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Serum TNF-A Level and Haematological Indices in HIV-TB Co-Infections in Northern Nigeria
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Abstract

Both TB and HIV have profound effects on the immune system, as they are capable of disarming the host's immune responses through mechanisms that are not fully understood. In high-burden settings, HIV co-infection is the most important risk factor to develop active TB, which dramatically increases the susceptibility to primary infection or reinfection and also the risk of TB reactivation for patients with latent *M. tuberculosis* infection. TNF- α is a pro-inflammatory cytokine which exerts multiple biological effects, and is produced primarily by monocytes, macrophages, and dendritic cells when stimulated by mycobacterial metabolites. Consequently, TNF- α is likely involved in host protective responses against *M. tuberculosis* infection. The aim of the study therefore was to assess serum levels of TNF and haematological parameters among patients with HIV-TB co-infection and those with HIV mono-infection. Eighty-eight participants were enrolled in the study, 44 with HIV/TB co-infections and 44 with HIV mono-infection. Serum TNF- α levels, and haematological parameters were estimated using ELISA and automated haematology analyser respectively. Serum TNF α was significantly reduced in the study group compared to the control group ($p=0.001$). The WBC count was also significantly reduced in the study group compared to the control group ($p=0.038$). The HGB, HCT, MCV and MCH were significantly reduced in the study group compared to the control group ($p=0.001$, 0.001 , 0.002 and 0.001) respectively. Participants with HIV-TB co-infection have reduced serum TNF- α levels, low total WBC, lymphocyte and monocyte counts

compared to those with HIV mono-infection. TNF- α in the study the group correlated positively and significantly with monocyte counts ($r=0.319$, $p=0.043$).

Keywords: HIV, TB, TNF- α , Co-infections and Mono-infection

Introduction

Human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (MTB) infections are major causes of illness globally with the highest rates in developing countries with each infection potentiating the morbidity and mortality associated with the other (Mohan *et al.*, 2001). The dual epidemic of HIV infection and tuberculosis (TB) is one of the most formidable health challenges in sub-Saharan Africa (Maartens and Wilkinson, 2007). TB ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (WHO, 2018). However, the proportion of patients with TB/HIV co-infection in Nigeria is 19.1% (NTBLCP, 2014). Nigeria and other high TB burden countries have shown that TB/HIV co-infected patients have poorer treatment outcomes (Daniel and Alausa, 2006). Tuberculosis is one of the most frequent opportunistic infections in AIDS patient. HIV positive individuals are 50 times more susceptible to MTB infection, and once infected, are 800 times more likely to develop an active TB (WHO, 2005). Susceptibility to TB increases soon after HIV infection, far before the decrease of the CD4+ T-cell counts below 500 cells/mL, clearly showing that the mechanisms underlying

the increased susceptibility of HIV-infected individuals to active TB goes beyond the CD4 T-cell drop (Sonnenberg *et al.*, 2005). Both TB and HIV have profound effects on the immune system, as they are capable of disarming the host's immune responses through mechanisms that are not fully understood.

TNF- α is a pro-inflammatory cytokine which exerts multiple biological effects, which is produced primarily by monocytes, macrophages, and dendritic cells when stimulated by mycobacterial metabolites; therefore, TNF- α is likely involved in host protective responses against *M. Tuberculosis* infection (Azad *et al.*, 2012). An increased production of TNF has been suggested to cause increased susceptibility to active TB (Roca and Ramakrishna 2013). TNF- α production in response to *M. tuberculosis* infection is required for control of bacterial growth, TNF- α is known to activate HIV replication in macrophages indicating that the host immune response initiated against one pathogen may promote the replication of another (Kedzierska *et al.*, 2003). Thus, both HIV and *M. tuberculosis* stimulate TNF- α release from infected cells, and TNF- α hampers bacterial growth while enhancing HIV replication. *M. tuberculosis* has been reported to target DC-SIGN (Dendritic cells-specific intercellular-adhesion-molecule-3-grabbing non-integrin) by a mechanism that is distinct from that of HIV, leading to inhibition of pro-inflammatory IL-12 and TNF- α production and induction of IL-10 by dendritic cells and, hence, down-regulation of protective immune responses (Geijtenbeek *et al.*, 2003). TNF- α also stimulates the migration of immune cells to the infection site, contributing to granuloma formation, postulated to control the disease progression (Mohan *et al.*, 2001). Tumour necrosis factor-alpha (TNF- α) plays an essential role in preventing reactivation of persistent TB, modulates the pulmonary expression of specific immunologic factors and limits the pathological response of the host (Mohan *et al.*, 2001).

