



## C- REACTIVE PROTEIN IN TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS INFECTIONS IN ABEOKUTA, NIGERIA

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### ABSTRACT

*This study was conducted to evaluate C-reactive protein (CRP) levels in Mycobacterium tuberculosis and human immunodeficiency virus (HIV) infections and the follow-up therapeutic response to tuberculosis (TB) among patients aged 19-68 years attending out-patient clinics of two hospitals in Abeokuta, Southwestern Nigeria. Of 246 blood samples examined, the CRP value was highest (4.0%) among age group 21-40 years and there was significant difference between CRP values of age groups ( $p < 0.001$ ). More males (4.6%) had higher CRP value than females (1.5%), however there was no significant difference between their CRP values ( $p = 0.173$ ). C-reactive protein values was significantly higher (30.8%) among patients with severe anaemia ( $p < 0.001$ ). Also, the CRP value was significantly higher (57.1%) among patients with elevated erythrocyte sedimentation rate value greater than 100mm/h ( $p < 0.001$ ) and patients (38.1%) with Mycobacterium tuberculosis infection ( $p < 0.001$ ). C-reactive protein value was also significantly highest (50.0%) among patients infected with HIV only and HIV patients co-infected with TB ( $p < 0.001$ ). The elevated CRP values were progressively reduced to normal values (0-10mg/L) among TB infected patients but not HIV co-infected patients within the eight weeks therapeutic period. In conclusion, CRP level in blood could be regarded as a sensitive indicator to monitor the response to chemotherapeutic treatments of Mycobacterium tuberculosis infection.*

**Keywords:** C-reactive protein, Tuberculosis, Human Immunodeficiency, Virus, Outpatient, Abeokuta, Nigeria

### INTRODUCTION

C-reactive protein (CRP) was first discovered by Tillet and Francis in 1930, in patients infected with *Streptococcus pneumoniae* (Jaye and Waites, 2007). It appears to be produced by hepatocytes within 4-6 hours after onset of tissue injury or inflammation, doubling every 8 hours, before peaking at around 36 hours. Its half-life is short (4-8 hours) (Fraunberger *et al.*, 2006).

CRP is an inflammatory marker whose concentration increases with acute or chronic inflammation. It is produced by the liver in response to stimulation by cytokines such as interleukin-1 beta, interleukin-6, and tumor necrosis factor alpha (Nylen, *et al.*, 2008). High-sensitivity measurement of CRP has been shown to add prognostic information at all levels of Framingham risk, (Ridker *et al.*, 2000) but CRP has not been consistently shown to be an independent risk factor across all studies (Van der Meer *et al.*, 2003). C-reactive protein (CRP) is an acute-phase protein and nonspecific marker of systemic inflammation (Black *et al.*, 2004). The erythrocyte sedimentation rate (ESR) also provides a measure of inflammation, both elevated in the presence of inflammation, although, CRP response appears sooner than the rise in ESR. The CRP level falls to normal if treatment is successful but the ESR levels may still be abnormal for a longer period (Meisner *et al.*, 2006).

Roughly, a one third of the world's population has been infected with *M. tuberculosis*, and

new infections occur at a rate of one in every second (WHO, 2009). However, not all infections with *M. tuberculosis* cause disease and many infections are asymptomatic (Lambert *et al.*, 2003). An estimated 13.7 million people had active TB disease, with 9.3 million new cases and 1.8 million deaths; the annual incidence rate varied from 363 per 100,000 in Africa to 32 per 100,000 in the Americas and the leading cause of death among people with HIV/AIDS (Sobero, 2006).

