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Ionic Calcium verses Total Calcium in Relation to Disease Severity and Inflammation in Pulmonary Tuberculosis

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ABSTRACT

Ionized Calcium, the physiologically active fraction reflects true Calcium status of the body in health and disease. Stratigies either to measure Ionic Ca directly or to calculate it from Total Ca have emerged and is significant especially in condition of critical illness. Pulmonary Tuberculosis is associated with muscle wasting and malnutrition and therefore require estimation of Ionic Ca to understand Calcium homeostasis.

Aim: The aim of this study was to analyze Calcium status in Pulmonary tuberculosis patients. Correlation of Ionic Ca, Albumin adjusted Ca and Measured Total Ca with disease severity and inflammation were also evaluated.

Material and Method: 120 adult PTB patients and 60 healthy controls were recruited. Sputum positivity was assessed by counting number of Acid Fast Bacilli in sputum smear microscopically and disease severity by Bandim TB score. After written consent, serum was used for investigating routine test, Calcium, Phosphorus and Inflammatory Markers (Adenosine Deaminase and C-Reactive protein). Ionic Ca and Albumin adjusted Ca were calculated by standard formulas.

Result and Discussion: Ionic Ca and Albumin adjusted Ca were significantly high in patients than controls but no significant difference was seen in Total calcium level. Ionized hypercalcemia was seen in 16.6% of Tuberculosis patients but most were asymptomatic. Ionic Ca and Albumin adjusted Ca showed weak correlation to disease severity (r=0.297 and r=0.300 respectively) and non significant relation to inflammatory parameters.

Conclusion : Both Ionic Ca and Albumin adjusted Ca were significantly high in patients than Total Ca. Ionic Ca provide better indicator of disturbed Ca balance in PTB patients and hence must be estimated routinely. It should be monitored before any initiation of Calcium or Vitamin D supplementation in Pulmonary Tuberculosis to prevent its excess and related harmful effects.

Keywords: Ionic Calcium, Pulmonary Tuberculosis, Disease severity.

INTRODUCTION

Calcium, the king of all minerals is the most abundant elements in the earth crust and is also the most abundant mineral in human body. Through interacting with numerous proteins distributed indifferent cellular compartments, calcium is involved in various aspects of life, such as muscle contraction, enzymeactivation, cell differentiation, immune response, programmed cell death and neuronal activity . Such broad functions are maintained by tightly controlled calcium concentration in extra-cellular fluid and cellular compartments (1). Hence, Calcium estimation is of great clinical importance in many disease. Abnormalities in calcium homeostasis are common in critically ill patients that manifest as both hypocalcemia and Hypercalcemia. Hyper parathyroidism and Malignancy accounts for 80-90 % of all cases of hypercalcemia. Amomg Granulomatous diseases, Sarcoidosis, Tuberculosis and Coccidiomycosis are also associated with abnormal Ca metabolism, however incidence in TB varies from 2% to 25% depending on Geographical

area and multiple other factors such as Calcium and Vitamin D intake, amount of sun exposure and laboratory criteria for defining hypercalcemia (2).

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. If serum calcium is reduced, as often occurs in anorexia and catabolic wasting that accompany TB, then Total calcium may be normal, although ionized hypercalcaemia and its resultant symptoms may be present. It is, therefore, essential to correct serum calcium for serum albumin concentration or, ideally, to measure serum ionized calcium (3). Free Ca is useful index than Total Ca and provide better indication of Ca status because it is independent of protein concentration and tightly regulated by calcium binding hormones (4). Direct measurement of iCa is costlier and not routinely done but can be estimated by standard formula from Total Ca values, which is significant in cases where protein and Albumin level is severely affected. Pulmonary Tuberculosis (PTB) is associated with malnutrition and hypoalbuminemia is a widespread cause of morbidity and mortality in our country. Keeping in mind its high prevalence, all aspects of the disease need to be thouroughly studied.