Anaemia is a frequent complication of both TB and HIV infection, and in both infections, it is associated with increased morbidity and mortality. The affected haematological indices include Packed Cells Volume (PCV),

thrombocytes, total and differential counts, with neutropenia, lymphopenia and thrombocytopenia as common features (Johnson and Godwin, 2006). Anaemia enhances the progression to HIV/AIDS and risk of death in patients with HIV. Bone marrow dysfunctions lead to cytopenia and prevalence and severity of diseases directly related to HIV disease progression (Belperio *et al.*, 2004).

Mycobacterium tuberculosis–HIV co-infections pose particular diagnostic and therapeutic challenges and exert immense pressure on health care systems in African and Asian countries with large populations of co-infected individuals (Getahun *et al.*, 2010). Understanding the human host response to this co-infection is therefore important and, would assist in the understanding of the pathology of HIV/TB co-infection. The aim of this study is to establish the premise of TNF- α and haematological indices as pathological signatures in HIV/TB co-infection.

Objectives

The objectives of our study were to evaluate the serum levels of TNF- α and haematological indices in patients with HIV-MTB co infection in North Eastern Nigeria and also examine for any relationships.

1. To evaluate the levels of serum Tumor necrosis factors-alpha (TNF- α) in patients with HIV and TB co-infections and HIV patients without TB as controls.
2. To evaluate haematological indices (WBCs, Platelets, PCV and neutrophils) in HIV positive patients co-infected with TB and HIV without TB as controls.
3. To correlate haematological indices with serum TNF- α obtained from same patients and controls.

Methodology

Study participants

A total of eighty-eight (88) patients were enrolled for the study. They were within the age limits of 15-60 and attended the antiretroviral therapy (ART) clinic of FMC Yola, Adamawa, Nigeria. Forty-four (44) were antiretroviral therapy naive patients with HIV/TB co-infections (study group) and 44 have HIV mono-infection were included as controls.

Data collection and laboratory analysis

An interviewer- administered questionnaire was designed and used to collect information on personal bio-data of the participants such as gender and age and clinical details. Five (5) and (4) milliliters of venous blood samples were collected from each participant in both plain and EDTA BD Vacutainer tubes respectively. The samples in the plain containers were separated and aliquoted into vials containing a drop of trasylol (aprotinin) and stored at -70°C until batch analysis of the cytokine. TNF- α was estimated using ELISA (Boster-Bio, USA LOT NO.9513124209) and values determined using the BioRad microplate reader PR 3100. Full Blood Count was done using Sysmex Automated Haematology Analyzer (XP-300), according to the operator's manual/User's guide. If for any reason, the EDTA samples could not be analyzed within 24 hours, the sample was stored for no longer than 24 hours at 4°C in the refrigerator.

Ethical Considerations

Approval from Health Research Ethical Committees of Federal Medical Center, Yola

(FMCY/SUB/96/VOLT/70) and informed consent from the participants was obtained prior to the commencement of sample collection. Participants were assured of confidentiality of information and freedom to withdraw from the study amongst others.

Statistical analysis

Following normality tests, haematological data was summarized using mean and standard deviation and TNF was summarized using median and interquartile range. Mann Whitney U test was used to compare TNF levels in the study and control groups respectively. Independent samples t-test was used compare haematological parameters across the two groups. Pearson's correlation analysis was used to compute the relationship between TNF levels and haematological parameters.

Results

Figure 1. Serum TNF- α significantly decreased ($p=0.001$) in HIV/TB co-infected patient compared to HIV mono-infected counterpart.

