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ORIGINAL RESEARCH ARTICLE

Determination of Serum IL-8, $CD4^+$ and $CD8^+$ in Patients with Human Immunodeficiency Virus

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ABSTRACT

Background: Human Immunodeficiency Virus (HIV) is associated with a decline of immunity and progression to Acquired Immunodeficiency Syndrome (AIDS). This current study was aimed at evaluating the serum level of Interleukin-8 (IL-8), $CD4^+$ and $CD8^+$ T-cells counts among newly diagnosed Human Immunodeficiency Virus (HIV)-positive adults in Sokoto-Nigeria.

Materials and methods: A total of 60 adults were enrolled into the study, comprising of 30 newly diagnosed HIV seropositive subjects and 30 age-and sex-matched apparently healthy controls. $CD4^+$ and $CD8^+$ T-cells were enumerated using flow cytometry. Serum IL-8 was analyzed using ELISA kit. Data were analyzed using SPSS 20.0 statistical package. A p-value ≤ 0.05 was considered significant in all statistical comparisons.

Results: The mean of $CD4^+$ (632.63 ± 34.83 cells/µl), $CD8^+$ (579.98 ± 30.74 cells/µl) and $CD4^+$/$CD8^+$ ratio (1.10 ± 0.03 cells/µl) were significantly higher ($p < 0.05$) in controls compared to newly diagnosed HIV patients (160.60 ± 29.47 cells/µl, 521.10 ± 46.34cells/µl and 0.32 ± 0.52 respectively. The mean of IL-8 (6.56 ± 0.09 pg/ml) was significantly ($p < 0.05$) lower in controls compared to newly diagnosed patient IL-8 (6.60 ± 0.07 pg/ml). There were insignificant negative correlation between IL-8 and $CD4^+$ ($r = -0.064$, $p > 0.05$) as well as $CD8^+$ ($r = -0.074$, $p > 0.05$) in controls. And conversely, an insignificant positive correlation occurred between IL-8 and $CD4^+$ ($r = 0.025$, $p > 0.05$) as well as $CD8^+$ ($r = 0.016$, $p > 0.05$) in newly diagnosed HIV patients. Moreover, it has also shown a statistically insignificant positive correlation between IL-8 and $CD4^+$/$CD8^+$ ratio ($r = 0.039$, $p > 0.05$) in controls compared to newly diagnosed HIV patients where it shows a statistically insignificant negative correlation between the IL-8 and $CD4^+$/$CD8^+$ ratio ($r = -0.076$, $p > 0.05$).

Conclusion: It could be concluded that, both $CD4^+$, $CD4^+$/ $CD8^+$ ratio in newly diagnosed HIV patients are significantly decrease compared to controls ($p < 0.05$), while serum IL-8 was significantly increased, the serum levels of IL-8 did not correlate with $CD4^+$ T-cells and $CD8^+$ T-cells population, as well as $CD4^+$/$CD8^+$ ratio.

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus belonging to the family Lenti viruses, which are responsible for chronic and long lasting infections [1]. HIV pandemic is a major public health problem with an estimated 33millions people living with the virus globally [2]. Available data indicated that sub-Saharan Africa is bearing the greatest brunt of the global HIV scourge with an estimated 25.8millions people equivalent to 70% out of the number of people living with HIV

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worldwide [3]. When the HIV viral DNA is inserted into the host genomic cells, its becomes practically impossible to eliminate or destroys it, except by total destruction of the infected cells. The viral DNA, now well established in the host genome, hijack the producti machinery of the host by directing the exergerated production of proviral RNAs. The replication may start at the site of infection with the effector cells or within lymphocytes and monocytes, and these may be followed by differentiation and production of cells in the lymphoid tissues of the body. Its worthy to note that replication of virus is brought about by a different types of cytokines, example of which are, Tumor Necrosis Factor (TNF) and Interleukins (IL). These groups of cytokines has the potency to activate $CD4^+$ T-cells, making them ever susceptible to human immunodeficiency viral infections [4].

