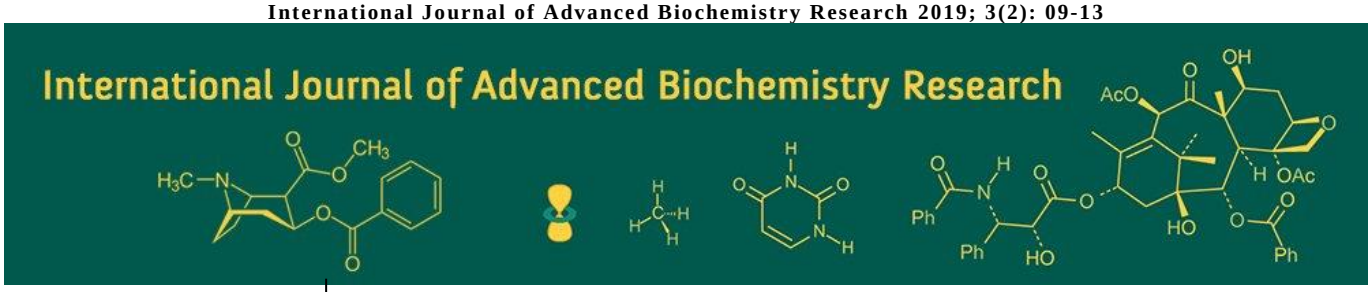

ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2019; 3(2): 09-13
www.biochemjournal.com
Received: 06-05-2019
Accepted: 10-06-2019

Harissh Ganesan
II M.B.B.S., Student, Government Villupuram Medical College and Hospital, Mundiyambakkam, Villupuram, Tamil Nadu, India

Poonguzhali Gopinath
Professor, Department of Biochemistry, Government Thiruvannamalai Medical College and Hospital, Mundiyambakkam, Villupuram, Tamil Nadu, India

Corresponding Author:
Poonguzhali Gopinath
Professor, Department of Biochemistry, Government Thiruvannamalai Medical College and Hospital, Mundiyambakkam, Villupuram, Tamil Nadu, India

Prevalence of hypoalbuminemia among tuberculosis patients receiving anti tuberculosis therapy: A cross sectional study

Harissh Ganesan and Poonguzhali Gopinath

Abstract
Background: Tuberculosis (TB) is one of the most common disease seen in overcrowding population. The high prevalence of tuberculosis in developing countries is due to various factors like poverty, malnutrition, overcrowding and poor socioeconomic status. It is having also been recorded that malnutrition is one of the major causes for the incidence of this disease in healthy individuals. Malnutrition can lead to poor prognosis of the Anti-tuberculosis therapy (ATT). Hence, Prevalence of hypoalbuminemia is of major concern in determining the prognosis of the disease.
Objective: To estimate the serum total protein, albumin and globulin of patients with TB and compare albumin levels with Pulmonary Tuberculosis (PTB) patients and Extra Pulmonary Tuberculosis (EPTB) patients. Also, to correlate albumin levels with Body Mass Index (BMI) and Waist Hip Ratio (WHR) of the patients.
Method: This cross-sectional study was conducted in 100 patients in two groups namely PTB and EPTB. The albumin levels were noted along with the BMI and WHR of the patients in both groups of TB.
Results: The average age of the patients was 38.9 years. There was 65% of patients with PTB and 35% of patients with EPTB. The mean albumin, BMI and WHR of the patients were 3.2 ± 0.6, 19.7 ± 3.7 and 0.96 ± 0.01 respectively. The albumin levels of PTB group was 3.1 ± 0.6 and EPTB was 3.4 ± 0.6. the WHR of PTB patients was 0.99 ± 0.12 and EPTB was 0.90 ± 0.15. Albumin and WHR showed statistical significance with p value 0.007 and 0.003 respectively.
Conclusion: Hypoalbuminemia in TB patients correlated with the BMI and with WHR. Sputum positivity was independent of the albumin levels. The results highlighted the prevalence of low albumin levels and malnutrition in patients with TB, especially PTB.