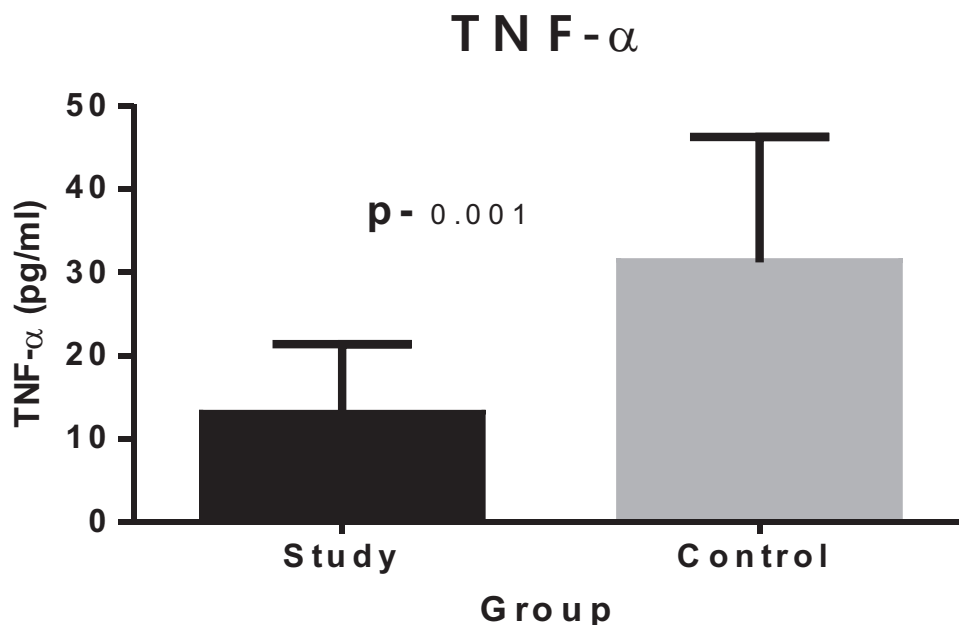


Figure: 1 Serum TNF- α Level in Both Study and the Control Groups

Data presented as Median/IQR; Statistical tool; Mann-Whitney test * = $p \leq 0.05$. TNF- α Tumour Necrosis Factor alpha.

Table 1 show significantly decreased values of WBC, HGB, HCT, MCV and increased Eosinophil among the subjects compared to controls ($p \leq 0.05$) while other parameters were insignificant ($p \leq 0.05$).

Table: 1 Haematological Indices in Study and Control Group

| Parameters | Mean±SD | | P-value |
|--------------------------|--------------|----------------|---------|
| | Study (n=44) | Control (n=44) | |
| WBC(x10 ⁹ /L) | Study | 4.855 ± 2.460 | 0.038* |
| | Control | 5.405 ± 1.831 | |
| RBC (cells/mcl) | Study | 3.983 ± 1.319 | 0.327 |
| | Control | 4.061 ± 0.796 | |
| HGB (g/dl) | Study | 10.19 ± 2.644 | 0.001* |
| | Control | 11.95 ± 2.350 | |
| HCT (%) | Study | 30.80 ± 7.980 | 0.001* |
| | Control | 38.59 ± 7.268 | |
| MCV(FL) | Study | 87.08 ± 12.53 | 0.002* |
| | Control | 96.40 ± 14.91 | |
| MCH (pg) | Study | 26.59 ± 3.427 | 0.001* |
| | Control | 29.94 ± 5.449 | |
| MCHC (g/dl) | Study | 30.51 ± 5.007 | 0.231 |
| | Control | 31.00 ± 2.397 | |
| PLT(x10 ⁹ /L) | Study | 267.1 ± 121.9 | 0.958 |
| | Control | 265.1 ± 124.0 | |
| LYMP (%) | Study | 42.39 ± 15.86 | 0.748 |
| | Control | 43.39 ± 13.13 | |
| MONO (%) | Study | 4.841 ± 3.348 | 0.806 |
| | Control | 4.977 ± 3.331 | |
| EOS (%) | Study | 5.273 ± 4.521 | 0.002* |
| | Control | 2.818 ± 2.072 | |
| NEU (%) | Study | 47.66 ± 14.28 | 0.854 |
| | Control | 48.23 ± 14.64 | |

Data presented as Mean±SD; Statistical tool: Two-tailed Un-paired t-test and *= p ≤ 0.05. WBC White blood cells; RBC Red blood cells; HGB haemoglobin; HCT Haematocrit; MCV Mean corpuscular volume; MCH Mean corpuscular haemoglobin; MCHC Mean corpuscular haemoglobin concentration; PLT Platelet.

Table 2 indicated a statistically positive linear correlation of TNF-α with monocytes in both study and control groups (p<0.05).