It is one of the most common AIDS-defining illnesses in Africa, despite the fact that treatment is available for it (Westreich *et al.*, 2009). Active tuberculosis may boost HIV replication in vivo (Small *et al.*, 2003), and results of recent empirical studies show significant increases in mortality from tuberculosis in HIV infected individuals with advanced immunosuppression and in patients with acquired immunodeficiency syndrome (Goletti *et al.*, 2006). Therefore, this study examines the C-reactive protein in tuberculosis and human immunodeficiency virus infections among hospital patients in Abeokuta with the possible clinical application of CRP assay in the diagnosis, treatment and monitoring of the infections.

### MATERIALS AND METHODS

#### Study Area

The study was conducted in Abeokuta, Ogun State, Southwest Nigeria with a population of 593,140 of 2005 census (Dimeji, 2010).

The study was carried out between June 2010 and November 2010 among patients of medical out-patients and in-patients unit of the Sacred Heart Hospital, Lantoro and State General Hospital, Ijaiye, Abeokuta. Ethical approval was obtained from each hospital ethical committee.

### **Sample Collection**

A total of two hundred and seventy-one (271) sputum and blood samples (246 patients and 25 control group subjects) were collected for this study. Each patient was made to produce about 10 ml early morning sputum sample into a clean, sterile, wide-mouth container with fitting screw cap and stored at 4°C until ready for analysis. Venous blood samples were obtained from each patient into ethylene diamine tetraacetate (EDTA) anticoagulated and non-anticoagulated tubes. The anticoagulated blood was used to determine PCV and ESR while the non-anticoagulated tube was centrifuged at 2000 revolution per minute (rpm) for 5 minutes to obtain serum for serologic assay.

### **Microscopic Examination**

Sputum sample were pre-treated with 4% sodium hydroxide, concentrated by centrifugation, smear made from the sediment, heat fixed, stained by Ziehl-

### **Calculations:**

$$\text{CRP}_{\text{patient}} = \frac{\text{Patient Absorbance}}{\text{Standard Absorbance}} \times \text{Concentration of Standard Solution (20mg/L)}$$

### **Haematocrit and Erythrocyte Sedimentation Rate Determination**

The haematocrit (Hct) which is also known as the packed cell volume (PCV) of each patient was determined by centrifugation of EDTA anticoagulated blood in capillary tubes (with one end sealed) using Hawksley haematocrit centrifuge. The erythrocyte sedimentation rate (ESR) of each patient was determined by Westergren-micro method using EDTA anticoagulated blood and the reading was taken at the end of one hour. The normal values for PCV and ESR are 34%-54% and 2-9 mm/hr respectively.

### **Statistical Analysis**

The study was carried out and the proportion of individual CRP levels was calculated. The CRP among the samples were cross tabulated with age, sex, packed cell volume, erythrocyte sedimentation rate, human immunodeficiency virus infection and tuberculosis infection using SPSS version 15. Relevant chi-square and significant values were computed using Pearson models.

### **RESULTS**

Two hundred and forty-six patients were examined in this study as shown in Table 1. There were more patients in the age group 21-40 years 176 (71.5%) while fewer were seen in the 1-20 years age group 2(0.8%). The overall CRP value was highest among age group 21-40 years 7(4.0%). The computed chi-square statistics for the test of no association between CRP values and age had a value of 45.476 and

Nelson's method and examined for acid fast bacilli (AFB).

### **Human Immunodeficiency Virus (HIV) Test**

The HIV-1 and HIV-2 screening kits used in this study were Determinekit (Abbot Laboratory, USA) and Chembo HIV-1\2, USA) as recommended by World Health Organization. These are immunochromatographic (rapid) methods for qualitative detection of antibodies of all isotypes (IgG, IgM, IgA) specific to HIV-1 and HIV-2 simultaneously in serum, plasma or whole blood. These methods used were highly sensitive, specific with very suitable control incorporated.

