

Study of serum protein and electrophoretic pattern in pulmonary tuberculosis patients

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Received: 20th January, 2018

Accepted: 7th June, 2018

Abstract

Tuberculosis, one of the oldest diseases known to affect humans, particularly in under developed and developing countries and is a major cause of death worldwide. This study deals with the estimation of total serum proteins, albumin levels and its electrophoretic pattern in pulmonary tuberculosis patients and analyses, the changes with reference to the severity of the disease. The present study included a total number of 40 subjects comprising of 20 cases and 20 controls. Total serum protein was estimated by modified biuret end point assay method, albumin by bromocresol green end point assay method and serum protein electrophoresis using Helena electrophoretic apparatus SAS-MX serum protein gel. Total proteins were slightly decreased in cases compared to controls value. Albumin was significantly decreased in cases compared to controls. Alpha-1 globulins slightly increase in cases compared to controls. No change in levels of alpha-2 globulins in controls and cases. Beta globulins very slightly decrease in cases compared to controls. Gamma globulins significantly increases in cases compared to controls. Student's t-test was performed to test the difference between the groups. The level of significance selected was P-value <0.05. The present study shows that, Albumin levels are decreased and gamma globulins are elevated. The result confirms that Albumin and Globulin levels are changed in pulmonary tuberculosis patients when compared to normal indicating their effect on pulmonary tuberculosis patients.

Keywords: MTB: Mycobacterium Tuberculosis, Electrophoretic pattern of proteins.

Introduction

Our country has the highest burden of tuberculosis in the world. It accounts to approximately, one-fifth (20%) of global burden of tuberculosis.^{1,2} According to the statistical analysis, every year approximately 1.8 million persons develop tuberculosis. Of which about 0.8 million are new smear positive and are highly infectious cases.³⁻⁵ Two out of every five Indians are infected with TB bacillus. Every day about 5,000 people develop the disease. About 10-15 people are getting infected per year from infectious patients. About 0.37million people die per year with tuberculosis. This increase in Mycobacterium tuberculosis (MTB) infections focused considerable attention on the development of assays and molecular methods for the rapid diagnosis of MTB infection. Electrophoretic separation of serum proteins is a diagnostic tool and it is also helpful in monitoring the treatment progress.⁶ M.tuberculosis is a rod-shaped, non-spore-forming, aerobic bacterium measuring 0.5 µm by 3µm belonging to the family Mycobacteriaceae and the order Actinomycetales. Mycobacterium tuberculosis is a facultative intra cellular parasite and it is resistant to intracellular killing.⁷ Patients remain infective till they stay untreated.⁸ M. tuberculosis is commonly transmitted from an infectious tuberculosis patient to others by droplet nuclei (<5–10µm in diameter), which are aerosolized by coughing, sneezing, or speaking. The tiny droplets may remain in the air for several hours and will reach the air passages when inhaled. Droplet

nuclei, due to very small in size, when inhaled, bypass the mucociliary defense mechanism of the bronchi. Thus they get deposited in the terminal alveoli of the lungs. This leads to the formation of Ghons focus. Through lymphatics the bacilli reach the hilar lymph nodes. Bacilli may spread throughout the body through hematogenic route. A good immune response will stop the multiplication of bacilli. However, a few dormant bacilli may persist. A positive tuberculin skin test indicates that there is infection. Especially in few cases, where the immune response is low, the bacilli starts its multiplication and disease manifests within a few months.⁹⁻¹¹ Most of infected individuals develop tuberculosis within the first year or two of infection. Primary infection presents with no clinical disease, there will be positive tuberculin skin test, hypersensitivity reactions like (erythema nodosum, phlyctenular conjunctivitis, etc), pulmonary complications like (tuberculosis pneumonia, hyperinflation and segmental or lobar collapse/consolidation, pleuraleffusion, partial obstruction may cause obstructive emphysema, bronchiectasis, cervical lymphadenopathy, meningitis and pericarditis. Bacilli reach the bloodstream from the pulmonary lesion or the lymph nodes and disseminate into various organs, where they produce granulomatous lesions. Immunocompromised persons may develop miliary tuberculosis and/or tuberculous meningitis. Dormant bacilli, persist for years before reactivation, to produce secondary (or post primary) tuberculosis. This