Table: 2 Correlation of TNF- α With Haematological Indices of Study and Control Group

| Parameters | Study (N=44) | | | Control (n=44) | | |
|--------------------------------|-------------------|--------|---------|-------------------|--------|---------|
| | Mean \pm SD | R | P-value | Mean \pm SD | R | P-value |
| TNF-α | 16.80 \pm 16.00 | | | 44.16 \pm 64.56 | | |
| WBC (x10 ⁹ /L) | 4.855 \pm 2.460 | 0.094 | 0.540 | 5.405 \pm 1.83 | 0.030 | 0.842 |
| RBC (cells/mcl) | 3.983 \pm 1.319 | 0.173 | 0.259 | 4.061 \pm 0.796 | -0.076 | 0.623 |
| HGB (g/dl) | 10.19 \pm 2.644 | -0.119 | 0.440 | 11.95 \pm 2.350 | -0.125 | 0.417 |
| HCT (%) | 30.80 \pm 7.980 | 0.160 | 0.299 | 38.59 \pm 7.268 | -0.134 | 0.388 |
| MCV(FL) | 87.08 \pm 12.53 | -0.200 | 0.192 | 96.40 \pm 14.91 | -0.067 | 0.665 |
| MCH (pg.) | 26.59 \pm 3.427 | -0.154 | 0.316 | 29.94 \pm 5.449 | -0.053 | 0.729 |
| MCHC (g/dl) | 30.51 \pm 5.007 | 0.025 | 0.872 | 31.00 \pm 2.397 | 0.066 | 0.666 |
| PLT(x10 ⁹ /L) | 267.1 \pm 121.9 | 0.066 | 0.668 | 265.1 \pm 124.0 | -0.101 | 0.512 |
| LYMP (%) | 42.39 \pm 15.86 | -0.197 | 0.199 | 43.39 \pm 13.13 | 0.046 | 0.763 |
| MONO (%) | 4.342 \pm 1.348 | 0.319 | 0.043* | 4.977 \pm 3.331 | 0.327 | 0.030* |
| EOS (%) | 5.273 \pm 4.521 | 0.093 | 0.545 | 2.818 \pm 2.072 | 0.049 | 0.748 |
| NEU (%) | 47.66 \pm 14.28 | 0.120 | 0.435 | 48.23 \pm 14.64 | -0.090 | 0.558 |

Data presented as Mean \pm SD; Statistical tool: Two-tailed Un-paired t-test and *= $p \leq 0.05$. WBC White blood cells; RBC Red blood cells; HGB haemoglobin; HCT Haematocrit; MCV Mean corpuscular volume; MCH Mean corpuscular haemoglobin; MCHC Mean corpuscular haemoglobin concentration; PLT Platelet.

Discussion

Our study showed reduced TNF- α level in the study group compared to controls. This might have been associated with the fact that, HIV infection has been shown to impair TNF-mediated macrophage apoptosis upon infection with *M. tuberculosis* (Patel *et al.*, 2007). Furthermore, Wanchu *et al.* (2009) report showed that patients with advanced immunosuppression are unable to mount a significant inflammatory response that can reflect in high levels of TNF- α level. According to Kindler *et al.* (1989) TNF alpha increases early in the disease and takes part in the pathogenesis and prevention of mycobacterial infection, and appears crucial for the formation of *M. tuberculosis*-constraining granulomas, infection control and elimination of mycobacteria. The findings of De Castro Cunhan *et al.* (2005) reported that T cell defects in TNF- α production are also consistent with the recognized role of TNF- α in granuloma formation, as granuloma formation is defective in HIV/TB co-infection, which suggests that

TNF- α produced by T cells may be particularly critical for granuloma development.

This finding is however contrary to previous reports (Bekker *et al.*, 1998; Silver *et al.*, 1998) which indicated that there is an association between TNF- α production and *M. tuberculosis* virulence in human monocytes, as well as a correlation between the increase in serum TNF- α levels and the clinical deterioration in patients with severe forms of TB. It further contradicts the finding of Vanham *et al.* (1996) which indicated a dramatic elevated serum levels of TNF- α and neopterin in HIV/TB co-infected patients which could be induced by mycobacterial stimulation of blood monocytes either directly or via IFN- γ .

The study revealed a significantly decreased value of total WBC count in HIV/TB co-infected patients compared to HIV mono-infected counterparts. This finding agreed with previous reports (Akpan *et al.*, 2012; Shareef *et al.*, 2012)

which indicated that the mean total WBC count in PTB patients is usually normal or not significantly elevated as compared to the normal mean of control groups. However, this study disagreed with the finding of Amilo *et al.* (2013) which indicated a statistically higher total WBC count among PTB and PTB/HIV comorbid patients, where neutrophilia is the main contributor to the increase.