### **C- reactive protein (CRP) Assay**

The CRP level was assayed using an immunoturbidimetric latex agglutination (Cypress Diagnostics, Belgium). This is an immunoturbidimetric assay. The CRP reagent was a suspension of positive latex particles coated with the gamma globulin fraction of anti human CRP specific serum. When CRP is present in the sample, the resulting turbidity was measured colorimetrically at 430nm. The CRP in each sample was calculated using a standard CRP solution. The normal CRP value for this assay is 0-10mg/L.

statistically significant at less than 1% level. Thus null hypothesis of no association is rejected.

The CRP value distribution by sex is shown in Table 2. The patients comprised 109 (44.3%) males and 137(55.7%) females aged 19-68 years. Of the 246 patients examined, 219 (89.0%) had CRP values of 0-10mg/L and 6 (2.4%), 6 (2.4%), 8 (3.3%) and 7 (2.8%) had respectively CRP values of 11-40mg/L, 41-70mg/L, 71-100mg/L and greater than 100mg/L. The overall CRP value was highest (>100mg/L) among male patients 5 (4.6%). The computed chi-square statistics for the test of no association between the CRP values and sex in Table 2 had a value of 6.368 which is not significant at 1% level and thus null hypothesis of no association is accepted.

Table 3 showed that patients with severe anaemia (PCV <26%) had highest CRP values 8 (30.8%) than those with moderate anaemia 0 (0%) and normal PCV 0 (0%). The computed chi-square statistics for the test of no association between CRP values and anaemia had a value of 196.963 and significant at less than 1%. Therefore the null hypothesis of no association is rejected.

The frequency distribution between the CRP and ESR in Table 4 showed that 6 (2.9%) and 1(0.5%) of the patients with high CRP values of 11-40mg/L and 71-100mg/L respectively had normal ESR (2-9mm/h) while 1 (14.3%), 2 (28.6%) and 4 (57.1%) patients with elevated CRP values of 41-70mg/L, 71-100mg/L and greater than 100mg/L had abnormal ESR (>10mm/h).

The computed chi-square statistics for the test of no association between CRP and ESR levels had a value of 248.514 and is significant at less than 1% level. Thus the hypothesis of no association is rejected.

The cross tabulation between CRP and tuberculosis infection of patients examined in Table 5 shows that, of 21 (8.5%) with *Mycobacterium tuberculosis* infections, 6(28.6%), 8(38.1%) and 7(33.3%) had elevated CRP values 41-70mg/L, 71-100mg/L and greater than 100mg/L respectively. The chi-square status computed for the test of no association between CRP and *Mycobacterium tuberculosis* infections had a value of 246.000 and statistically significant at less than 1% level and therefore the null hypothesis of no association is rejected.

Table 6 shows the TB that coexists with HIV in relation to CRP among the patients examined. The overall prevalence of TB co-infection with HIV was 4 (1.6%), of which 2 (50%) and 2 (50%) had respective elevated CRP values of 71-100mg/L and greater than

100mg/L. The chi-square status computed for the test of no association between CRP and TB co-infection with HIV had a value of 62.916 and statistically significant at less than 1% level. Thus rejection of the null hypothesis of no association.

It was observed that all the selected subjects for the control group were negative for *Mycobacterium tuberculosis* and HIV infections. Also, the C-reactive protein, packed cell volume and erythrocyte sedimentation rate values were within the normal values.

The frequency distribution of C-reactive protein and chemotherapeutic response of *Mycobacterium tuberculosis* and human immunodeficiency virus infections in Figure 1 showed that the elevated CRP values were progressively reduced to normal values (0-10mg/L) among TB infected patients but not HIV co-infected patients within the eight weeks of therapeutic period.