leads to frequent cavitation, which is more infectious than the primary disease. Early in the course of disease, symptoms and signs are often nonspecific and insidious, consisting mainly of fever and night sweats, weight loss, anorexia, general malaise, and weakness. However, in the majority of cases, cough eventually develops, which is, initially nonproductive and subsequently accompanied by the production of purulent sputum, sometimes with blood streaking. Massive hemoptysis may occur as an erosion of a blood vessel in the wall of a cavity. Pleuritic chest pain develops in patients with sub pleural parenchymal lesions. Extensive disease may produce dyspnea and, rarely leads to, adult respiratory distress syndrome (ARDS). Extra pulmonary tuberculosis commonly involve, the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. As a result of hematogenous spread in HIV-infected individuals, extrapulmonary tuberculosis is seen more common. Cytokines are responsible for clinical and laboratory alterations which occur during the inflammatory process, such as fever, leukocytosis, thrombocytosis, and acute-phase hepatic responses.¹² There are changes in levels of serum proteins in response to both acute and chronic infections. However, the change in level of each protein at any particular time usually reflects the net effect of the rate of synthesis and rate of catabolism, as a result of host microbe interaction. In chronic infectious TB disease, the albumin shows a decrease while globulin content shows an increase leading to low Albumin to Globulin (A/G) ratio and albumin to alpha-2 globulin ratios.¹³ Our aim to note the alterations in the Serum proteins in relation to Mycobacterium tuberculosis.

The following biochemical parameters are estimated as per the procedures indicated and compared with normal (non pulmonary tuberculosis) patients.

1. Total serum proteins
2. Estimation of albumin
3. Serum protein electrophoresis

Albumin is the most abundant serum protein. Low levels of albumin is an indicator of poor health and it is a predictor of a bad outcome. Optimal Range: 4.5-5.0 g/dl. The term globulin means a heterogeneous group of proteins with typical high molecular weight, and having both solubility and electrophoretic migration rates

lower than for albumin. The normal concentration in blood is 2.60 to 4.60 g/dl.

Protein electrophoresis is used to categorize globulins into the following four categories: Alpha 1 globulins, alpha 2 globulins, beta globulins, gamma globulins (Immunoglobulins, are one of the type of gamma globulins, that function as antibodies) optimal range of alpha-1 globulin is 0.2-0.3 g/dl, alpha-2 globulin is 0.6-1.0 g/dl, beta globulin is 0.7-1.2 g/dl and gamma globulin is 0.7-1.6 g/dl.

Material and Methods

This study was carried out in the Department of Biochemistry, S.V.S Medical College and Hospital Mahabubnagar after taking the consent from the patients and institutional ethical approval. All the subjects who were included in the study were admitted in the Department of Pulmonology, SVS Medical College and Hospital. We have taken 20 controls as normal patients and 20 cases as pulmonary tuberculosis patients we estimated the levels of serum proteins. Patients were selected on the basis of vital signs like cough; fever, headache, AFB-positive, Montoux test-positive chest x-ray etc. Total Serum Proteins was estimated by Modified Biuret, end point assay method.

Assay Principle: Peptide bonds of proteins react with the cupric ions to form a coloured complex in the alkaline medium. The absorbance is measured at 578nm. The Biuret reagent containing sodium-potassium tartrate, helps in maintaining solubility of this complex at alkaline pH. The colour obtained is directly proportional to the concentration of total protein in the sample.

Reagent Composition: Biuret reagent – copper sulphate, sodium hydroxide, sodium potassium tartrate, surfactant and a Protein standard

Working Reagent Preparation: Reagents are ready to use.

Reagent Storage and Stability: Reagent 1 can be stored at room temperature (15-30°C) and reagent 2 can be stored at 2-8°C until the expiry date.

Specimen Collection and Handling: Collection – patient should be fasting for 10-12 hours and be in upright positioning for at least 2 hours.

