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Original Research Article

Role of iron metabolism in pulmonary tuberculosis: a case control study in Katra

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ABSTRACT

Background: Tuberculosis (TB) disease still carries an appreciable mortality, representing the world's second leading cause of death from a single infectious agent. In a living organism, iron (Fe) is an essential micronutrient, as a co-factor of enzymes and involved in various cellular functions. Fe homeostasis is maintained by various mechanisms is disturbed in diseased. The aim of study was estimating the Fe metabolism in pulmonary tuberculosis patients in relation to sputum bacterial load and inflammation and severity.
Methods: This present case control study was conducted in department of medicine CHC Katra, Jammu, Jammu and Kashmir from June 2019 to September 2019. A total of 100 adult patients diagnosed with pulmonary TB (PTB) and 74 healthy, age matched individuals were included in the study.
Results: Out of 100 patients, 65% were males with average age being 43.56±15.63 years. Mean serum protein at 6.32±0.78 g/dl and mean serum albumin at 3.45±0.52 g/dl showed significance. Mean serum Fe (39.68±18.32 ug/dl) and mean hemoglobin level (9.36±1.52) was significantly lower as compared to controls. Serum TIBC, serum ferritin and serum CRP showed higher values among cases. Raised serum ferritin levels corresponded to the raised CRP and TB is seen causing significantly low levels of transferrin.
Conclusions: CRP and ferritin should be regarded as useful markers of PTB activity and also to the risks associated to it and also while monitoring therapeutic response.

Keywords: Pulmonary tuberculosis, *Mycobacterium tuberculosis*, Iron metabolism

INTRODUCTION

TB disease carries an appreciable mortality, representing the world's second leading cause of death from a single infectious agent.[1] Variability in disease progression, with approximately 10% of TB-infected individuals developing clinical disease in the absence of immune-suppression, suggests that individual factors may play a role in the response to infection. Micronutrient status, an important contributor to immune function and cytokine kinetics has been increasingly suggested to play a role in the individual response to TB. In living organism, Fe is an essential micronutrient for both humans and pathogenic microbe, as a co-factor of enzymes and involved in various cellular functions. Studies have often documented high prevalence of anemia in TB patients (upto 94%) and even sometimes suggesting that anemia in TB increases risk of death.[2] At the same time, studies also showed that excess iron could enhance growth of *Mycobacterium tuberculosis* (MTB) and worsen the outcome of tuberculosis disease.[3] TB caused by mycobacterium tuberculosis which has an absolute requirement of Fe for growth and multiplication. In MTB,

Fe enters via siderophore mediate uptake where it is required for bacterial growth and multiplication, but any excess if occurs in MTB is toxic due to its catalytic role in generation of free radicals.[4] In a diseased patient, high Fe stores can also be related to many infectious diseases and inflammatory response.[5] Fe homeostasis, often maintained by various mechanisms in a human body, can be disturbed in diseased state mediated by acute phase response and infection.

The aim of the present study was to analyze the iron metabolism in pulmonary tuberculosis patients in relation to disease severity, sputum bacterial load and inflammation.

METHODS

This present observational case-control study was conducted in department of medicine CHC Katra, Jammu, Jammu and Kashmir from June 2019 to September 2019 after due approval from the ethical committee. A total of 100 adult patient including both male and female diagnosed with PTB, patients who are giving written consent with age more than 30 years were recruited for the study. 74 healthy, age matched individuals were also taken as controls. All the patients and controls were selected by simple random sampling technique.

Inclusion criteria for cases

Patients diagnosed with PTB, patients of both genders with age >30 years and patients willing and giving written consent were included in the case group study.

Inclusion criteria for controls

Age matched individuals tested free of MTB and without any present or previous symptoms of TB or any other pulmonary disease were included in the control group study.

Exclusion criteria

Patients with multidrug resistant TB (MDR-TB), extra-PTB, patients with significant renal, cardiac, neoplasm or respiratory disease (other than PTB like lung cancer), patients with diabetes, endocrine or genetic disorder, pregnant or lactating women and those on any nutritional supplements were excluded from the study.

Data was analyzed as mean±SD and comparison was made by using student t test. P value was also determined and $p<0.05$ was considered significant. Microsoft excel 2010 was used as reliable software for complete data analysis.

RESULTS

Out of 100 patients, 65% were males and the remaining 35% were females. Among controls, similarly higher a number (71.62%) of males were there. Average age of PTB patients was 43.56±15.63 years, while that of controls was 41.80±14.43 years. Routine blood sugar among cases was 82.13±16.50 mg/dl and for controls was 80.67±15.51 mg/dl (mean±SD). Mean serum urea and mean serum creatinine also did not vary significantly among cases and controls. However, mean serum protein and mean serum albumin, which was 6.32±0.78 g/dl and 3.45±0.52 g/dl among PTB patients, varied significantly among healthy controls and stood at 7.82±0.72 g/dl and 4.65±0.61 g/dl, respectively, with $p<0.05$ (Table 1).

Table 1: Characteristics and biochemical profile of cases and controls (n=174).

S. no.	General characteristics	Cases (N=100) (%)	Controls (N=74) (%)	P value
1	Number of males	65 (65)	53 (71.62)	0.078
2	Number of females	35 (35)	21 (28.38)	
3	Average age (in years)	43.56±15.63	41.80±14.43	0.349
4	Sputum status			
	Negative	41	74	
	+1	30	0	
	+2	19	0	
	+3	10	0	
5	Blood sugar (mg/dl)	82.13±16.50	80.67±15.51	0.215
6	Serum urea (mg/dl)	28.69±9.88	28.04±8.95	0.636
7	Serum creatinine (mg/dl)	1.02±0.47	0.96±0.39	0.082
8	Serum albumin (g/dl)	3.45±0.52	4.65±0.61	0.006*
9	Serum protein (g/ dl)	6.32±0.78	7.82±0.72	0.041*

*$p<0.05$ is significant.