**Table 1: C - reactive protein Distribution by Age**

Age (year)	Total Examined (n)	C-Reactive Protein (mg/L)				
		0-10 n(%)	11-40 n(%)	41-70 n(%)	71-100 n(%)	>100 n(%)
1-20	2	0(0)	0(0)	1(50)	0(0)	1(50)
21-40	176	155(88.1)	5(2.8)	3(1.7)	7(4.0)	6(3.4)
41-60	62	59(95.2)	1(1.6)	1(1.6)	1(1.6)	0(0)
>60	6	5(83.3)	0(0)	1(16.7)	0(0)	0(0)
Total	246	219(89.0)	6(2.4)	6(2.4)	8(3.3)	7(2.8)

**Table 2: C - reactive protein Distribution by Sex**

Sex	Total Examined (n)	C-Reactive Protein (mg/L)				
		0-10 n(%)	11-40 n(%)	41-70 n(%)	71-100 n(%)	>100 n(%)
Male	109	97(89.0)	4(3.7)	1(0.9)	2(1.8)	5(4.6)
Female	137	122(89.1)	2(1.5)	5(3.6)	6(4.4)	2(1.5)
Total	246	219(89.0)	6(2.4)	6(2.4)	8(3.3)	7(2.8)

**Table 3: Haematocrit Level in Relation to C - reactive protein**

PCV (%)	Total Examined (n)	C-reactive protein (mg/L)					Anaemia Status
		0 – 10 n (%)	11 – 40 n (%)	41 – 70 n (%)	71 – 100 n (%)	> 100 n (%)	
34 – 54	52	49 (94.2)	3 (5.8)	0 (0)	0 (0)	0 (0)	Normal
26 – 34	168	165 (98.2)	3 (1.8)	0 (0)	0 (0)	0 (0)	Moderate
< 26	26	5 (19.2)	0(0)	6(23.1)	8 (30.8)	7 (26.9)	Severe
Total	246	219 (89.0)	6 (2.4)	6 (2.4)	8 (3.3)	7 (2.8)	

**Table 4: Erythrocyte Sedimentation Rate in Relation to CRP Level.**

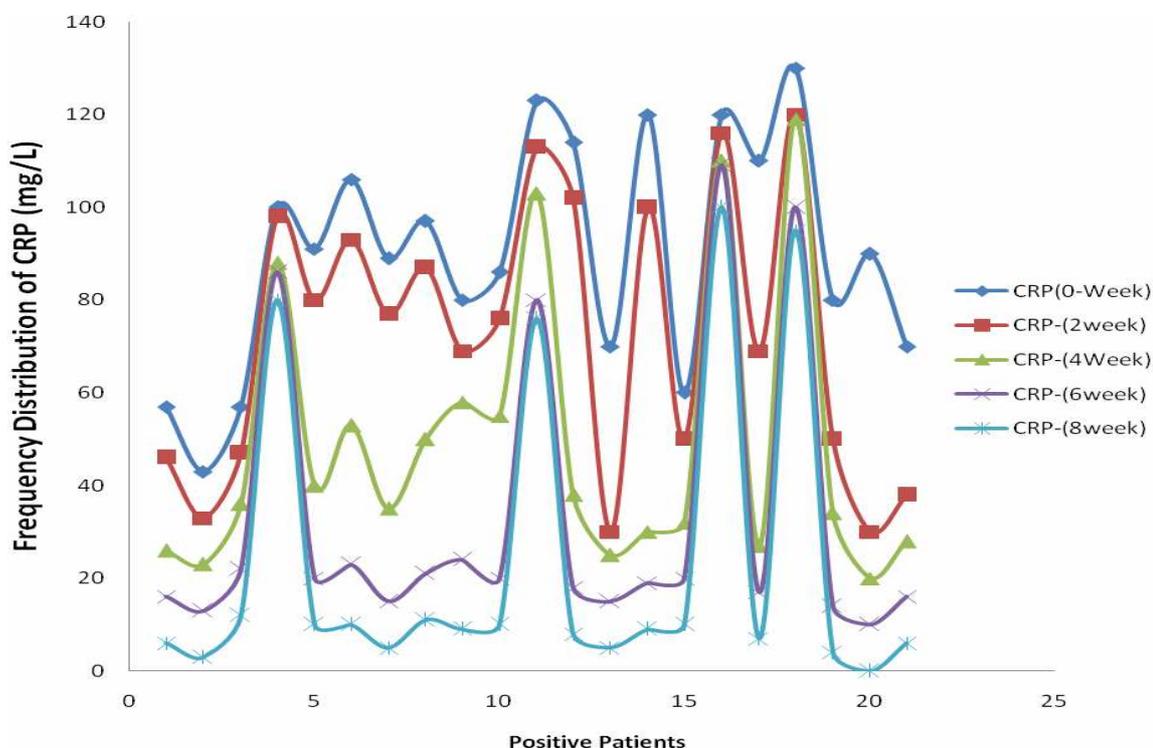
ESR (mm/hr)	Total Examined (n)	C-reactive protein (mg/L)				
		0 – 10 n (%)	11 – 40 n (%)	41 – 70 n (%)	71 – 100 n (%)	> 100 n (%)
2 – 9	205	198 (96.6)	6 (2.9)	0(0)	1 (0.5)	0 (0)
10 – 40	23	21 (91.3)	0 (0)	1 (4.3)	0 (0)	1 (4.3)
41 – 70	5	0 (0)	0 (0)	2 (40.0)	2 (40.0)	1 (20.0)
71 – 100	6	0 (0)	0 (0)	2 (33.3)	3 (50.0)	1 (16.7)
> 100	7	0 (0)	0 (0)	1 (14.3)	2 (28.6)	4 (57.1)
Total	246	219 (89.0)	6 (2.4)	6 (2.4)	8 (3.3)	7 (2.8)