This study focuses on the use of both ionic Calcium and Albumin adjusted Ca as indicators of Calcium status in PTB. Further, correlation of Measured Total Calcium, Ionic Calcium (iCa) and Albumin adjusted Ca with Disease severity and Inflammatory Marker (i.e Adenosine Deaminase and C-Reactive Protein) was analyzed. Severity was assessed by "Bandim TB Score" method that involves symptoms specific for TB. Sputum Bacterial Load/ Sputum Positivity and CRP also reflect degree of severity and inflammation respectively.

MATERIAL AND METHODS: The study was conducted in the Institute of Respiratory Diseases (IRD) in association with Department of Biochemistry, SMS Medical College, Jaipur. 120 Adult patients (both male and female) from low socio-economic status diagnosed with Pulmonary Tuberculosis (PTB) (both Newly diagnosed and Relapse) were recruited for the study. 60 healthy, age matched individuals tested free of Mycobacteria without any previous or present symptoms of Tuberculosis or any other pulmonary disease and non family member of patients were taken as Controls. Following diagnostic criteria was used for PTB 1. Positive culture for MTB. 2. Positive (2 consecutive samples) smear for AFB. 3. Typical chest X-ray showing bilateral upper zone involvement with or without cavitations & with/without +ve sputum smear but with typical PTB symptoms. 4. Patients with 2 or 3 criteria had to show clinical and radiological improvements with anti tuberculosis therapy. Patients with multidrug resistant TB (MDR-TB), extrapulmonary Tuberculosis, those with significant renal, cardiac, neoplasm or respiratory disease (other than PTB like lung cancer) etc., diabetes, endocrine or genetic disorder were excluded from the study. HIV positive cases, Pregnant or lactating women and those on oral nutritional supplements were also excluded. All subjects gave their written consent to participate in the study.

Sample collection and bacteriological examination: Two consecutive sputum sample of each patient were collected and subjected to Acid fast Staining. In order to determine sputum positivity, number of Acid Fast Bacilli (AFB) were counted and analysed as follows:1. No AFB in 100 fields-negative; 1-9 AFB in 100 fields-scanty ; 10-99 AFB in 100 fields- +1 ; 1-10 AFB per field-+2 and more than 10 AFB per field= +3.

Assessment of Disease severity by "Bandim TB Score" system: It classifies PTB into different classes of severity. Severity Class I (for score 0-5) is least severe, Severity Class II (for score 6-7) is moderately severe and Severity Class III (for score 8-13) is most severe. The score was counted on the basis of 5 self reported symptoms i.e. cough, hemoptysis, dyspnoea, chest pain and night sweats as well as 6 signs identified at the time of examination : Anemia, pulse >90 beats/min, positive finding at lung auscultation, temperature > 37º C, BMI <18 Kg/m^2 and Mid Upper Arm Circumference (MUAC) < 220 mm. Each of the above clinical variables contribute to 1 point. BMI <16 Kg/m^2 and Mid Upper Arm Circumference (MUAC) < 200 mm contributed an extra point to the score. Final TB score is the sum of all individual points. Maximum score of any patient could be 13 (5).This method of severity assessment based on clinical features and investigations was validated by number of workers and was found suitable especially in a resource poor setting (5).

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Measurement of Biochemical parameters: After an overnight fast (12 hrs), venous blood was drawn for all subjects. After routine investigation, Total Calcium (Arsenzo method), Phosphrous (Phosphomolybdate UV method), Serum Adenosine Deaminase (Enzymatic Method) and CRP (Turbidilatex) were estimated on Randox imola3 fully autoanalyzer using commercially available kits. Ionized and Corrected Calcium were calculated using Standarised formula (6).

STATISTICAL ANALYSIS: Quantitative data were expressed as Mean ± SD. Comparison was made using student-t test (independent sample t-test). P value less than 0.05 was considered significant. Pearson Correlation was used to assess correlation between various parameters.