Lymphocyte Subsets of great significance in determining the responses of the host to infection. The most important of these subset are TH1 (T Helper 1) and TH2 (T Helper 2). The TH1 acts through endogenous pathway and its activities are mediated through MHCI and is responsible for coordinating Cytotoxic Immune Responses ($CD8^+$), while the TH2 subset acts through exogenous pathways, where it tries to prevent the body from being infected by virus, while increasing secretion of antibody. Individuals, who have a dominant, TH1 but infected with HIV tend to survive longer than those recessive TH1. It's on record that $CD8^+$ T-cells has the capacity to inhibit HIV infection through, HLA-restricted cytolysis as well as suppressive activity mediated by the secretions of multiple suppressive factors collectively referred to as $CD8^+$ Antiviral Factor (CAF) [5]. Interleukin-8 (IL-8, CXCL8) is a member of the proinflammatory CXC cytokine family implicated in mediation of inflammatory responses, including angiogenesis, leukocyte degranulation and cell migration [6]. CXC chemokines are small proteins (8-12 kDa) that contain a conserved CXC residue motif (C-cysteine, X-any other residue) proximal to the N-terminal region of the protein [7]. Biologic actions of IL-8 include the induction of respiratory burst [8], induction of chemotaxis of neutrophils. T-cells [9] and basophils [10]. Promoting release of lysosomal enzymes from neutrophils, and enhanced killing of various microorganisms including *M. tuberculosis* [11].

Lane, et al. [12] Shows that increased levels of IL-8 are present in the lymphoid tissue of patients with AIDS. Antibodies that neutralize IL-8 activity, and antibodies that block binding to the receptors CXCR1 and CXCR2, can inhibit HIV-1 replication in macrophages and T-cells. Blocking the actions of IL-8 with a small molecule inhibitor of CXCR2 SB225002 also markedly reduces HIV-1 replication. A major property of IL-8 during the inflammatory process is chemotaxis of targe T-cells to the site of inflammation, in particular neutrophils. IL-8 also has chemotactic activity against T-cells and basophils. Neutrophil adhesion to and transmigration across the endothelium are regulated by IL-8 and once neutrophils arrive to the site of inflammation, IL-8 further stimulates those cells to carry out phagocytosis, thus increasing the efficiency of tissue repair. Studies have also shown that IL-8 also has other immunomodulatory effects including the ability to induce matrix metalloproteinase-9 expression, release of TNF-Related Apoptosis-Inducing Ligand (TRAIL) and prime respiratory burst in neutrophils [13].

This research study was designed to evaluate serum levels of IL-8, plasma $CD4^+$ T-cell and $CD8^+$ T-cell counts in newly diagnosed HIV patients and compared with that in the healthy controls. This study may help to find out if the levels of IL-8 is in any way related to the severity of HIV infection, which may predict the HIV disease progression to AIDS, thus exploring the possibility for effective management of these patients.

MATERIALS AND METHODS

Study location

This research study was done in the State Specialist hospital Sokoto, and School of Medical Laboratory Sciences, Immunology Department, Usmanu Danfodiyo University Sokoto-Nigeria. The State has a semi-arid climatic condition, with a vegetation, which is largely of Sudan Savannah. The annual rainfall is in the range of 550- 1400 mm, with a temperature ranges 140C to 500C in an extreme condition SSBD, 2007).

Study subjects

A total of Thirty (30) newly diagnosed adults male and female HIV patients, attending ART Clinic in some major hospitals in the state and Thirty (30) age-and sex-matched apparently healthy controls who passed all the inclusion criteria were randomly recruited into the study informed consent was obtained from each prior to the commencement of the study.

Ethical approval

The ethical approval for this research was sought from the Ethics and Research Committee of Specialist hospitals Sokoto. The research was carried out in accordance with the declaration of Helsinki concerning the ethical principles for medical research involving human subjects.

Study design

A cross sectional study where eligible HIV-positive male and female patients attending some selected hospital Sokoto, were included in the study. All the HIV patients were evaluated clinically by the Consultant Physicians and relevant clinical data obtained. Eligible subjects were assigned to into two groups, Group A consisting of 30 HIV-negative controls and Group B consisting of 30 newly diagnosed HIV patients.