**Table 5: Tuberculosis Infection and C - reactive protein**

TB Status	Total Examined (n)	C-reactive protein (mg/L)				
		0 – 10 n (%)	11 – 40 n (%)	41 – 70 n (%)	71 – 100 n (%)	> 100 n (%)
Negative	225	219 (97.3)	6 (2.7)	0 (0)	0 (0)	0 (0)
Positive	21	0 (0)	0 (0)	6 (28.6)	8 (38.1)	7 (33.3)
Total	246	219 (89.0)	6 (2.4)	6 (2.4)	8 (3.3)	7 (2.8)

**Table 6: TB and HIV Co-infection in relation to C - reactive protein**

TB+HIV Status	Total Examined(n)	C-Reactive Protein (mg/L)				
		0-10 n(%)	11-40 n(%)	41-70 n(%)	71-100 n(%)	>100 n(%)
Negative	242	219(90.5)	6(2.5)	6(2.5)	6(2.5)	5(2.1)
Positive	4	0(0)	0(0)	0(0)	2(50)	2(50)
Total	246	219(89.0)	6(2.4)	6(2.4)	8(3.3)	7(2.8)



**Figure 1: Frequency distribution of C-reactive protein and chemotherapeutic response of *Mycobacterium tuberculosis* and Human Immunodeficiency Virus (HIV) infections.**

**DISCUSSION AND CONCLUSION**

The twin epidemics of TB and HIV place enormous strain on the limited healthcare resources in west-Africa (Howie *et al.*, 2005). C-reactive protein levels have been studied as markers of bacterial lower respiratory tract infection in a number of populations and the results have so far been consistent (High *et al.*, 2004). C-reactive protein (CRP) has a greater practical value than does the elevated sedimentation rate, and also since there is no borderline value in the sedimentation rate, the difference between normal and abnormal elevated sedimentation rate may be small, while the presence of CRP is an indication of pathology, and disappearance of CRP is concomitant with

effectiveness of drugs which were used in treatment ( Nylen *et al.*, 2008;).

This study showed that the CRP was highest in the age group 21-40 years among patients in Abeokuta metropolis. This report corresponds with previous reports (Cushman *et al.*, 2009 and Zacho *et al.*, 2009). This may be attributed to Tuberculosis (TB) diseases risk development in young adults (Marnell *et al.*, 2005 and Cushman *et al.*, 2009). This study is in contrast to the previous report by Ford *et al.* (2004) that CRP levels increases with age. Previous investigation also recorded that young age is a risk factor for TB infection, for progression from infection to diseases and for spread of diseases to other parts of the body (Nachega, 2003; and WHO, 2007).