Keywords: Tuberculosis, hypoalbuminemia, malnutrition, anti-tuberculosis therapy

Introduction
Tuberculosis (TB) is a worldwide known communicable disease that has been a challenge to mankind for long. It is caused by Mycobacterium tuberculosis that has a predilection to the lungs causing Pulmonary Tuberculosis (PTB) though tuberculosis of pleura, lymph node, abdomen, genitourinary tract, skin, meninges, joints and bones are not uncommon. According to the National tuberculosis statistics for India collected by the Revised National tuberculosis Control programme, the incidence in 2018 is estimated to be about 2.9 million cases of TB in our country. Every year there are about 8.6 million new cases of tuberculosis globally, out of which 2.2 million cases are reported from India. India has the highest number of cases in the world and most of the cases are due to reoccurrence, especially in South India. The high prevalence of tuberculosis in developing countries is due to various factors like poverty, malnutrition, overcrowding and poor socioeconomic status. The interaction between malnutrition and tuberculosis is bidirectional [1]. Protein malnutrition has been shown to impair the cell mediated immunity against Mycobacterium by decreasing the production of Interferon –γ as well as CD4 and CD 8 cells. Inflammatory cytokines such as interleukin and TNF released during the infection will increase the synthesis of acute phase reactants in the liver thereby decreasing the synthesis of Albumin [2].
Although documentations from previous studies states the prevalence of hypoalbuminemia among TB patients confirms albumin to marker of prognosis and mortality in TB, a metanalysis by Si LM *et al* has shown no significant difference in albumin even after nutritional support to TB patients [1]. Achim schwenk *et al* suggests that serum albumin

improves with treatment and is the most accurate indicator of nutritional improvement in tuberculosis patients especially with regard to crucial fat free mass [4]. Hypoalbuminemia is also known to be predictive of extrapulmonary tuberculosis [5]. Additionally, low albumin levels have been associated with increased risk of Drug induced liver injury (DILI) with anti-tuberculous therapy [6].

India- An endemic for tuberculosis

With the increasing Endemicity of TB in India, the government of India has set a target of for TB elimination by the year 2025. Despite all efforts taken by the government TB continues to cause a formidable challenge to public health. Social determinants such as poverty, overcrowding, malnutrition need to be addressed for effective control and prevention. Patients support for reducing out of pocket expenditure & nutrition support are key features of national strategy plan (2017- 25).

The reactivation of the latent infection may continue to perpetuate new cases in the future despite the implementation of effective Directly Observed Treatment Short course (DOTS) due to emergence of multi-drug resistance strains [7].

Role of albumin and its importance

The most abundant plasma protein is serum albumin and it is produced in the liver.

The human serum albumin, normally constitutes about 50% of human plasma protein [9]. Endogenous albumin is also produced exclusively by the hepatocytes at the rate of 9 to 12 g/day [9]. Even though, Hypoalbuminemia decreases hepatic interstitial oncotic pressure and stimulates albumin synthesis, malnutrition decreases the synthesis of albumin. Hence, malnutrition and synthesis are indirectly proportional [10].

Significance of monitoring albumin levels in tuberculosis patients

Protein malnutrition has been shown to impair the cell mediated immunity against Mycobacterium by decreasing the production of Interferon –γ as well as CD 4 and CD 8 cells. Inflammatory cytokines such as interleukin and TNF released during the infection will increase the synthesis of acute phase reactants in the liver thereby decreasing the synthesis of Albumin [11]. Hence leading to low albumin levels-hypoalbuminemia.

Tuberculosis is endemic in our country affecting nearly 40 percent of the population in whom the infection is latent. The malnutrition still prevalent in various part of the country perpetuates the infection. This adds to the disability adjusted life years (DALY) of the individual that is reflected in the cost of resources in terms of health care and manpower lost. This study would reveal the extent of hypoalbuminemia in our population and its association with treatment. This would pave way for interventional approach nationwide that would address the hypoalbuminemia and its complications in tuberculosis patients.