Anthropometric measurements

Body weight: At enrolment, the subjects was weighted with minimum clothing to the nearest 0.1kg by using a regularly calibrated weighing health scale; model ZT 120 (manufactured by Seca Gmbh and Co., Germany).

Height: The heights of the subjects were measured by using a calibrated Stadiometer, model 220 (manufactured by Seca Gmbh and Co., Germany). For height measurement, the subject stand erected and barefooted on a Stadiometer with a movable head piece. The head piece was levelled with skull vault and height recorded to the nearest 0.5 cm.

Body mass index: Body Mass Index (BMI) for each subject was calculated using the following formula:

$$\text{BMI}\left(\text{kg}/\text{m}^2\right) = \frac{\text{Body Weight}\left(\text{kg}\right)}{\text{Height}\left(\text{m}^2\right)}.$$

Blood samples collection and processing

From each selected subject, a total of five millilitres (5.0ml) of venous blood specimen was collected using a sterile vacutainer blood specimen bottles, holder and needle. Three millilitres (3.0ml) of blood specimen was collected into a sterile plain vacutainer blood specimen bottle, and allowed to clot at room temperature and later centrifuged at 3000rpm/min for 5 minutes, then obtained a clear unhaemolyzed serum. The serum was harvested into sterile serum-separation tubes and rapidly stored at -20°C until assayed in batches; for serum levels of Interleukin-8 (IL-8). Two millilitres (2.0ml) of the blood specimen was collected into a sterile EDTA vacutainer blood specimen bottle, and used to re-determined and confirmed HIV-status and for the enumeration of $CD4^+$ T-cell and $CD8^+$ T-cell count within 3 hours of the blood sample collection.

Laboratory analysis

Evaluation of $CD4^+$ and $CD8^+$ cell count: The $CD4^+$ or $CD8^+$ T-Cells were enumerated using Cyflow Counter manufactured by Partec, Munster, Germany, which operate on the principle of flow cytometry method by Cassens.

Determination of $CD4^+/CD8^+$ ratio: The $CD4^+/CD8^+$ Ratio was calculated using, the number of $CD4^+$ T-cells count (cells/µl of blood) / Number of $CD8^+$ - cells count (cells/µl of blood).

Evaluation of serum Interleukin-8 (IL-8): Serum level of Interleukin-8 (IL-8) was measured using quantitative ELISA method and the kit was procured from Invitrogen Corporation KHC0081. The analysis was done in strict adherence to the manufacturer's instructions. The result was read spectrophotometrically using Elisa reader at a wavelength of 450nm.

Statistical analysis

The data obtained was analyzed using Microsoft Office Excel 2013 and Statistical Package for Social Sciences (SPSS) version 20. The results were expressed as mean ± SEM. Group comparisons was made using one-way Analysis of Variance (ANOVA), correlation analysis was done between the groups, paired comparisons was carried out using the Student's T-test, and p-value of equal to or less than 0.05 ($p \leq 0.05$) was considered as significant.

Presentation of results

Socio-economic and demographic characteristic of the study subjects: Table 1 shows the gender, marital status, occupation and educational level in the study groups, among which 20(66.7%) and 15(50.0%) were males for controls and newly diagnosed HIV patients respectively. While females were 10(33.3%) and 15(50.0%) for controls and newly diagnosed HIV patient respectively. The result also indicated that 4(13.3%) of the subjects in controls were married as compared with 16(53.3%) in newly diagnosed HIV patients. Most of the subjects in controls group were students 17(56.7%) as compared to newly diagnosed, where the highest percentage of them were marketers 13(43.3%). Moreover, it has also shown that in control group the highest educational level attained (tertiary) belong to the control group with 25(83.3%) as compared to newly diagnosed HIV patient group where majority were illiterate 16(53.3%).