Specimen	Storage	Stability	Remarks
	At Room temperature(15-30°C)	7 days	Un haemolysed serum/ plasma should be used. If serum proteins are to be estimated, blood should be collected in fasting state without any anticoagulant. However for plasma total proteins, anticoagulant like EDTA should be used.
Serum/plasma	2-8°C	30 days	
	-20°C	6 months	

Assay parameters:

Mode	End point
Wavelength	578nm(550-580)
Flow cell temperature	37°C
Optical path length	1cm
Blanking	Reagent blank
Sample volume	10µL
Reagent volume	1000 µL
Incubation time	5minutes
Concentration of standard	6.5g/dl
Stability of final colour	2hours
Permissible reagent blank absorbance	<0.2AU
Linearity	Upto 20g/dl
Units	g/dl

Procedure: 1000 µL of reagent 1, is pipette in to Blank test tube (B). 1000 µL of reagent 1 and 10 µL of reagent 2 is pipetted in to the Standard test tube (S). 1000 µL of reagent 1 and 10 µL of serum/ plasma is taken in the Test tube (T). All the tubes are mixed well and incubated at 37°C for 5 minutes. The analyzer was Programmed as per assay parameters. The analyzer was blanked with reagent blank. Absorbance of the standard was measured followed by the test. The results were calculated as per the given calculation formula.

Blanking	Reagent blank
Sample volume	10µL
Reagent volume	1000 µL
Incubation time	1minute
Concentration of standard	4.0g/dl
Stability of final colour	2hours
Permissible reagent blank absorbance	<0.1AU
Linearity	Upto 6g/dl
Units	g/dl

Calculation:

$$\text{Total protein concentration (g / dl)} = \frac{\text{Absorbance of test} \times 6.5}{\text{Absorbance of standard}}$$

Globulins = total protein – albumin

Reference Range: Newborn - 4.6-7.0g/dl, 1-2 years - 5.6-7.5g/dl, 3years - 6.0-8.0 g/dl, Adults - 6.4-7.8g/dl
Serum Albumin was estimated by Bromocresol green, End point assay method

Assay Principle: At pH 3.68, albumin acts as a cation and binds to the anionic dye bromocresol green [BCG], and forms a green coloured complex. The absorbance is measured at 630nm. The intensity of the coloured complex is directly proportional to albumin concentration in the sample.

Reagent Composition: Albumin reagent contains: – succinic acid, bromocresol green, sodium hydroxide, buffer at pH3.68

Albumin standard contains: –BSA, Preservative

Specimen Collection: A fasting specimen is not required but is advisable, as marked lipaemia interferes with the assay. Avoid venostasis during specimen collection to avoid haemoconcentration. Hemoglobin concentration causes an apparent increase in albumin and other plasma protein concentrations.

Assay parameters:

Mode	End point
Wavelength	630nm(600-630)
Flow cell temperature	37°C
Optical path length	1cm

Procedure: 1000 µL of reagent 1 is taken in the Blank test tube (B), 1000 µL of reagent1 and 10 µL of reagent 2 are taken in the Standard test tube(S), 1000 µL of reagent 1 and 10 µL of serum /plasma is taken in the test tube(T). All the test tubes were mixed well and incubated at 15-30°C for 1 minute. The analyzer was programmed as per assay parameters. The analyzer was adjusted with the reagent blank. The absorbance of the standard and test was measured. The results were calculated as per the given calculation formula.

Calculation:

$$\text{Albumin concentration (g / dl)} = \frac{\text{Absorbance of test} \times 4}{\text{Absorbance of standard}}$$

Globulins = Total protein – Albumin

Conversion Factor: Albumin concentration in g/L = Albumin concentration in g/dl x10

Reference Range: 0-4 days - 2.8-4.4 g/dl, 4 days-14 years - 3.8-5.4 g/dl, Adults- 3.5-5.2 g/dl, >60yrs - 3.2-4.6 g/dl.

Serum protein electrophoresis was done by Helena Electrophoretic apparatus in cases and controls.

Composition: SAS-MX Serum protein gel: It contains agarose in a tris/barbital buffer with thiomersal and has sodium azide as a preservative. The gel is ready for use.

Tris/barbital Buffer Concentrate: It contains barbital and sodium barbital with sodium azide as preservative. The contents of the bottle (100ml) are diluted with purified water (400ml) and it is mixed well.

Acid Blue Stain Concentrate: It contains concentrated acid blue stain. The contents of the bottle are diluted to 700ml with purified water and is filtered before use. It is then stored in a air tight bottle.

Destain Solution Concentrate: It contains concentrated destain solution. The contents of the bottle is diluted with 2 litres of purified water and it is stored in the air tight bottle.

Other Kit Components: Each kit contains instructions manual for use and sample application templates and blotters A and C.

Sample Collection and Preparation: Serum is freshly collected. Samples can be stored at 15-30°C temperature for up to 4 days. At 2-6°C temperature for up to 2 weeks or up to 6 months at -20°C temperature. Samples / controls are diluted 1:4 (1+3) with buffer before use.

