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Original Research Article

Study of Iron Metabolism in Pulmonary Tuberculosis Patients

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ABSTRACT

Introduction: Iron deficiency anemia and Malnutrition is common in developing countries and is a major pre-disposing factor in Pulmonary Tuberculosis (PTB). Iron metabolism which is tightly regulated in normal condition is often found to be disturbed in various pathological conditions. Both deficiency and excess of free iron compromise cellular and immune functions and also affect disease susceptibility and outcome.
AIM: The aim of this work was to study iron metabolism in PTB patients in their relation to severity of disease and sputum bacterial load
Material and Method: 100 adult PTB patients (both male and female) were recruited from Institute of Respiratory Disease, Jaipur and 60 age matched healthy individuals served as controls for comparison. Standard diagnostic procedure was followed for PTB patients and Sputum positivity was assessed by counting number of Acid Fast Bacilli in sputum microscopically. After written consent, serum was used for investigating routine and specific Biochemical parameters i.e. serum Iron, Total Iron binding capacity, Transferrin and Ferritin for all subjects. Ferritin was analyzed by Chemiluminescence on Immulite 2000 (Siemens Co). Iron, TIBC, Transferrin and CRP were analyzed on fully automatic Biochemistry Analyzer. C- Reactive Protein was determined as indicator of systemic inflammation in PTB.
Result and Discussion: Serum Protein, Albumin, Iron, Transferrin and Transferrin Saturation were significantly decreased in PTB patients than controls. Protein malnutrition and Iron deficiency anemia are not just predisposing factors but also affect mortality and outcome of disease. Both Ferritin and CRP were significantly higher in PTB than Controls ($p<0.001$) due to their nonspecific rise in inflammation. Significant correlation of Ferritin and CRP with disease severity ($r=0.49$ and $r=0.26$ respectively) and with Sputum positivity ($r=0.57$ and $r=0.62$ respectively) suggest their potential in severity assessment. Sequestration of Iron in the form of Ferritin makes Fe non available to MTB and thus limits its growth and multiplication. Transferrin was also found to be correlated negatively and strongly to Disease severity ($r=0.68$).
Results: It was concluded that hemostatic mechanism was altered in PTB. Fe and its metabolites especially Transferrin and ferritin correlated to disease severity and sputum positivity. In other words, these can be used as indicator of disease severity or mortality risk.

Keywords: Iron metabolism, Pulmonary Tuberculosis.

INTRODUCTION

Tuberculosis (TB) is an infectious diseases and an important public health problem occurring worldwide specially in developing countries. Increasing spread of TB and development of drug resistance makes it a matter of utmost concern. Malnutrition and infection forms a vicious circle; each aggravating the other. Malnutrition reduces immune competence

and leads to infection and infection in turn causes nutritional deficiency.

In living organism, Fe is an essential micronutrient for both humans and pathogenic microbe, as a co-factor of enzymes and involved in vital cellular functions ranging from energy metabolism or respiration to DNA replication, oxygen transport and effective immune competence. Iron deficiency Anemia (IDA) manifested by generalized weakness and enhanced susceptibility to infection is a common complication in PTB. Many studies had documented high prevalence of anemia in TB patients (30-94 %) and evidence is there to suggest that anemia in TB increases risk of death. [(1)] Studies also suggest that excess iron may enhance growth of MTB and worsen the outcome of human tuberculosis. [(2)] In host, excess Fe leads to cellular toxicity by Fe catalyzed generation of harmful Reactive oxygen intermediates and hydroxyl radicals that damage lipids, DNA and Proteins. Build up of Fe in tissue and organs increases risk of arthritis, cancer, liver problems, diabetes and heart failure. High iron stores are related to many infectious diseases and inflammatory response, as exemplified by malaria, viral and neurodegenerative diseases. [(3)] TB is caused by Mycobacterium tuberculosis (MTB) which has an absolute requirement of Iron (Fe) for growth and multiplication. In MTB, Fe enters via siderophore mediated 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)] However, Fe metabolism in MTB is regulated at the level of uptake. In host, Iron hemostasis is maintained by various mechanisms at the level of uptake, transport and storage in healthy conditions this hemostatic mechanism is disturbed in diseased state mediated by acute phase response and effect of infection. The study here will discuss the effect of mycobacterial load and clinical severity of PTB on Fe acquisition by the host in the form of Transferrin and Ferritin.

The aim of this work was to study Iron metabolism in PTB patients in relation to disease severity, sputum bacterial load and inflammation. CRP was estimated as indicator of systemic inflammation in PTB.