RESULT AND DISCUSSION: Measured Total Calcium in serum consist of approximately 15% bound to organic and inorganic ions, about 40% bound to albumin and remaining as biologically active ionic form. There are reports indicating both hypocalcemia (7) and hypercalcemia (8) in tuberculosis; however, only few reports showed symptoms associated with abnormal calcium status. Hypercalcemia is a serious clinical condition that can increase the risks of acute gastrointestinal events, kidney stone, and cardiovascular diseases such as myocardial infarction and stroke. Incidence vary widely among countries, for example Hypercalcaemia was detected in 25% of Greek and 27.5% of Malayasian TB cases with symptoms present in only 5% and 12% of these patients respectively (9). On the contrary, low prevalence of Hypercalcemia was seen in PTB cases in Hongkong (10). All the above studies showed alteration in Calcium metabolism in Tuberculosis that can lead to adverse disease outcome and secondary manifestations.

Since iCa is independent of protein level, it may better reflect Ca status than presently used Total Ca and assessing effect of severity on Ca level in PTB. Studies from India and U.S. that did not use correction for hypoalbuminaemia indicated that 16% to 28% of TB patients may develop hypercalcaemia. In contrast, studies using albumin- adjusted serum calcium concentration have reported higher prevalence rate ranging from 15% to 51% (11). Above observation also suggest that iCa can be more effective in classifying patients as hypo-, normo- and hypercalcemic in diseased condition. In our study, measurement of both Ionic Ca and Albumin adjusted Ca ensures accurate evaluation of Ca abnormalities in PTB.

As seen in table 1. Out of 120 PTB patients, 77.5% were males and 22.5% females. The average age of PTB patients was 51.22±17.2 years. 60 healthy subjects that served as control for comparison includes 83.4% males and 16.6% females and had an average age of 40.9 ± 16.8 years. No significant difference was seen between PTB patients and controls with regard to age and routine biochemical parameters (Sugar, Urea, creatinine) as seen in table 1. Mean Albumin level in PTB cases was 3.22 ± 0.63 g/dl which was significantly lower than controls i.e 4.36 ± 0.69 g/dl respectively ($p<0.001$). Low albumin was related to severe chacexia, weight loss, anorexia and malnutrition found commonly in PTB patients. Albumin is a component of plasma antioxidant activity and a negative Acute Phase Protein whose concentration decreases in any inflammatory condition, injury or stress as a result of increased metabolic need for tissue repair and free radical utilization (12). Relatively high occurance of hypoalbuminemia could be related to malnutrition, partly due to weak economic background of our patients and partly because of chronic ill health in TB.

Both CRP and ADA , used as Inflammatory markers were significantly high in PTB patients than control ($p<0.001$) (Table 1). CRP is an established marker of acute inflammation and its serum concentration is frequently determined to assess the grade of systemic inflammation. CRP is synthesized by hepatocytes under the influence of Interleukin-1 and other cytokines arising at the site of infection. Inflamed lung or pulmonary epithelial cells have been shown to express Interleukin-6 and CRP suggesting its beneficial role in clinical evaluation of Respiratory tract infection in adults (13). ADA acts in proliferation and differentiation of lymphocytes, maturation of monocytes and transforming them into macrophages . The enzyme is widely distributed in human tissue specially in T- lymphocytes. ADA is a significant indicator of active cellular immunity, the level of which would rise in disease where cell immunization is stimulated like Tuberculosis. Various studies indicate diagnostic and prognostic

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utility of Serum ADA in differentiating tuberculous and other pulmonary disease (14). It is simple and cost effective with high sensitivity and specificity to Pulmonary tuberculosis.

Both ionized Ca (iCa) and Albumin adjusted Ca were significantly higher in PTB patients (4.71±0.69 mg/dl ; 8.81± 1.3 mg/dl) than controls (4.2±0.56 mg/dl ; 7.5±1.1 mg/dl) respectively (Table 2). Only few of our PTB patients showed symptoms related to high Ca level. Serum Phosphorus did not show significant difference between PTB patients and controls (p=0.765) and poor correlation to disease severity. Phosphorus is a widely distributed element with skeleton as the major reservoir providing phosphate for both intracellular and extracellular pools. Since PTB is associated with muscle wasting, there may be slightly high serum phosphorus level in patients than controls. Further Phosphorus tends to be higher in those with elevated polymorphs suggesting its association with active phase of disease and tissue destruction. Both ionized Ca (iCa) and Albumin adjusted Ca showed some correlation to disease severity i.e r=0.297 and 0.300 (Figure 1 & 2) respectively (Table 5).