Step-by-step procedure:

1. The gel is removed from the pack and is placed on a paper towel. The overlaying transparent sheet is removed and the gel surface is blotted with a blotter C paper and then blotter paper was discarded.
2. Then the sample application template was aligned with the arrows at the edge of the gel. The blotter paper A was placed on the top of the template and rubbed with a finger, across the slits to have good contact. The blotter paper A is removed and it is retained, so as to use it in the step 5.
3. 3µl of sample is applied to each slit and is allowed to absorb for 4 minutes.

4. 25ml of buffer is poured into each inner section of the SAS-MX chamber.
5. After 4 minutes, the template is blotted with the blotter paper A which was retained from step 2 and then both blotter paper and the template were removed.
6. The gel was positioned in the chamber agarose side down, aligning the positive (+) and negative (-) sides with the corresponding positions on the chamber.
7. Electrophoretic apparatus was adjusted to 80 volts for 30minutes.
8. After electrophoresis, the gel is dried at 60-70°C. The slides are fixed in the gel for 5 min in methanol prior to drying.
9. The dry gel slide is immersed in the stain solution for 10 minutes.
10. The slide is dipped in Destain solution until the background of the slide is clear.
11. The gel was washed with distilled water and was dried at room temperature.

Statistical Analysis

The data was analysed by Graph Pad Prism software 6.01 version. The numerical data is expressed in terms of mean±SD. Comparison between two groups was done by unpaired 't' test for continuous data. The p value of <0.05 was considered statistically significant.

Results and Discussion

The study included a total 40 subjects. Out of them 20 are cases and 20 are controls.

Table 1: Shows the amount of serum proteins in control subjects

S. No.	Age	Sex	Total Proteins (grams/dl)	Albumin (grams/dl)	Globulins			
					Alpha-1	Alpha-2	Beta	Gamma
1	42	M	6.4	3.74	0.12	0.66	1.12	0.76
2	56	M	6.02	3.26	0.23	0.79	1.06	0.68
3	61	M	6.88	4.31	0.18	0.58	0.98	0.83
4	55	M	7.45	4.27	0.24	0.81	1.21	0.92
5	48	F	8.21	3.93	0.11	0.87	1.09	1.41
6	41	M	7.01	4.09	0.31	0.74	0.64	1.31
7	45	F	5.91	3.71	0.09	0.61	0.72	0.76
8	51	M	6.08	3.50	0.34	0.57	0.87	0.80
9	57	M	6.86	3.86	0.27	0.81	0.72	1.20
10	40	F	7.35	3.78	0.34	0.92	1.07	1.24
11	44	M	7.73	4.34	0.24	0.89	0.85	1.41
12	49	M	7.08	3.89	0.19	0.99	1.12	0.89
13	50	M	5.82	3.40	0.29	1.06	0.53	0.54
14	42	M	8.15	4.68	0.10	1.01	0.88	1.48
15	36	M	6.63	3.76	0.17	0.60	0.79	1.31
16	26	F	7.09	4.41	0.21	0.77	0.87	0.93
17	29	M	7.28	5.02	0.25	0.64	0.61	0.76
18	24	M	7.85	5.45	0.10	0.83	0.77	0.70
19	34	M	7.36	3.80	0.18	0.69	1.29	1.40
20	37	M	5.89	3.27	0.20	0.61	0.88	0.93
Total	-	-	139.05	80.47	4.16	15.45	18.07	20.26
Mean	-	-	6.9525	4.0235	0.208	0.7725	0.9035	1.013
SD	-	-	0.750255	0.565679	0.078847	0.151584	0.208914	0.297977