Serum IL-8, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ ratio of the study subjects: The mean of $CD4^+$ (632.63 ± 34.83 cells/µl), $CD8^+$ (579.98 ± 30.74 cells/µl) and $CD4^+/CD8^+$ ratio (1.10 ± 0.03 cells/µl) were significantly higher ($p < 0.05$) in controls compared to newly diagnosed HIV patients (160.60 ± 29.47 cells/µl, 521.10 ± 46.34 cells/µl and 0.32 ± 0.52 respectively), as shown in table 2. The mean of IL-8 (6.56 ± 0.09 pg/ml) was significantly ($p < 0.05$) lower in controls compared to newly diagnosed patient IL8 (6.60 ± 0.07 pg/ml).

Table 1: Socio-economic and demographic characteristic of the study subjects.

Characteristics	Controls (n = 30)	Newly diagnosed HIV patients (n = 30)
Gender		
Male	20(66.7%)	15(50.0%)
Female	10(33.3%)	15(50.0%)
Marital Status		
Single	26(86.7%)	9(30.0%)
Married	4(13.3%)	16(53.3%)
Widowed	0(0.00%)	5(16.7%)
Divorced	0(0.00%)	0(0.00%)
Occupation		
Business	8(26.6%)	13(43.3%)
Student	17(56.7%)	1(3.3%)
Civil servant	3(10.0%)	5(16.7%)
Unemployed	2(6.7%)	11(36.7%)
Educational Level		
Primary	1(3.3%)	1(3.3%)
Secondary	4(13.3%)	9(30.0%)
Tertiary	25(83.3%)	4(13.3%)
No formal education	0(0.00)	16(53.3%)

Table 2: Serum IL-8, $CD4^+$, $CD8^+$counts and $CD4^+$/ $CD8^+$ratio of the study subjects.

Parameters	Controls (*n* = 30)	Newly diagnosed HIV patient (*n* = 30)	*p*-value
$CD4^+$(cells/µl)	632.63 ± 34.83	160.60 ± 29.47	<0.05
$CD8^+$(cells/µl)	579.98 ± 30.74	521.10 ± 46.35	>0.05
$CD4^+/CD8^+$(cells/µl)	1.10 ± 0.03	0.33 ± 0.05	<0.05
IL-8(pg/ml)	6.56 ± 0.09	6.60 ± 0.07	<0.05

Values are expressed in Mean ± SEM, $CD4^+$ = Cluster of Differentiations Four Type 4; $CD8^+$ = Cluster of Differentiations Type 8; *n* = Number of Subjects; pg/ml = Picogram per Miles; µl = Microlitre; IL8 = Interleukin 8.

Table 3: Correlation of serum IL-8 with $CD4^+$ counts, $CD8^+$ counts and $CD4^+/CD8^+$ ratio.

Parameters	Control (*n* = 30)		Newly diagnosed HIV patients (*n* = 30)	
	r - value	*p* - value	*r* - value	*p* -value
$CD4^+$(cells/µl)	-0.064	>0.05	0.025	>0.05
$CD8^+$(cells/µl)	-0.074	>0.05	0.016	>0.05
$CD4^+/CD8^+$(cells/µl)	0.039	>0.05	-0.076	>0.05

Correlation of serum IL-8 with $CD4^+$ counts, $CD8^+$ counts and $CD4^+/CD8^+$ ratio: r = Correlation coefficient; p = Level of significance; $CD4^+$ = Cluster of Differentiations Four (4); $CD8^+$ = Cluster of Differentiations Eight (8); Pg/ml = Picogram Per Miles; Ml = Microlitre and N = Number of Subjects.

Correlation studies of serum IL-8, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ ratio: There were insignificant negative correlation between IL-8 and $CD4^+$ (r = -0.064, p > 0.05) as well as $CD8^+$ (r = -0.074, p >0.05) in controls. And conversely, an insignificant positive correlation occurred between IL-8 and $CD4^+$ (r = 0.025, p > 0.05) as well as $CD8^+$ (r = 0.016, p > 0.05) in newly diagnosed HIV patients, as shown in table 3. Moreover, it has also shown a statistically insignificant positive correlation between IL-8 and $CD4^+/CD8^+$ ratio (r = 0.039, p > 0.05) in controls compared to newly diagnosed HIV patients where it shows a statistically insignificant negative correlation between the IL-8 and $CD4^+/CD8^+$ ratio (r = -0.076, p > 0.05).