Incidence of hypercalcemia in our PTB population was 16.6% (taking ionic Ca into account) while only 2 out of 60 controls (3.33%) had ionized hypercalcemia. Only 10.8% of PTB cases exhibit more than normal calcium (8.4 – 10.4 mg/dl) when Albumin correction was not made. Hence, hypoalbuminemic adjustment is required while evaluating Ca status in Tuberculosis (table 6). It was slightly higher to the incidence rate in Hongkong (15%) and comparable to other studies conducted in India (16%) and lower than that reported in Malaysia (27.5%), USA (28%), much lower from that of Greece (48%) and of Australia (51%) (15). Studies conducted in Ethopia showed hypercalcemia (Ca >10.5 mg/dl) in 62.6% and 43.2% of TB patients with and without HIV-co infection respectively (15). Dosomu EA (2006) reported hypercalcemia in 27.5% of TB patients but only 12% showed symptoms like polyuria, polydipsia and constipation. Albumin adjusted Ca in TB patients before treatment was 2.53±0.22 mmol/l which was significantly higher than controls (2.38±0.09 mmol/l) (15). Patients with symptomatic hypercalcemia had higher Ca (3.16±0.35 mmol/l) than those with asymptomatic hypercalcemia (2.74±0.13 mmol/l) (15).

Memon ZM et al, 2014 acknowledged hypercalcemia in various granulomatous disease with mean Ca level of 16.67± 6.7 mg/dl that was more than normal range (8.4 – 10.4 mg/dl) and controls (8.8 ± 4.3 mg/dl) (16). Amare B et al (2012) supported our finding and observed hypercalcemia during the active phase of disease which was related to Calcium and Vitamin D in diet and sun exposure. Further, involvement of bone in severe TB has been postulated as one of the cause (17). Another study demonstrated significant increase in serum Ca in TB patients (9.4±0.9 mg/dl) when compared to controls (8.6±5.8 mg/dl) due to increased influx of Ca^{+2} into extra cellular compartment from skeleton, intestine and kidneythat occurs in tuberculosis (18). A recent study showed high Ca level in PTB patient group (n=79; 9.95 ±1.42 mg/dl) than in chronic obstructive pulmonary disease group (n=79; 9.45±0.81 mg/dl) supplemented with the same dose of vitamin D. Hypercalcemia was seen when sputum was positive for AFB (Acid fast bacilli) and while patients were on treatment during which they received 400 IU of vitamin D in diet. The elevated Ca becomes normal as soon as sputum gets negative for mycobacteria despite continuous supplementation with same dose of vitamin D (19).

Apart from TB, in condition such as malignancies (20) and renal failure (21), iCa proved to be a better investigation than Total Ca in studying overall Ca homeostasis. Our study showed however weak but positive correlation between Albumin adjusted Ca and disease severity (r=0.300). Absence of Correlation with CRP and ADA indicates a generalized increase of inflammatory markers mediated by cytokines that is not related to Calcium homeostasis (Table 5). Similar positive correlation was found between Albumin adjusted Ca concentration and extent of chest radiographic changes peculiar to PTB in other studies as well (22). Thus, ionic Ca and albumin adjusted Ca can be better parameters to study the effect of disease activity on Ca status in the body.

The metabolic active form of vitamin D (1,25diOH vitD) is known to have specific immunomodulator function and inhibit Mycobacterial growth by stimulating cell mediated immunity and enhancing antimycobacterial activity of macrophages and lymphocytes. Here, cultured alveolar macrophages obtained from patients with PTB express 1-α

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hydroxylase enzyme (that converts circulating vitamin D form 25OHvitD to active 1,25diOH vitD form). This extra renal 1-α hydroxylase activity of immune cells is not regulated by parathyroid hormone but instead is activated by other mechanism involving γ-interferon and cytokines. 1,25diOH vitD produced locally by immune cells constitute an important component of T- cell mediated immune response in Pulmonary tuberculosis. If large quantity of 1,25diOH VitD is produced, it overspills in circulation resulting in hypercalcemia and hypovitaminosis D during the active phase of the disease as seen in this study.