Serum albumin levels in tuberculosis

In 2018 a study done by Lee *et al* in Republic of Korea showed that TB unrelated death was commonly seen in old aged patients having low albumin levels [12]. In 2018, Janmeja *et al* has documented that BMI and albumin levels are reliable factor for prognosis in TB [13]. In 2017, Christina Yoon *et al* concluded that DILI would decrease the production of albumin in patients undergoing anti-tuberculosis therapy [14]. Wang *et al* found that the immune status also decreased in pulmonary tuberculosis when the albumin levels were low. As the serum albumin levels decreased the chance of death increased especially in HIV patients with tuberculosis [15]. A study done by Svenson *et al* in the year 2016 at Sweden stated that in multi drug - resistant tuberculosis (MDR-TB) the albumin concentration and body weight are altered; this potential change will affect the drug disposition in long treatment period [16].

A study done by Matos *et al* suggest that malnutrition is frequently seen in patients with tuberculosis. Hypoalbuminemia is itself can be a major cause for malnutrition. In patients undergoing antituberculotic therapy showed increase in the albumin levels as the treatment progressed highlighting that albumin to be a prognostic marker [18]. Kim *et al* in 2010 had found that the nutritional status was significantly very poor in patients suffering with active pulmonary tuberculosis. Additionally, albumin synthesize was also low [19].

Aim

To assess the serum total protein and albumin levels in tuberculosis patients and its association with the clinical manifestations and treatment.

Objectives

a) To estimate the serum total protein, albumin, globulin and albumin globulin ratio in tuberculosis patients.
b) To compare the albumin levels between pulmonary and extrapulmonary TB patients
c) To correlate the albumin levels with the sputum positivity and treatment received
d) To correlate the albumin levels with Body mass Index (BMI), Waist hip ratio (WHR)

Materials and Methods

The present study is a cross sectional study conducted in the Department of Biochemistry with the subjects recruited from the RNTCP OPD in Government Villupuram Medical College and Hospital. The ethical clearance was obtained from the Institutional Ethical Clearance Committee. After getting the written informed consent the subjects were recruited based on the inclusion and exclusion criteria. The inclusion criteria were patients diagnosed with Tuberculosis by using Revised National tuberculosis control Programme (RNTCP) diagnostic algorithm [20] and on Anti-tuberculous therapy. The patients suffering from active liver disease, other associated pulmonary diseases, pregnant and lactating females and patients suffering from HIV were excluded from this study.

The details regarding age, type of TB, sputum positivity, category of D.O.T.S. received, duration of treatment was collected from the study subjects. The patients were divided into two groups - PTB and EPTB based on the WHO guidelines. Then a sample of 5 ml of blood was collected for the study subject for biochemical analysis. The biochemical parameters were estimated using Beckmann Coulter AU 480 by standard methods. The distribution of all biochemical parameters is expressed as mean with S.D and they were statistically analyzed and it was carried out at 5% level of significance and P value less than 0.05 was considered as statistically significant.

Observation and Results

Out of the 100 subjects included in the study, 1 out layered subject with age less than 5 months was excluded for data analysis. In the study population 60 were males and 40 were females. The mean age of the study subject was 38.9 years with a range of 5 to 75 years. The data regarding the study parameters were shown in Table 1 and the comparison/correlation between the two groups are shown in Table 2, Table 3 and Table 4.

Table 1: Characteristics of the study population.

S. No	Parameters	Data
1	Age (in years)	38.91 ± 15
2	Sex Male (n)	60
	Female (n)	40
3	WHR (cm/cm)	0.96 ± 0.01
4	BMI (kg/m2)	19.7 ± 3.7
5	Type of TB PTB (n)	65%
	EPTB (n)	35%
6	Sputum positivity (n)	80
11	Glucose (mg/dl)	132 ± 73
12	Urea (mg/dl)	25 ± 20
13	Creatinine (mg/dl)	1.0 ± 0.4
14	Total bilirubin (mg/dl)	0.6 ± 0.2
15	Direct bilirubin (mg/dl)	0.2 ± 0.1
16	Indirect bilirubin (mg/dl)	0.4 ± 0.1
17	Total protein (g/dl)	6.7 ± 1.3
18	Albumin (g/dl)	3.2 ± 0.6
19	Globulin (g/dl)	3.5 ± 0.6
20	AGR	1.2 ±1.5
21	AST (IU/l)	23 ± 0.9
22	ALT (IU/l)	19 ± 12

Table 2: Comparison between the two groups.