Finally, previous investigation (Sobero, 2006; Kumar *et al.*, 2007 and WHO, 2009) reported that 25%-50% of adolescents were infected with TB by the age 18 years and below. This may be due to the fact that adults are relatively immunosuppressed and their TB antibody levels are high (WHO, 2009).

There was no significant difference between sex and CRP, although more men had extremely elevated CRP values than women in this investigation which is in contrast to the previous report (Martin, 2006) of high prevalence of increased CRP levels in women than men. The differences may be due to socio-economic, geographical and ethnic groups in the study areas (Tso *et al.*, 2004 and Cobat *et al.*, 2010). Some studies reported that there is an increase in CRP levels in both men and women with TB infection (Lambert *et al.*, 2003; Wilson, 2009; WHO, 2009; Selwyn *et al.*, 2009 and Konstantinos, 2010). Many studies have been conducted that link CRP levels to other medical conditions, demographic, and socioeconomic factors (Lambert *et al.*, 2003).

In the report of Kanfer and Pepys (2001) which is similar to the finding in this study, increased CRP was significantly observed in patients that had severe anaemia (PCV < 26%). This observation is also supported by previous reports (Wetteland *et al.*, 2006 and Zacho *et al.*, 2009). Previous investigation (Thea *et al.*, 2005 and Volanakis *et al.*, 2009) also reported that TB patients with anaemia may be due to increase in age.

In this study, increased CRP values were observed in patients with extremely elevated erythrocyte sedimentation rate (ESR). Previous reports (Cook *et al.*, 2006) are in support of this finding that the levels of ESR and CRP are useful indicators for inflammatory reactions.

The result of this study showed significant increase in the CRP levels of TB-positive patients which is in agreement with the previous investigations (Murphy *et al.*, 2005; Van den Broek *et al.*, 2008 and Meintjes,

2010). Previous reports on TB-positive patients suggested that CRP is more likely to be elevated where more serious tissue damage has occurred in the lungs as a result of TB diseases (Wilson, 2009).

The findings in this study showed a significant increase in CRP level of TB/HIV co-infected patients which agrees with previous reports (Van den Broek *et al.*, 2008; Meintjes *et al.*, 2009a & b). This high level may be due to serious inflammation in TB among HIV-infected patients (Malkin *et al.*, 2007 and Mark *et al.*, 2007).

In this study, CRP values were elevated at presentation in all the TB infected patients and TB-HIV co-infected patients. The finding of an elevated CRP among TB infected patients and TB-HIV co-infected patients at presentation with an acute respiratory illness are consistent with observations from other studies (WHO, 2009). In the present study, higher CRP values were observed in TB patients with HIV- co-infection compared with patients with only pulmonary tuberculosis, which corroborate with previous studies (Jens *et al.*, 2005 and Hsiao and Baker, 2005). In this study, the follow-up chemotherapeutic treatment shows that the elevated CRP values were progressively reduced to normal which indicate effective response to therapeutic treatment as observed in previous records (Hsiao and baker, 2005; Goletti *et al.*, 2006 and Harries *et al.*, 2010).

Finally, it was established that CRP is of clinical significance in the follow-up and prognosis of TB, HIV and TB/HIV co-infection. All the patients with an acute pulmonary TB infection and TB-HIV co-infection had an elevated CRP while the CRP levels were progressively reduced to normal values in TB infected patients but not in HIV and TB/HIV co-infected patients after several weeks of chemotherapy. Therefore CRP levels in blood appear to be a sensitive indicator to monitor the response to chemotherapeutic treatments of *Mycobacterium tuberculosis* infection.

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