Table 2: Shows the amount of serum proteins in case subjects

S. No.	Age	Sex	Total Proteins (grams/dl)	Albumin (grams/dl)	Globulins			
					Alpha-1	Alpha-2	Beta	Gamma
1	44	M	6.00	2.06	0.28	0.80	0.85	2.01
2	51	M	5.40	1.34	0.19	0.53	0.72	2.62
3	60	M	6.52	1.85	0.34	0.97	0.88	2.48
4	52	F	6.44	1.58	0.42	0.75	0.79	2.90
5	29	M	6.30	1.75	0.43	0.64	1.00	2.48
6	37	M	6.47	1.82	0.42	0.81	1.12	2.30
7	45	F	5.10	1.20	0.27	0.67	0.74	2.22
8	50	M	6.34	1.82	0.30	1.15	0.53	2.54
9	61	M	6.50	2.10	0.41	0.58	1.07	2.34
10	57	F	5.80	1.33	0.39	0.63	0.75	2.70
11	42	F	6.27	2.25	0.26	0.73	0.68	2.35
12	44	M	6.66	1.66	0.42	0.75	1.09	2.74
13	19	M	6.70	2.48	0.27	0.71	0.88	2.36
14	25	M	5.33	1.41	0.34	0.76	0.64	2.18
15	39	M	6.34	1.83	0.45	0.90	0.72	2.44
16	48	M	6.80	2.88	0.30	0.72	0.87	2.03
17	55	M	5.40	1.72	0.32	0.64	0.72	2.00
18	59	F	6.4	2.98	0.34	0.72	0.64	1.72
19	61	M	6.96	3.12	0.29	0.91	0.75	1.89
20	50	M	6.67	2.68	0.37	0.86	0.79	1.97
Total	-	-	124.4	39.86	6.81	15.23	16.23	46.27
Mean	-	-	6.22	1.993	0.3405	0.7615	0.8115	2.3135
SD	-	-	0.536852	0.570264	0.071117	0.144778	0.159515	0.31147

Table 3: Shows the amount of total proteins in controls and cases (Summary of the results)

S. No.	Investigation	Values	Controls	Cases
1.	Total Proteins	Mean	6.9525	6.22
		S.D	0.750255	0.536852
		S.E	0.1678	0.1200
		t-value	3.5509	
		p-value	0.0010	
2.	Albumin	Mean	4.0235	1.993
		S.D	0.565679	0.570264
		S.E	0.1264	0.1275
		t-value	11.3051	
		p-value	0.0001	
3.	Alpha 1 Globulin	Mean	0.208	0.3405
		S.D	0.078847	0.071117
		S.E	0.0176	0.0159
		t-value	5.5806	
		p-value	0.0001	
4	Alpha 2 Globulin	Mean	0.7725	0.7615
		S.D	0.151584	0.144778
		S.E	0.0338	0.0323
		t-value	0.2326	
		p-value	0.8174	
5	Beta Globulin	Mean	0.9035	0.8115
		S.D	0.208914	0.159515
		S.E	0.0467	0.0356
		t-value	1.5653	
		p-value	0.1258	
6	Gamma Globulin	Mean	1.013	2.3135
		S.D	0.297977	0.31147
		S.E	0.06662	0.0696
		t-value	13.49	
		p-value	0.0001	