S. No	Parameters	PTB	EPTB	p Value
1	Number	65	35	
2	Age (in years)	40.0 ± 15.3	36.7 ± 17.1	0.3
3	Waist circumference (cm)	37 ± 20	34 ± 18	0.6
4	Hip circumference (cm)	37 ± 20	39 ± 19	0.7
5	WHR (cm/cm)	0.99 ± 0.12	0.90 ± 0.15	0.003 *
6	Height (cm)	150 ± 10	147 ± 10	0.3
7	Weight (cm)	44 ± 8	45 ± 12	0.6
8	BMI (kg/m2)	19.5 ± 3.2	20.1 ± 4.5	0.4
9	Glucose (mg/dl)	137 ± 85	121 ± 40	0.2
10	Urea (mg/dl)	26.7 ± 24	23 ± 8	0.4
11	Creatinine (mg/dl)	1.0 ± 0.4	0.9 ± 0.3	0.4
12	Total bilirubin (mg/dl)	0.6 ± 0.2	0.6 ± 0.1	0.7
13	Direct bilirubin (mg/dl)	0.2 ± 0.1	0.2 ± 0.1	0.4
14	Indirect bilirubin (mg/dl)	0.4 ± 0.1	0.4 ± 0.1	0.9
15	Total protein (g/dl)	6.7 ± 1.5	6.8 ± 0.6	0.7
16	Albumin (g/dl)	3.1 ± 0.6	3.4 ± 0.6	0.007 *
17	Globulin (g/dl)	3.6 ± 1.7	3.3 ± 0.7	0.3
18	AGR	1.2	1.1	0.6
19	AST (IU/l)	22 ± 9	26 ± 8	0.1
20	ALT (IU/l)	7 ± 12	22 ± 13	0.6

p value is statistically significant

Table 3: Correlation of albumin with BMI and WHR

S. No	Parameter	r Value	p Value
1	BMI	1.09	0.2
2	WHR	-1.07	0.2

Table 4: Correlation of albumin with sputum positivity

Sputum				
S. No	CONC. of Albumin	Positive	Negative	P Value
1	ALBUMIN < 3mg/dl	28	4	0.187
2	ALBUMIN > 3mg/dl	51	16	

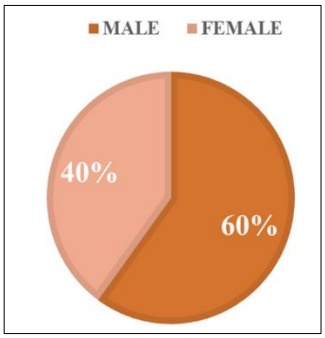

Fig 1: Distribution of Males and Females in the study population

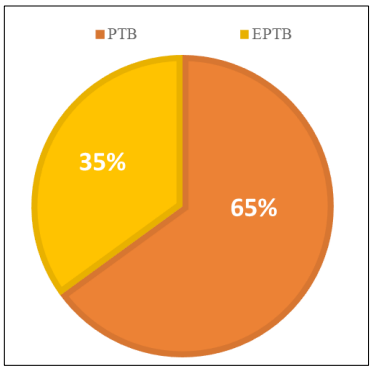

Fig 2: Distribution of patients with Pulmonary Tuberculosis (PTB) and Extra-Pulmonary Tuberculosis (EPTB)

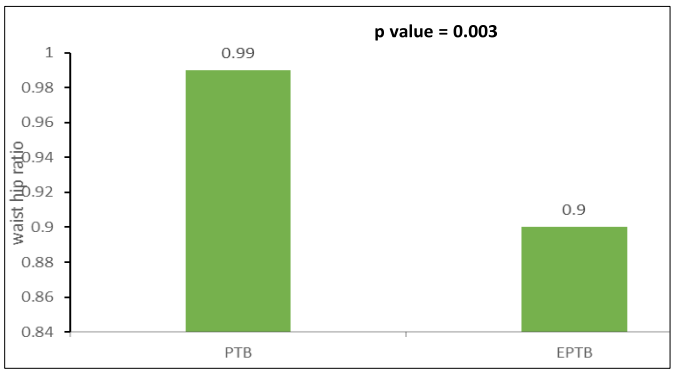

Fig 3: Comparison of waist-hip ratio between Pulmonary Tuberculosis (PTB) and Extra Pulmonary Tuberculosis (EPTB)