MATERIAL AND METHODS

The study was conducted in the Institute of Respiratory Diseases, SMS Hospital in association with Department of Biochemistry, SMS Medical College, Jaipur. 100 Adult patients (both male and female) from low socio-economic status diagnosed with Pulmonary Tuberculosis (PTB) were recruited for the study. 60 healthy, age matched individuals tested free of MTB without any previous or present symptoms of Tuberculosis or any other pulmonary disease and non family member of patients were taken as Controls. 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.This method of severity assessment based on clinical features and investigations was validated by number of workers and was suitable especially in a resource poor setting. [(5)]

Measurement of Biochemical

Parameters: After an overnight fast (12 hrs), venous blood was drawn in plain and EDTA vials and serum was separated for all subjects. Serum was used for analysis of Iron & TIBC (Ferrozine method) on semiautoanalyzer (ERBA), Transferrin (Immunoturbidimetric) on autoanalyzer EM-360 (Transasia), CRP (Turbidilatex) on Randox imola3 fully autoanalyzer and Ferritin (Chemiluminescence method) on Immulite, 2000 Siemens Co. EDTA sample was used for Hemoglobin estimation on 5 part cell counter, Sysmex XT-1800i, Siemens Co.

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. Medcalc. 14.0.0 version software was used for data analysis

RESULTS AND DISCUSSION

TB by all means is a poverty related disease, mainly affecting the most vulnerable population in the developing countries. Among various micronutrients, Fe deficiency is most commonly observed in general population as well as in TB patients. Fe metabolism is most tightly regulated with control existing at the level of absorption. Altered Fe level and/or dysregulated homeostasis has been associated with several lung disease, lung cancer, Cystic fibrosis, idiopathic pulmonary fibrosis and asthma. [(6)] Among all organs of the body, lungs are most prone to metal induced oxidative stress due to its unique anatomical role in massive oxygen exchange along with large blood supplies and hence Fe metabolism in studied here in Pulmonary Tuberculosis. Both Iron deficiency and excess can compromise immune and cellular functions. Low iron status may impair motor activity and enhance disease susceptibility and excess iron contributes to toxicity by catalyzing reactive oxygen species. Fe overload that causes heavy Fe deposit within macrophages and parenchymal cells could conceivably enhance MTB growth and impairs ability of macrophages to suppress invading micro-organism and associated with morbidity and mortality in PTB. [(7)] Thus, in order to reduce harmful effects of excess iron in humans, tightly controlled mechanism exist at the level of absorption, systemic transport and cellular uptake and storage. This controlled mechanism gets perturbed in various infectious diseases like PTB. The ongoing discussion compares various Fe and its metabolites between PTB and healthy subjects and also studies their relation to severity of disease and inflammation.

General characteristics of study population are depicted in table 1. Out of 100 PTB patients, 79% were males and 21% females. The average age of PTB patients was 40.1±17.6 years. 60 healthy subjects that served as control for comparison includes 83.4% males and 16.6% females and average age 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 protein and Albumin level in PTB cases was 6.40±0.60 & 3.1±0.58 g/dl respectively

which were significantly lower than controls 7.65±0.87 & 4.36±0.69 respectively ($p<0.001$) due to severe cachexia, anorexia, malabsorption and malnutrition 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 neutralization. [(8)]

Table 1. General characteristics and Biochemical profile of study population

S. No.	General Characteristics	PTB patients	Controls	Significance (p value)
1.	No. of cases (n)	100	60	
2.	No. males	79 (79)	50 (83.4)	0.041 N S
3.	No. females	21 (21)	10 (16.6)	
4.	Average Age (in years)	40.1± 17.6	40.9 ± 16.8	0.526 NS
5.	Sputum Status			
	Negative	39 (39)	60 (100)	
	+1	37 (37)	0 (0)	
	+2	15 (15)	0 (0)	
	+3	9 (9)	0 (0)	
6.	Blood Sugar (mg/dl)	80.57±20.66	81.12±17.88	NS
7.	Serum Urea (mg/dl)	28.5±11.6	31.66±8.43	NS
8.	Serum Creatinine (mg/dl)	1.04±0.54	0.92 ± 0.43	NS
9.	Serum Protein (g/dl)	6.40 ± 0.60	7.65 ± 0.87	<0.001 S
10.	Serum Albumin (g/dl)	3.1 ± 0.58	4.36 ± 0.69	<0.05 S