Further, in countries with abundant sunlight, synthesis of vitamin D in skin and dietary intake causes increase in circulating vitamin D (substrate for the enzyme 1-α hydroxylase) available for extra renal conversion to 1,25diOH vitD. In such cases, if Calcium intake is high, gut absorption of Ca is also relatively high that explain occurance of hypercalcemia in TB patients in tropical countries. Increased 1,25diOH vitD i.e the active form of vitamin D has direct suppressive effect on PTH synthesis and secretion. Abnormal PTH production and release along with enhanced consumption of vitamin D affects overall Calcium homeostasis. The active form of vitamin D increases fractional absorption of Ca from the gut that can also lead to ionized hypercalcemia . All the above discussion suggest disturbed Calcium level (both ionized and Albumin adjusted) in PTB which should be evaluated properly before starting any mineral supplementation.

CONCLUSION: The present study suggests abnormality in Calcium metabolism with ionized hypercalcemia in PTB patients as compared to healthy controls. Enhanced extra renal 1-α hydroxylase activity along with increased absorption of dietary calcium may account for the above. Further, correction for hypoalbuminemia, commonly seen in tuberculosis is required while interpreting hypercalcemia for better understanding of Calcium status. Calcium and vitamin D supplementation in PTB should be managed promptly. This will help in improving disease outcome and quality of life.

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Table 1. General characterstics and Biochemical profile of study population

S. No.	General Characterstics	PTB patients	Controls	Significance (p value)
1.	No. of cases (n)	120	60	
2.	No. males	93 (77.5)	50 (83.4)	0.3628
3.	No. females	27 (22.5)	10 (16.6)	
4.	Average Age (in years)	51.22± 17.20	40.9 ± 16.8	0.0018 S
5.	Sputum Status			
	Negative	43 (35.8)	60 (100)	
	+1	52 (43.3)	0 (0)	
	+2	16 (13.33)	0 (0)	
	+3	9 (7.5)	0 (0)	
6.	Blood Sugar (mg/dl)	82.6± 19.0	81.12±17.88	NS
7.	Serum Urea (mg/dl)	31.7 ± 8.77	31.66±8.43	NS
8.	Serum Creatinine (mg/dl)	1.01 ± 0.56	0.92 ± 0.43	NS
9.	Serum Albumin (g/dl)	3.22 ± 0.63	4.36 ± 0.69	<0.05 S
10.	Serum ADA (U/L)	12.76± 8.7	1.77± 0.76	<0.001
11.	Serum CRP (mg/L)	21.7 ± 14.5	4.3± 3.0	<0.001

Values are mean ± SD; values in parenthesis are percent. P < 0.05 is significant. NS: Not Significant
PTB: Pulmonary Tuberculosis; BMI: Body Mass Index ; MUAC: Mid upper arm circumference.
CRP: C-reactive Protein, ADA: Adenosine Deaminase

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Table 2: Calcium and Phosphorus level in PTB patients and Controls

S. No.	Biochemical Parameters	**PTB patients (n= 120)**	**Controls (n= 60)**	**Significance (p value)**
1.	Total Calcium (mg/dl)	8.68 ± 1.18	8.26 ± 0.8	0.0133
2.	Ionic Calcium (mg/dl)	4.71± 0.69	4.20± 0.56	<0.001
3.	Albumin adjusted Calcium (mg/dl)	8.81± 1.3	7.5± 1.1	<0.001
4.	Serum Phosphorus (mg/dl)	4.38 ± 0.89	4.34 ± 0.85	0.765

Values are mean ± SD; P < 0.05 is significant. NS: Not Significant PTB: Pulmonary Tuberculosis.