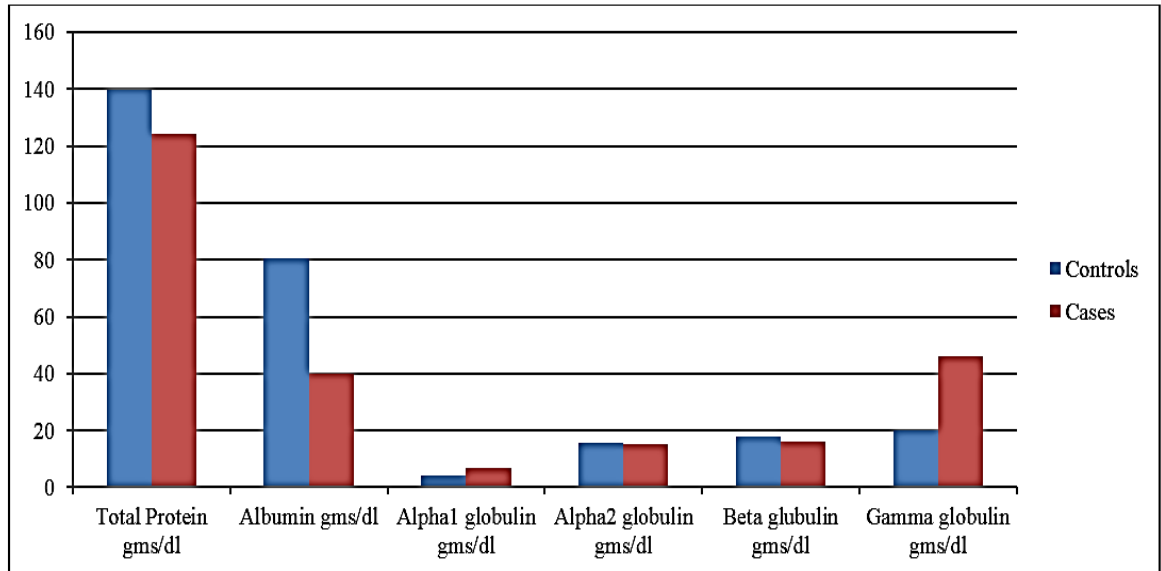


Fig. 1: Comparison of total serum proteins (grams/dl) in controls and cases

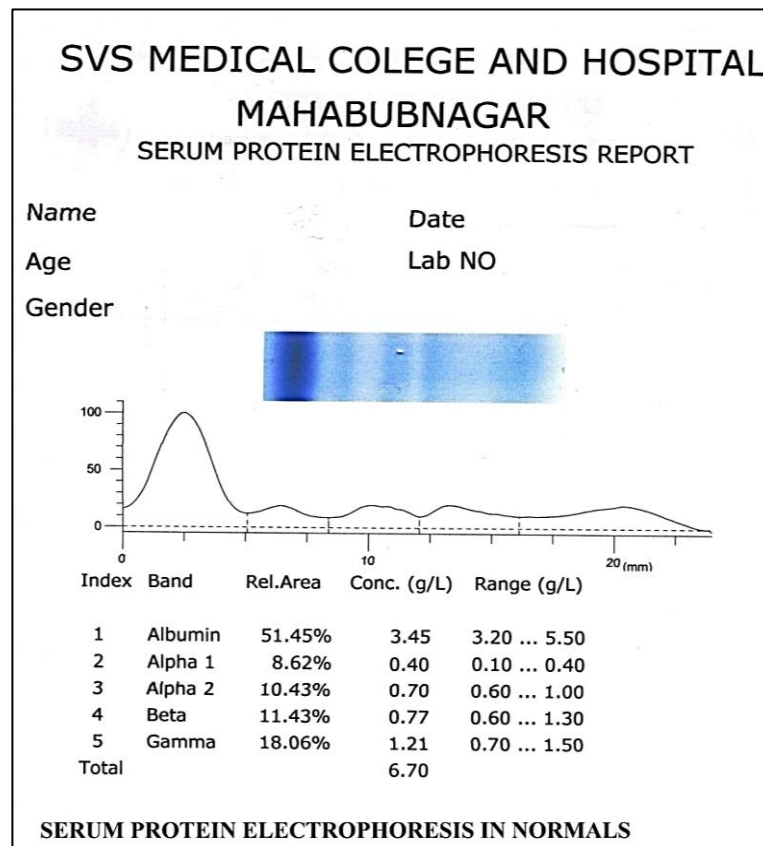


Fig. 2: Electrophoretic pattern of serum proteins in controls

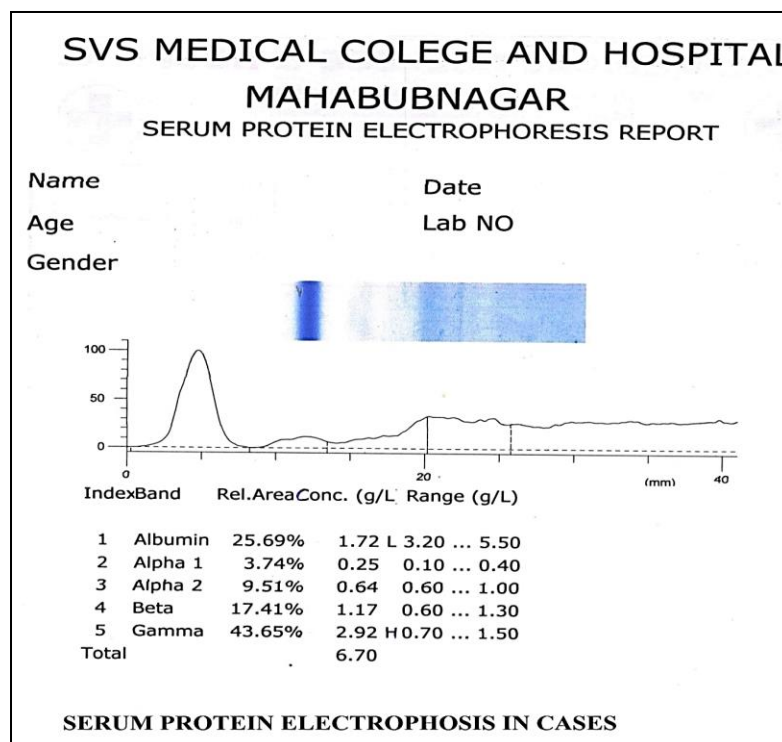


Fig. 3: Electrophoretic pattern of serum proteins in cases

Mean of total proteins in controls 6.9525 ± 0.750 Grams/dl and cases 6.22 ± 0.536 Grams/dl respectively. Total proteins are slightly reduced in cases compared to controls. This might have been caused by anorexia, mal-absorption and impaired cell mediated immunity as noted by Narwadiya.¹⁴ P-value 0.0001. Mean of Albumin in controls 4.0235 ± 0.565 Grams/dl and cases 1.933 ± 0.570 Grams/dl respectively. Albumin is significantly reduced in cases compared to controls P-value 0.0001. Albumin levels are affected in tuberculosis disease this might be due to association of immunoglobulin and cellular immunity in the process. This is in consonance with previous studies on Tuberculosis patients reported by Sasaki et al., (1999)¹⁵ and Yamanaka et al., (2001),⁶ but at variance with Adedapo et al., (2006),¹⁷ Akiibinu et al., (2007),¹⁸ Nnodim et al., (2012)¹⁹ and Damburam et al., (2012)²⁰ who reported decreased total protein and albumin levels in Tuberculosis. Our findings were in correlation with other studies that were done by Gupta et al.,²¹ Gaitonde et al.,²² Vyas et al.²³ and Koul et al.,²⁴ have found a decrease in the values of total proteins and serum albumin, which was more marked in advanced cases which may be a reflection of their immune system (CD4+ T lymphocyte). Mean of alpha-1 globulins in controls 0.208 ± 0.078 Grams/dl and cases 0.340 ± 0.071 Grams/dl respectively. Alpha-1 globulins slightly increase in cases compared to controls P-value 0.0001. Mean of Alpha-2 globulins in controls 0.7725 ± 0.151 Grams/dl and cases 0.7615 ± 0.1447 Grams/dl respectively. No change in levels of alpha-2 globulins

