclusion criterion was applied on case and control. Then following evaluation was preformed
- Detail clinical history
- Physical examination to look for nutritional status
- Chest x ray
- Electrocardiogram and Echocardiography (if required)
- Sputum for AFB
- Serum calcium
- Serum phosphorus
- Serum alkaline phosphatase
- Vit –D

Patient's name, age, sex, race, marital status, occupation and address were recorded.
Symptoms such as dyspnoea, cough, fever, sputum, haemoptysis, chest pain, loss of appetite, loss of weight, dysphasia, and night sweat were recorded and analyzed.
Past history of anti- tubercular treatment, any associated co-morbidity, any medication patient taking, patient any hormonal therapy, any congenital or acquired heart diseases, any history of allergy and any history of surgery in past.
Personnel history of smoking habit, alcohol intake, any other exposure to smoke and dust and any other addiction.
Family history of infertility, diabetes, systemic hypertension and heart diseases Menstrual history of age of menarche, last menstrual period, and age of menopause.
General physical examination includes height, weight, body mass index, pulse, blood pressure, oedema, pallor, icterus, peripheral lymphadenopathy, cyanosis, clubbing and thoroughly respiratory, abdominal, central nervous and cardiovascular examination done.

Sample Collection and Storage
The blood samples of about 5 to 10 ml taken from Tuberculosis patients in morning after overnight fasting. Blood samples of control group will be taken after overnight fasting. The samples will be left standing for one hour; Serum will be separated at 2500 rpm centrifugation and analyzed on fully automated analyzer randox (Imola). Then it was subjected to nutritional and endocrinal assessment. And sample which is taken in EDTA vial are subjected for Haemoglobin and ESR

Statistical Analysis
The collected data was revised, coded, tabulated and introduced to a PC using Statistical Software SPSS and primer. Pearson correlation coefficient will be used to find out correlation between continuous variables.
Medcalc.14.0.0 version software will be used for all statistical calculations. Results for p value < 0.05 will be taken as significant.
Quantitative variables are expressed as mean and SD. Qualitative variables are expressed as frequencies and percent's. Student t test was used to compare a continuous variable between two study groups.

Results
Age range of the study patients was between 18 – 80 years. The global prevalence of physiologically defined Tuberculosis in adults aged ≥14 year is approximately 10 - 15% with more prevalence in male then in female.

Table 1: demographic characteristic of the participants

Parameter	Group	N	Mean	Std. Deviation	'p' Value*
Age	Case	82	40.82	18.30	0.801
	Control	82	40.11	17.52	
Weight	Case	82	46.73	8.73	<0.001 Highly Significant
	Control	82	59.48	8.28	
BMI	Case	82	17.53	3.23	<0.001
	Control	82	21.51	2.90	
Pulse	Case	82	86.66	17.18	<0.001
	Control	82	71.05	3.52	
Spo2	Case	82	85.77	5.52	<0.001
	Control	82	95.40	3.30	

In this study BMI shows significant difference between the cases and control groups. The mean BMI of healthy control subject and case group were 21.51±2.90 and 17.7±3.23 kg/m^2 respectively. A highly significant decrease in BMI ($p<0.001$) was found in Tuberculosis cases group. There significant difference observed between moderate to severe Tuberculosis. BMI doesn't correlate with severity of disease.

Table 2: sex wise distribution of the participants

Sex	Case		Control		Total	
	No.	%	No.	%	No.	%
Male	45	54.88	50	60.98	95	57.93
Female	37	45.12	32	39.02	69	42.07
Total	82	100.00	82	100.00	164	100.00

Table 3: Symptom wise distribution of tuberculosis patients (N=82)

Symptom	No.	%
Sputum Positive	55	67.07
Cough	75	91.46
Night Sweat	73	89.02
Hemoptysis	58	70.73
Tiredness	80	97.56
Dyspnoea	66	80.49
Decreased apetite	82	100.00
Chest Pain	72	87.80
Weight Loss	82	100.00
Grand Total	82	100.00

The above table represents that the symptoms of Weight loss is 100%, Cough was 91.46%, and Chest pain was 87.80%

Table 4: Comparison of hemogram between case and control Group

	Group	N	Mean	Std. Deviation	'p' Value*
Hb	Case	82	11.05	8.28	0.513
	Control	82	11.66	1.31	
ESR	Case	82	40.62	14.27	<0.001
	Control	82	6.43	2.35	

Table 5: Comparison of various biochemical parameters between between case and control Group

Parameter	Group	N	Mean	Std. Deviation	'p' Value*
S. Vitamin-D	Case	82	19.33	5.88	<0.001 Highly Significant
	Control	82	46.23	12.63	
S. Calcium	Case	82	7.74	2.11	0.080
	Control	82	9.27	2.77	
S. Phosphorus	Case	82	3.52	1.07	0.019
	Control	82	3.92	1.14	
S.ALP	Case	82	181.95	18.95	0.000
	Control	82	63.16	19.40	

In our study evaluated some statistical significant decrease in serum calcium Tuberculosis case and control group as 7.74± 2.77, 9.27± 2.11 mg/dl Respectively with p value 0.080.