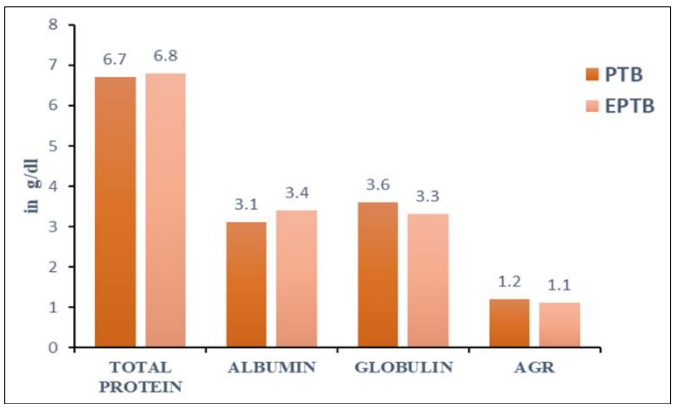

Fig 4: Comparison of serum protein levels between pulmonary tuberculosis (PTB) and extra pulmonary tuberculosis (EPTB)

Discussion

Early studies stated 63% of the tuberculosis patients were lesser than 40 years old which was similar to our study. In our study 20% of the study population had total protein lesser than 6 g/dl which was similar to the study done by Chavan *et al* in the Indian population which was about 23% of the study population. Chavan *et al* also stated that the albumin levels were 3.5 g/dl and above in mild cases and 2.7 g/dl in severe cases as it included both out patients and in-patient cases and, in our study, the mean albumin levels were about 3.2 g/dl which is similar. In this study it was found that 60% of PTB patients had albumin lesser than 3.5g/dl having similar values to the study done by Morris *et al*, where 72% of PTB had lesser albumin and severe cases with plural effusion, disseminated tuberculosis along with PTB had very minimal values of albumin but it has no diagnostic value and indication response to the infected population.

In a study conducted by Kim *et al*, it was concluded that patients with increased levels of albumin had less chance of involvement of extra-pulmonary tuberculosis but in this study the levels of albumin of extrapulmonary tuberculosis cases was comparatively higher than that of pulmonary tuberculosis. This could be probably due to the systemic involvement of the disease as 30% of the cases included were of milaiary tuberculosis. Wherein the present study did not include the site of EPTB as the patients were out-patients receiving ATT [21].

Janmeja *et al* has documented serum albumin was independently associated with treatment success with an odds ratio of 3.71. Hence a normal albumin levels in the present study group can be considered as a good sign of clinical outcome in the management of TB. They have suggested that nutritional interventions rather than DOTS plus strategy is helpful in the improvement of success rate. The albumin levels were not significantly low in the study population as documented in the other studies probably because the patients were out patients and the pathogenesis of the disease would be less severe compared to in patients as evaluated in other studies [13].

Muthuraj *et al* conducted a study in patients with PTB along with HIV infection and has substantiated the importance of nutritional supplementation in such active TB cases in addition to Anti-Retroviral Therapy. Similar recommendation for all TB patients may benefit those proportion of patients with low albumin levels. NACO provides nutritional supplements to those receiving Anti-retroviral therapy. According to a systematic review and metanalysis of 19 studies done by LI SI *et al* states that nutritional supplementation improves sputum smear conversion rates but not the serum albumin levels. Similarly, in the present study also sputum positivity and albumin were independent factors and didn't have significant correlation. A South Indian study conducted in 50 TB patients receiving Anti Tuberculosis therapy, serum albumin significantly improved after 6 months of treatment. Hence a prospective study of the recruited patients for monitoring the serum albumin levels at the end of the therapy would explain the variations in albumin levels of the patients [7].

Conclusion

Low albumin levels were seen in 60% of the newly diagnosed PTB patients. The albumin levels were normal in most of the TB patients attending the out-patient department for initiation of anti-tuberculosis therapy. The albumin levels correlated with BMI and WHR but not with sputum positivity. However, further follow up of these patients could indicate the change in albumin levels with respect to disease progression and treatment.

Acknowledgement: Indian council of medical research-short term studentship 2018.