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

Table 2: Iron profile and CRP level in PTB patients and Controls

S. No.	Biochemical Parameters	PTB patients (n= 100)	Controls (n= 60)	Significance (p value)
1.	Hemoglobin (g/dl)	9.67± 1.9	13.1± 2.0	<0.05
2	Serum Iron (ug/dl)	40.1± 17.5	49.4± 18.7	<0.001
3.	Serum TIBC (ug/dl)	556.8 ± 401.0	309.1± 95.2	<0.05
4.	Serum Transferrin (mg/dl)	117.0 ± 37.0	160.6± 59.6	<0.001
5.	Transferrin saturation (%)	12.4 ± 9.7	19.3± 12.0	<0.001
6.	Serum Ferritin (ng/ml)	381.5 ± 102.0	276.4±82.0	<0.001
7.	Serum CRP (mg/l)	21.7 ± 14.5	4.3± 3.0	<0.001

Values are mean ± SD; P < 0.05 is significant. NS: Not Significant
PTB: Pulmonary Tuberculosis; CRP: C - reactive protein

The present study showed decrease in Iron, Hb, Transferrin and Transferrin Saturation (TS%) whereas increase levels of TIBC, Ferritin and CRP in PTB (table 2). Both Ferritin and CRP were significantly high in PTB cases than controls. 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, normalizing over time with therapy and thereby correlating with clinical response. [(9)] Breen et al found that elevated CRP detected 85% of proven TB cases in London. [(10)] Additionally, high CRP has been used as indicator to initiate antibiotic therapy with progressive lowering observed during treatment. [(10)]

Mean serum Iron in PTB and control was 40.1± 17.5 and 49.4±18.9 ug/dl respectively (table 2). Low Fe level in our population is multifactorial. Inadequate dietary Fe, malabsorption due to hookworm or other secondary infections and increased blood loss/hemoptysis in PTB may reduce body iron stores. MTB acquire Fe from host since it is an ideal catalyst for DNA replication and bacterial multiplication. For this reason, an important facet of innate immunity is to limit iron availability to pathogenic microbe which incidentally also deprives Erythroid precursors of their iron supplies. [(11)] Here, the host tends to induce

pathogenic Fe deficiency by causing a shift of available Fe (i.e. Transferrin form) to stored Fe (Ferritin form) and inhibits MTB growth. These changes are component of systemic inflammatory response and are the major factor in the pathogenesis of anemia in TB. Fe did not show any correlation to disease severity and sputum positivity, which indicated that both IDA and Anemia of Chronic Disease (ACD) co-exist in our patients. Both are characterised by low Fe but can be differentiated by Ferritin estimation. Low Ferritin in IDA and high values in ACD are typically observed.

Table 3: Iron profile and CRP level in PTB patients according to Clinical Severity

S. No.	Biochemical Parameter	Severity Class I N= 13	Severity Class II N= 23	Severity Class III N= 64
1	Hb (g/dl)	10.6± 2.1	10.1 ± 1.8	9.3± 1.8
2.	Serum Iron (ug/dl)	42.0± 25.6	41.1± 18.8	39.4± 15.2
3.	Serum TIBC (ug/dl)	390.8± 129.8	372.1± 95.4	383.0± 101.0
4.	Serum Transferrin (mg/dl)	177.0± 29.3	129.4± 34.2	100.3± 22.7
5.	Transferrin saturation (%)	12.5±10.2	13.1± 10.2	11.7± 7.9
6.	Serum Ferritin (ng/ml)	244.2± 215.0	450.3± 381.0	663.5± 406.0
7.	Serum CRP (mg/L)	15.8± 12.3	19.5± 14.4	23.7± 14.7

Values are mean ± SD; PTB: Pulmonary Tuberculosis, CRP: C - Reactive Protein

Table 4: Iron profile and CRP level in PTB patients according to Sputum Positivity.

S. No.	Biochemical Parameters	Sputum positivity			
		Negative (N= 39)	+ 1 (N= 37)	+2 (N= 15)	+ 3 (N= 9)
1	Hemoglobin (g/dl)	10.1± 1.9	9.5± 1.9	9.1± 2.1	9.4± 1.4
2.	Serum Iron (ug/dl)	40.6± 19.2	39.5± 19.1	37.9± 11.0	44.0± 12.3
3.	Serum TIBC (ug/dl)	308.5± 113.3	385.9± 92.0	408.3± 117.0	323.2± 50.4
4.	Serum Transferrin (mg/dl)	121.2± 36.7	121.5± 40.5	108.7 ± 32.0	94.3± 24.7
5.	Transferrin saturation (%)	13.2± 6.5	11.9± 9.0	10.6± 5.7	14.0± 4.8
6.	Serum Ferritin (ng/ml)	365.7± 189.5	495.8± 360.0	931.9± 381.0	1045± 395.2
7.	Serum CRP (mg/L)	13.1± 7.0	20.4± 13.4	37.6±13.5	37.5± 10.5