in controls and cases P-value 0.8174. Mean of Beta globulins in controls 0.9035 ± 0.208 Grams/dl and cases 0.8115 ± 0.1595 Grams/dl respectively. Beta globulins very slightly decrease in cases compared to controls P-value 0.1258. Mean of gamma globulins in controls 1.013 ± 0.297 Grams/dl and cases 2.3135 ± 0.311 Grams/dl respectively. Gamma globulins significantly increased in cases than in that of controls P-value 0.0001. This increased globulin level can be attributed to immunologic response to tubercle bacilli that elicit the production of gamma globulins as previously reported by Damburam et al., (2012).²⁰ Arinola and Igbi (1998)²⁵ also reported high levels of IgG and IgM in pulmonary tuberculosis. Nagayama et al., (1999)²⁶ and Paton et al., (2004)²⁷ had earlier stated that hyperglobulinaemia in tuberculosis is one of the predictive factors for the development of residual thickening in tuberculous pleurisy.

Conclusion

The results of present study of estimation of serum proteins in pulmonary tuberculosis patients shows that Total proteins and Albumin levels are decreased. Among the globulins, gamma globulins are elevated. The decrease in total protein and albumin may be as a result of low immunity and malnutrition. The results confirms that Mycobacterium tuberculosis has an effect on the levels of Total serum proteins in a pulmonary tuberculosis patient. We therefore advocate that serum proteins should be among the routine of tests required for pulmonary tuberculosis patients before, during and after treatment. For effective treatment of individuals

with tuberculosis in addition to the use of appropriate anti-tubercular drugs, patients must adhere to treatment and employ frantic effort in the control of associated diseases (co-infection). Since nutritional status influences cellular immunity of the body system, the public should be enlightened on the need to pay close attention on dietary intake that are necessary for maintaining and improving the immune system. Physicians should also be guided on the use of drugs which may serve for boosting the protein level, since proteins are involved in transportation of drugs and building of immune system.

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How to cite this article: Padugupati S, Kumar KK, Vasantha L, Sarma D.V.H.S. Study of serum protein and electrophoretic pattern in pumonarytuberculosis patients. *Int J Clin Biochem Res*. 2018;5(3):353-360.