Table 2: Iron profile and CRP levels among cases and controls.

S. no.	Biochemical parameters	Cases	Controls	P value
1	Serum iron (ug/dl)	39.68±18.32	48.66±20.12	0.029
2	Serum transferrin (mg/dl)	110.3±36.4	155.0±63.6	0.011
3	Transferrin saturation (%)	14.6±6.9	22.8±13.0	0.009
4	Hemoglobin (g/dl)	9.36±1.52	12.62±1.40	0.026
5	Serum TIBC (ug/dl)	520.4±261.3	347.7±70.6	0.003
6	Serum ferritin (ng/ml)	372.2±96.6	260.4±74.0	<0.001
7	Serum CRP (mg/l)	17.8±9.3	4.0±2.5	<0.001

*p<0.05 is significant.

Mean serum Fe among cases was significantly lower (39.68±18.32 ug/dl) as compared to controls (48.66±20.12). Mean serum transferrin and percent saturation showed similar results. Hemoglobin level among cases was also significantly low among cases with mean±SD at 9.36±1.52. However, serum TIBC, serum ferritin and serum CRP showed significantly higher values for cases than in controls (Table 2).

DISCUSSION

TB is identified as disease of the poor, mainly affecting the venerable population of developing nations. Fe deficiency, on the other hand is also prevalent in such a population. Levels of Fe have been associated with several kinds of diseases associated to lungs, like lung-cancers, fibrosis and asthma.[6] Lungs are having a unique anatomical roll in massive oxygen exchange with blood supplies. Lungs are therefore prone to metal induced oxidative stress. Low Fe as well as excess Fe leads to compromised immune system and altered cellular activity. Fe deposits within macrophages and parenchymal cells enhances MTB growth and clearly affects the ability of macrophages against the microorganisms, leading to morbidity and mortality in PTB.[7]

Albumin being a component of plasma antioxidant activity, it is known that concentration of such acute phase protein decreases in any inflammatory condition, stress or injury, due to increased metabolic need for tissue repair and free radical neutralization.[8] Mean protein and albumin levels in PTB cases were found deranged significantly in our study, possibly due to severe cachexia, anorexia, malabsorption and malnutrition in patients.

The present study also showed decrease in Fe, transferrin, transferrin saturation and hemoblobin. However serum TIBC, ferritin and CRP showed marked increase among cases as compared to the controls. CRP is synthesized by hepatocytes, under the influence of interleukin-I and other types of cytokines at the infection site. CRP suggests a beneficial role in the evaluation of respiratory tract infection in adults and often normalizes with therapy and treatment. Breen et al showed that elevated CRP could detect TB cases also.[9]

Malabsorption due to hookworm or other infections, inadequate and iron-deficient diet or blood loss in pulmonary tuberculosis is bound to reduce iron stores in body.[10]

MTB acquires Fe from host since it is an ideal catalyst for DNA replication and bacterial multiplication. An important facet of innate immunity is to limit iron availability to pathogetic microbe which may deprive erythroid precursors of their iron supplies. The host shifts the available Fe, in transferrin form to stored Fe, in ferritin form and thus causing MTB growth.[11] In our study also Fe did not show any significant relation to sputum positivity, indicating co-existence of iron deficiency anemia (IDA) and anemia of chronic disease (ACD).

Ferritin found to be elevated in various infectious and non-infectious conditions. Very high ferritin level shows oxidative stress and association of ferritin with lung function and smoking habit has been seen, showing its role in pulmonary infections. As observed by Lee et al, Huang et al and in our study also, levels of CRP and ferritin reflected a possible extent of oxidative stress and inflammation among patients, making them useful markers of PTB and its associated risks.[12,13]

The observations from this study point out to the fact that ferritin can be used as an indicator to iron store, but in infections like TB, it is an acute phase protein, where its level increases non-specifically. In our study, raised serum ferritin levels corresponded to the raised CRP as well. Ferritin in PTB patients is more of an inflammatory marker and patients with adequate haemoglobin also showed lower ferritin levels. In studies by Sandhya et al ferritin has been found to be having positive correlation to inflammation and severity of disease.[14]

Transferrin typically decreases in any infectious conditions. It is both a marker of nutritional status as well as a negative acute phase protein, such that its level is affected by protein diet and malnutrition state. In the patients or cases studied here, it was found that TB is

seen causing significantly low levels of transferrin. It can be further attributed to the stress conditions and synthesis of immune mediators cytokines by liver, which decreases synthesis of proteins like albumin and transferrin. Improvement in transferrin levels during course of disease would indicate better therapeutic response and improved diet and nutrition.

It is a proven fact that serum ferritin levels are a sensitive marker for iron status, but ferritin is an acute-phase reactant and often becomes elevated in response to inflammation, complicating the diagnosis and forms a limitation to the present study as well. Besides the majority of our study population was composed of male individuals, which potentially restricts the inferential power of the results presented here. Additional studies in populations in which female patients are more proportionate are necessary to provide definite validation of our findings.

CONCLUSION

Quite clearly, this study has concluded that Fe metabolism is altered during PTB. TIBC, ferritin and CRP were higher in PTB patients. Transferrin showed strong relation to severity of disease. Increase in ferritin in response to infection was attributed to prevent iron availability to MTB and discourage its multiplication. CRP and ferritin should be regarded as useful markers of PTB activity and also to the risks associated to it and also while monitoring therapeutic response.

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