Table 3. Calcium and Phosphorus level in PTB patients according to Clinical Severity

S. No.	Biochemical Parameter	**Severity Class I N= 19**	**Severity Class II N= 29**	**Severity Class III N= 72**
1	Total Calcium (mg/dl)	8.4 ± 1.0	8.2 ± 0.96	8.9 ± 1.2
2.	Ionic Calcium (mg/dl)	4.5 ±0.60	4.42 ± 0.50	4.88 ± 0.73
3.	Albumin adjusted Calcium (mg/dl)	8.39 ± 1.1	8.26 ± 0.93	9.14 ± 1.38
4.	Serum Phosphorus (mg/dl)	4.5 ± 0.8	4.6 ± 0.79	4.2 ± 0.9

Values are mean ± SD; PTB: Pulmonary Tuberculosis

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Table 4: Calcium and Phosphorus level in PTB patients according to Sputum Positivity.

S. No.	Biochemical Parameters	Sputum positivity			
		Negative (N=43)	+ 1 (N= 52)	+2 (N= 16)	+ 3 (N= 9)
1	Total Calcium (mg/dl)	8.7± 1.2	8.4± 1.0	8.9± 1.1	9.6± 1.5
2.	Ionic Calcium (mg/dl)	4.7 ± 0.75	4.5 ± 0.57	4.8 ± 0.68	5.3 ± 0.80
3.	Albumin adjusted Calcium (mg/dl)	8.8 ± 1.4	8.47 ± 1.0	9.0 ± 1.16	10.0 ± 1.56
4.	Serum Phosphorus (mg/dl)	4.3± 0.7	4.4± 0.86	4.3 ± 1.2	4.6 ± 0.9

Values are mean ± SD; PTB: Pulmonary Tuberculosis.

Table 5. Correlation of Calcium and Phosphorus level with Disease severity and Inflammatory Markers

Biochemical parameters	Correlation coefficient (r)			
	Disease severity	Sputum Positivity	ADA	CRP
Total Calcium (mg/dl)	0.287	0.157	0.23	0.13
Ionic Calcium (mg/dl)	0.297	0.165	0.26	0.118
Albumin adjusted Calcium (mg/dl)	0.300	0.165	0.27	0.087
Serum Phosphorus (mg/dl)	-0.17	0.07	-0.16	-0.08

P < 0.05 is significant. PTB: Pulmonary Tuberculosis, CRP: C-reactive Protein, ADA: Adenosine Deaminase

Table 6. Prevalance of Hypercalcemia in Pulmonary Tuberculosis (PTB) cases and controls.

Serum Calcium (mg/dl)	PTB patients (N=120)		Controls (N=60)	
	Hypercalcemic N(%)	Normocalcemic N(%)	Hypercalcemic N(%)	Normocalcemic N(%)
Total Calcium	13(10.8)	107(89.16)	1(1.66)	59(98.33)
Ionic Calcium	20(16.6)	100(83.3)	2(3.33)	58(96.66)
Albumin adjusted Calcium	15(12.5)	105(87.5)	1(1.66)	59(98.33)