In our study has statistical Significant decrease seen in serum phosphorus between Tuberculosis case and control group as 3.52± 1.07, 3.92± 1.14 mg/dl respectively with p value 0.019.

This study showing that vit D level is Highly statistical Significant decrease between Tuberculosis case and control group as 19.33± 5.88, 46.23± 12.63 ng/ml respectively with p value <0.001.

This study reveals a Highly statistical Significant in ALP between Tuberculosis case and control group as 118.95±18.95, 63.16± 19.40 U/L respectively with P value <0.001.

Discussion

The global burden of TB is increasing, largely due to the spread of HIV/AIDS. HIV-infected persons are far more susceptible to TB, are more difficult to diagnose, and in addition, are also more difficult to treat. But decrease in weight and BMI are the basic characteristics of both HIV and PTB. HIV-infected people have much higher mortality in the period following TB treatment, with 30% dying within a year of diagnosis and treatment [6].

The association between tuberculosis (TB) and hypocalcaemia is well recognized. The reported incidence of hypocalcaemia in TB varies widely between countries, probably because of differences in the vitamin D and calcium intake, the amount of sun exposure, the extent of disease and the criteria for hypercalcaemia [7].

Disturbance in calcium metabolism leading to variations in blood calcium concentration can cause a spectrum of clinical features [7].

Serum levels of ionized calcium are maintained in the normal range by inducing increases in the secretion of PTH. PTH acts to increase bone resorption, renal calcium reabsorption, and increases the conversion of 25(OH)D to 1,25$(OH)_2$D in the kidney, thereby increasing gastrointestinal calcium absorption.[8] Every hormone involved in calcium homeostasis, and its activity is stimulated by PTH, estrogen, calcitonin, prolactin, growth hormone, low calcium and low phosphorus [8].

Serum calcium (macronutrient) levels are tightly controlled within a narrow range, usually 8.5–10.5 mg/dl. However, the serum calcium level is a poor reflection of overall total body calcium, as serum levels are only 0.1–0.2% of extracellular calcium, which in turn is only 1% of total body calcium [9].

Serum phosphorus significantly decreased but was within normophosphatemic limits in pulmonary tuberculosis. Chemotherapy for tuberculosis managed to raise serum levels of both the ions, with hypocalcaemia still persisting in majority of patients during treatment but getting resolved in a significant percentage of patients at the end of 6 months of treatment [10]. Results indicate the need for calcium and phosphorus supplements in tuberculosis patients during chemotherapy.

There is also new evidence that links vitamin D to function of our immune system as well. Even though our bodies can make vitamin D and can also obtain vitamin D from our diet; most adults, especially patients with tuberculosis have low vitamin D levels.

There are several benefits to correcting vitamin D deficiency (better bone health, better balance of calcium and phosphate), but it is not known whether correcting vitamin D deficiency will lead to a better immune response to tuberculosis.

Alkaline phosphatase (ALP) is one of the biochemical markers found in pleural effusion. ALP is a common term for a group of glycosylated enzymes with optimal activity in the alkaline pH range 9.8–10.5. The isoenzymatic forms of different origin (liver, kidney, bone, placenta and intestine) have different physicochemical and immunologic characteristics that are employed in the methods of isoenzyme separation [11]. The catalytic activity of ALP undergoes modification in childhood due to bone growth; it is moderately increased in the first three months of life, while in puberty it is two to three fold that in adults.

So Nutritional and Endocrinal assessment is very important in assessing the prognosis. Early detection of nutrition and endocrinal factor in Tuberculosis patient may help in early intervention early correction of derangement and may be helpful in pulmonary rehabilitation of patient for better survival and increase quality of life in Tuberculosis patients.

Conclusion

In conclusion, serum calcium and phosphorus significantly decreased in pulmonary tuberculosis. While the cationic levels decreased to hypocalcemic range, the decrease in phosphorus was within normophosphatemic range. High prevalence of vitamin D deficiency was found among newly diagnosed TB patients.

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