References

1. Si Z-L, Kang L-L, Shen X-B, Zhou Y-Z. Adjuvant Efficacy of Nutrition Support During Pulmonary Tuberculosis Treating Course: Systematic Review and Meta-analysis. Chin Med J (Engl). 2015; 128(23):3219-30.
2. Xing Z, Gauldie J, Cox G, Baumann H, Jordana M, Lei XF, *et al*. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. J Clin Invest. 1998; 101(2):311-20.
3. Adebisi SA, Oluboyo PO, Oladipo OO. The usefulness of serum albumin and urinary creatinine as biochemical indices for monitoring the nutritional status of Nigerians with pulmonary tuberculosis. Niger Postgrad Med J. 2003; 10(4):247-50.
4. Schwenk A, Hodgson L, Wright A, Ward LC, Rayner CFJ, Grubnic S, *et al*. Nutrient partitioning during treatment of tuberculosis: gain in body fat mass but not in protein mass. Am J Clin Nutr. 2004; 79(6):1006-12.
5. Kim MJ, Kim H-R, Hwang SS, Kim YW, Han SK, Shim Y-S, *et al*. Prevalence and its predictors of extrapulmonary involvement in patients with pulmonary tuberculosis. J Korean Med Sci. 2009; 24(2):237-41.
6. Devarbhavi H, Singh R, Patil M, Sheth K, Adarsh CK, Balaraju G. Outcome and determinants of mortality in 269 patients with combination anti-tuberculosis druginduced liver injury. J Gastroenterol Hepatol. 2013; 28(1):161-7.
7. Sujatha Narayanan *et al*. Molecular Epidemiology of Tuberculosis in a Rural Area of High Prevalence in South India: Implications for Disease Control and Prevention. J Clin Microbiol. 2002; 40.
8. Sanjay Mehendale. How is tuberculosis affecting public health globally and nationally? ICMR-Natl Inst Res Tuberc. 2016;
9. Wingfield WE. Fluid and electrolyte therapy. The veterinary ICU Book. Jackson, WY, Teton New Media, 2002.
10. Caceci T. Veterinary histology example: hepatocytes. Accessed. Va Md Reg. Coll. Vet Med, 2005.
11. Xing Z, Gauldie J, Cox G, Baumann H, Jordana M, Lei XF, *et al*. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. J Clin Invest. 1998; 101(2):311-20.
12. Si Z-L, Kang L-L, Shen X-B, Zhou Y-Z. Adjuvant Efficacy of Nutrition Support During Pulmonary Tuberculosis Treating Course: Systematic Review and Metaanalysis. Chin Med J Engl. 2015; 128(23):3219-30.
13. A.K. Janmeja *et al*. Factors predicting treatment success in multi-drug resistant tuberculosis patients treated under programmatic conditions. Indian J Tuberc, 2017.
14. Ariana Díaz. The clinical recovery of tuberculosis patients undergoing specific treatment is associated

with changes in the immune and neuroendocrine responses, 2017.
15. Christina Yoon *et al*. Point-of-care C-reactive protein-based tuberculosis screening for people living with HIV: a diagnostic accuracy study. Lancet Infect. 2017; (17):1285-92.
16. Wanli Kang. Factors associated with negative T-SPOT.TB results among smear negative tuberculosis patients in China. Sci Rep, 2018.
17. EM Svensson. Population Pharmacokinetics of Bedaquiline and Metabolite M2 in Patients with Drug-Resistant Tuberculosis: The Effect of Time-Varying Weight and Albumin. CPT Pharmacomet Syst Pharmacol, 2016.
18. H. Simon Schaaf. Nutritional status and its response to treatment of children, with and without HIV infection, hospitalized for the management of tuberculosis. Paediatr Int Child Health. 2012; 32(2).
19. E. D. Matos. Association between serum albumin levels and in-hospital deaths due to tuberculosis. Int J Tuberc Lung Dis. 2006; 10(12):1360-6.
20. Ji Hae Kim. Relation of ghrelin, leptin and inflammatory markers to nutritional status in active pulmonary tuberculosis. Clin Nutr. 2010; 29:512-8.
21. Central TB Division. Guidelines on programmatic manage-ment of drug resistant TB (PMDT) in India. India Dir Gen Health Serv, 2012.