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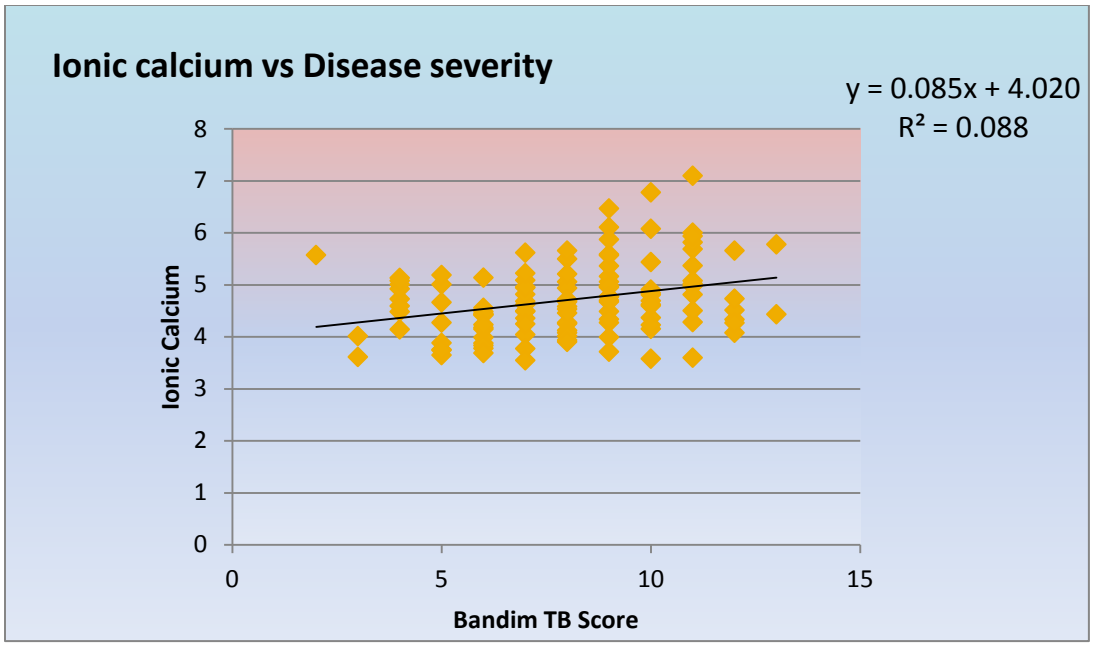

Fig 1: Correlation between Ionic Calcium and Disease severity

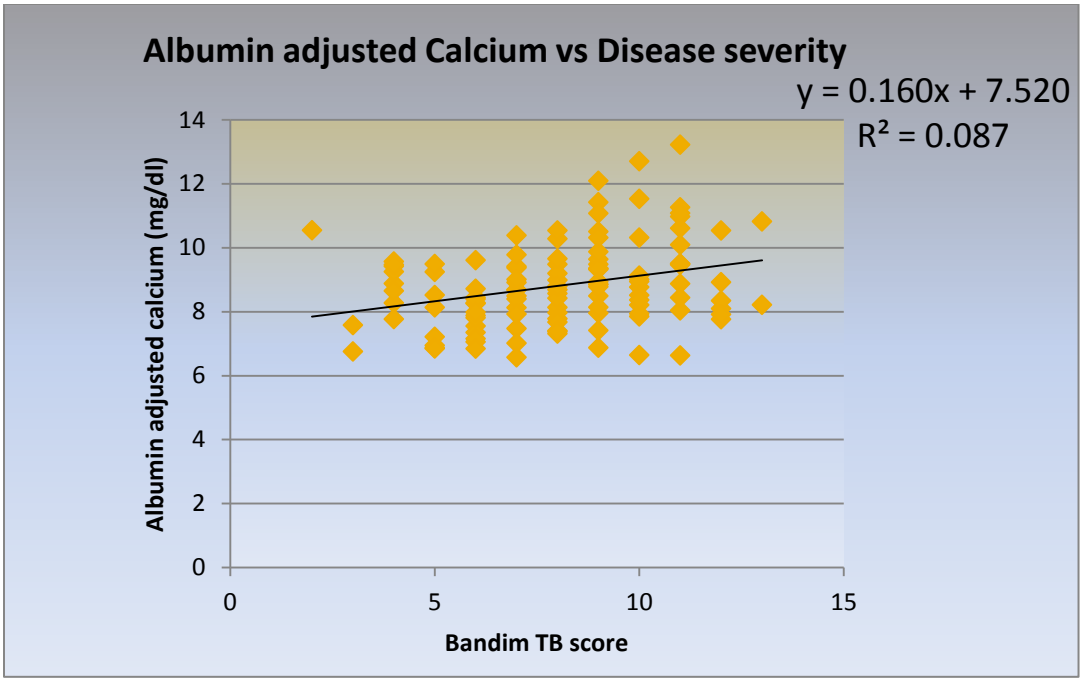

Fig 2. Correlation between Albumin adjusted Calcium and Disease severity

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