The study showed significant decrease in haemoglobin levels in HIV/TB co-infected patients. Anaemia is the most commonly encountered haematological abnormality in HIV positive patients, which increases as the disease progresses (Volberding *et al.*, 2002). Several factors play a role in the development of anaemia in patients with HIV, and those are chronic infections, associated opportunistic infections, enteropathy and nutritional deficiencies. Obirikorang and Yeboah (2009), reported anaemia, neutropenia and thrombocytopenia as common findings in HIV/TB co-infected patients, often caused by inadequate blood cell production because of bone marrow suppression by HIV infection mediated by abnormal cytokine expression and alteration of the bone marrow microenvironment.

The study showed significant decrease in haemoglobin levels in HIV/TB co-infected patients.

MCV and MCH values were significantly decreased in HIV/TB co-infected patients. This might have been due to decreased erythrocyte lifespan, impaired marrow response or impaired flow of iron (Fe) from macrophages to the plasma in iron cycle metabolism. This decrease in haemoglobin may also be due to a non-immune mechanism that develops secondary to granulomatous infiltration of the bone marrow.

Platelets are effector cells that play an important role in the inflammatory and immunological response and have the capacity to release cytokines and chemokine, thus acting as an immune regulator (Trzeciak-Ryczek *et al.*, 2013). This study revealed that there was no significant difference in the platelets count between the subjects and control group. This

may be due to the fact that when there is an immune response in PTB infection, platelets tend to increase. Also, this might be associated with the fact that most of the participants were on anti-retroviral agents and immune boosters which help to improve the immune and haematological parameters of the subjects. The findings are also consistent with the report of Dilkshit *et al.* (2009) who stated that HIV-infected patients are characterized with thrombocytopenia and platelet counts below $125 \times 10^3/\text{mm}^3$.

TB may independently suppress lymphocyte number, thereby worsening HIV-related immunosuppression. However, this study revealed a slightly increased lymphocyte count in patients with HIV/TB co-infections, compared to HIV mono-infected counterparts. This finding is not in agreement with previous reports which are either significantly increased or decreased. While Bozoky *et al.* (1997) reported mild lymphocytosis in PTB with or without HIV co-infection, Idigbe *et al.* (2005) confirmed that neutropenia, lymphopenia and thrombocytopenia were often noticed in HIV infected individuals, indicating that more than one haematopoietic lineage may be impaired. Indian researchers Rajasekaran *et al.* (2007) reported that a decline in absolute lymphocytes counts which may indicate advanced HIV infection; reflect depletion of CD4 T lymphocytes, enhanced immunosuppression and anaemia, hence suggesting that absolute lymphocytes counts could serve as an inexpensive laboratory indicator to help physicians predict treatment failure and also as a useful marker for staging disease and predicting progression to AIDS.

This study showed statistically significant increase in the value of eosinophil in HIV/TB co-infected patients when compared to HIV mono-infected counterparts. This might have been associated with the effects of some infections which this study was not able to rule out. Some of the red cell indices such as RBC, and MCHC were none significantly increased, and again this may not be unconnected with strict adherence to medication and the increased awareness of the disease which make subjects more careful.

This study found no correlation between TNF- α and haematological parameters except the monocyte count. The strong positive correlation between TNF- α and monocyte counts suggests the role played by the latter in monopoiesis and monocyte trafficking into the lungs to fight tuberculosis (Husain, 2010).

Conclusion

Participants with HIV-TB co-infection have reduced serum TNF level, low total WBC, lymphocyte and monocyte count compared to those with HIV mono-infection. TNF- α levels correlate positively with monocyte counts.

Conflict of interest

The authors declare no conflict of interest.

Limitation of the study

1. Inability to screen out other infectious diseases and related health disorders that might have been associated with changes in some of the parameters in the study.
2. This study has been limited to adult of 15-60 years of age, while other age groups were excluded from the study.

Author's contribution

Japtu conceived the idea; Musa and Bosan supervised the work and contributed in the refinement of the research objectives, methodology result and discussion. Japtu and Saidu performed the statistical analysis of the result and the draft of the final manuscript. All authors agreed on the final manuscript before publication.

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