Values are mean ± SD; PTB: Pulmonary Tuberculosis; CRP: C - Reactive Protein

Mean Serum Ferritin and CRP in PTB was 381.5±102.0 ng/ml & 21.7±14.5 mg/L respectively while in control was 276.4±82.0 ng/ml & 4.3±3.0 mg/L respectively (table 2). As seen in table 3 and 4, circulating level of both CRP and Ferritin increases with disease severity and sputum positivity. In the present study, CRP correlated strongly to clinical severity (r= 0.26) and to sputum positivity (r= 0.625) (table 5). Progressive increase in CRP with disease severity also suggests its potential as indicator of clinical outcome of disease and can be used in monitoring treatment efficacy. In another study, among various systemic inflammatory markers like ESR & Fibrogen, CRP emerged to be most sensitive in defining severity of PTB. [(12)] Our result was consistent to this and another similar study where CRP level was higher in patients with pulmonary cavity than patients without cavity. [(13)] Further, CRP was found to be significantly higher in smear +ve group of PTB as compared to smear –ve control group i.e. 43.65±23.6 mg/L and 4.64± 3.8 mg/L respectively. In their study, AFB +3 patients exhibits highest CRP level (65.28 mg/L), followed by AFB +2 group (35.9 mg/L), AFB +1 with 16.37 mg/L and AFB scanty patients with mean CRP level 10.92 mg/L. [(14)] Another recent report have shown positive correlation of CRP to clinical & radiological severity in PTB, need for ventilator support, mortality and treatment outcome in Pulmonary Tuberculosis. [(15)] In our study, similar trends were observed with regard to Ferritin. Ferritin is an Acute Phase Reactant (APR) and showed strong correlation to severity of disease (r= 0.49) and sputum positivity (r=0.57) (Table 5). Ferritin is elevated in various infectious and non-infectious conditions. Very high Ferritin level reflects oxidative stress and acute infectious conditions. In a study, patients selected whose Ferritin level was more than 10,000 ng/ml. Among all those case, MTB seemed to be the most common infectious cause

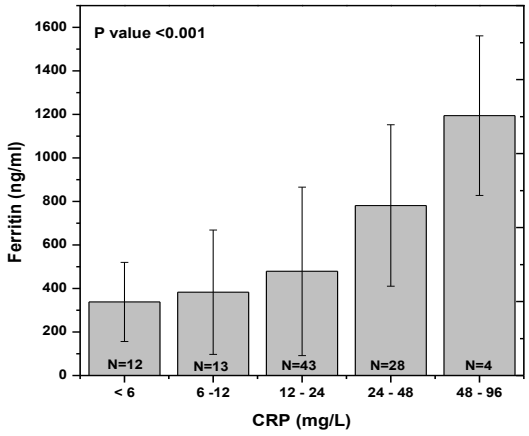
accounting for 42% of all cases. [16] Further, association of Ferritin with lung function and smoking habit was seen and this reflects its utility in pulmonary infections. [17] Morris et al found increased iron stores in 81% of their PTB patients [18] and some studies also showed gradual normalisation of Ferritin following chemotherapy. Ferritin level was found to be higher in smokers than in non smoker population. [19] Both CRP and Ferritin have been reported to reflect the extent of oxidative stress and inflammation in individual patients and may be useful marker of disease activity and mortality risk. [20]

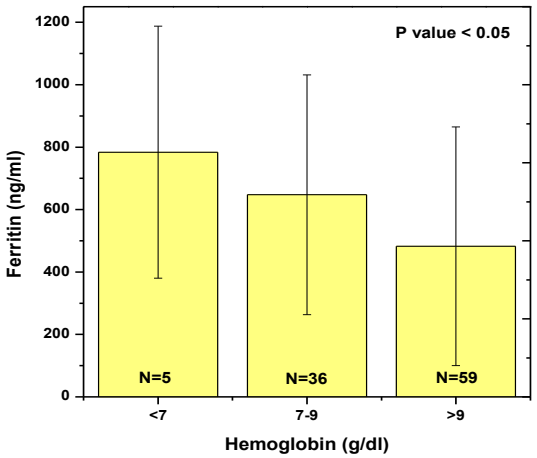
Table 5. Correlation of iron profile and CRP with Disease severity and sputum positivity

Biochemical parameters	Disease severity		Sputum Positivity	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Hemoglobin (g/dl)	-0.29	0.003	-0.13	0.19
Serum Iron (ug/dl)	-0.05	0.62	-0.01	0.92
Serum TIBC (ug/dl)	-0.07	0.48	-0.06	0.55
Serum Transferrin (mg/dl)	-0.68	<0.001	-0.20	0.04
Transferrin saturation (%)	-0.10	0.19	-0.03	0.73
Serum Ferritin (ng/ml)	0.49	<0.001	0.57	<0.001
Serum CRP (mg/L)	0.26	<0.008	0.62	<0.001

P < 0.05 is significant.

Inline to above studies, 74 host markers of inflammation were evaluated. Among all, concentrations of 11 markers were found to change with treatment and Ferritin was one of them. It indicates its usefulness in monitoring treatment response and effective management of chronic illness.[21] In the absence of infection, Ferritin can be used as indicator of Iron stores at a cut off <10 ug/L but in the presence of infection, due to non specific rise in Ferritin, some authors recommends a cut off <30.0ug/L.[22] The above observation support the fact that Ferritin could be used as iron store indicator normally but in infections like TB, it is more an acute phase protein where its level increases non specifically. Thus, raised serum Ferritin in TB as found in the current study is attributed to two factors: Firstly, monocytes and macrophages produce ferritin and monocytosis occurs commonly in TB. Secondly, ferritin is a positive APR that increases in both acute and chronic inflammatory condition and in support of this fact, a positive and strong correlation between serum ferritin and CRP was obtained in our study (Fig. I). Although Ferritin is used widely as iron store indicator but in PTB, it is more an inflammatory marker as seen in figures I and II. Patients with adequate haemoglobin had lowest Ferritin level (Figure II). Ferritin correlates positively and strongly to inflammation (p<0.001) indicating its role in severity assessment and inflammatory response.





With regard to Transferrin, irrespective of the nature of anemia (i.e. due to Fe deficiency or due to chronic disease), it typically decreases in any infectious conditions. Our study revealed significantly low concentration in PTB than controls 117.0± 37.0 mg/dl vs 160.6±59.6 mg/dl (table 2). Transferrin is both a marker of nutritional status and a negative acute phase protein. In other words, its level is affected by protein diet and malnutrition state as well as in inflammatory response to infection. During stress condition, liver tends to increase synthesis of immune mediators Cytokines and decrease synthesis of those proteins that are not essential for immune function for example albumin and Transferrin. The above factor is responsible for reduced Transferrin level as found in our patient group.

Further as discussed previously, shift of available iron (Transferrin form) to stored iron (Ferritin form) so as to reduce Fe availability to MTB is another cause for low Transferrin level. Other factors like pre-existing malnutrition, reduced hepatic protein synthesis, trans endothelial escape and anorexia due to TB also causes significantly low Transferrin level in cases than controls ($p<0.001$). Research also suggests decrease in concentration of Transferrin correlated with severity of PTB or the degree of inflammation. [(23)] In another study, Transferrin was lowest in newly diagnosed PTB patients (218±54.7mg/dl) as compared to on drug patients (244.6±61.1 mg/dl) and controls (270.4±22.8 mg/dl). [(24)] Strong correlation between transferrin and disease severity found in our study (Table 5) suggest its role in assessing severity of illness and in monitoring clinical recovery in PTB. Improvement in Transferrin level during course of disease indicates better therapeutic response and improved nutrition.

CONCLUSION

In the present study, it was concluded that Iron metabolism was altered in Pulmonary Tuberculosis. A low serum Fe, Transferrin and Transferrin Saturation was seen in patients group than controls. On the contrary, TIBC, Ferritin and CRP were higher in PTB patients. Fe did not showed any correlation to Clinical severity or sputum bacterial load and Transferrin correlated strongly to disease severity and thereby assumes role in severity assessment and monitoring treatment response. Ferritin plays essential role in iron hemostasis by binding and sequestering intracellular iron. Increase in Ferritin (an Acute Phase Reactant) in response to infection was attributed to prevent iron availability to MTB so as to inhibit its growth and multiplication. Here high Ferritin does not indicate high Fe stores. Both CRP and Ferritin were strongly associated to clinical severity and sputum positivity and may be regarded useful marker of disease activity, mortality risk and in monitoring therapeutic response.

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