Correlation of anthropometric and immune parameters in controls and patients: There was no significant negative correlation of age with $CD4^+$ and $CD8^+$ counts, but there was insignificant positive correlation of age with $CD4^+/CD8^+$ ratio and IL-8. However, there was an insignificant correlation of BMI with $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ ratio.

DISCUSSION

Human Immunodeficiency Virus (HIV) and its subtypes are retroviruses and the etiologic agents of acquired Immunodeficiency Syndrome (AIDS). According to De Cock, et al. [14] and Maarten, et al. [15] HIV once entered into the body destroys the immune system and progresses to AIDS, hence all HIV infected persons are at risk of illnesses and death from opportunistic infections and neoplastic complications due to inevitable manifestation of AIDS.

The result of this study shows a decrease in the number of $CD4^+$ and $CD8^+$ T-cells as a result of $CD4^+$ depletion and increase in viral load respectively, in newly diagnosed HIV patient compared to controls, this is brought about by the replicative actions of the virus which directly affects the population of the CD4 cells as new virions are in constant production, this finding is also supported by Catalfamo, et al. [16].

The level of IL-8 in this research was found to be highly upregulated compared to the controls. This elevation in the level of IL-8 could be attributed to increases in inflammation responses evident in newly diagnosed HIV patient. This research finding is consistent with the report of Robert, et al. [17] and Kolacinski, et al. [18]. Whose reported the there is a significant increase in the level of IL-8, in the HIV infected individuals. There was no significant correlation between the Anthropometric and Immune parameters in both controls and Patients evaluated in this research study.

Statistically insignificant correlation between high level of IL-8 and lower number of $CD4^+$ and $CD8^+$ T-cells in newly diagnosed HIV patients compared to controls, was also demonstrated in this study. This is consistent to the report of Pananghat, et al. [19], who also reported the same statistical in-significant correlation between the levels of IL-8, and that of $CD4^+$ and $CD8^+$ T-cells, but the findings is contrary to the report of Ping, who reported a statistical significancy. The destruction of $CD4^+$ T lymphocytes has generally been observed and acknowledged as a direct consequence of the immune-pathogenesis in HIV-1 infection, hence the depletion in their numbers as shown by this study.

During HIV infection IL-8 plays an important role in the recruitment of CD4-positive T-cells to the lymph nodes, thus generating more targets for viral replication, this is partly responsible for the elevated level of IL-8 in the serum of early HIV infected patients as demonstrated by this study. Matsumoto, et al. [20] have reported elevated serum levels of lL-8 in HIV-1 infected patients. Levels of IL-8 have also been reported to be significantly elevated in Cerebrospinal Fluid (CSF) of HIV-1 infected patients with cryptococcal

meningitis and in the plasma of asymptomatic HIV-l infected individuals, although not in AIDS patients.

IL-8 is an inflammatory and antimicrobial cytokine, it is a potent chemotactic factor for T-cells, NK cells, neutrophils and basophils [21]. IL-8 is upregulated and constitutively secreted following in vitro HIV-infection of MDM [22], but reduced in the chronically infected U937 monocytic cell line [23]. Elevated levels of IL-8 have been also observed in patients with HIV-1 infection, both in patients' serum [24] and bronchoalveolar fluid [25] HIV-1 infection at all stages of the disease is associated with chronic immune activation and dysfunctional cytokine production.

Increased production of proinflammatory cytokines (IL-1, IL-6, IL-8 and TNF-α) are also thought to activate HIV-1 replication and maintain active HIV-1 expression via binding of NF-κB to LTR.

CONCLUSION/RECOMMENDATION

In conclusion, it should be point out that, serum interleukin 8 increased significantly in newly diagnosed HIV patients and this is associated with significant reduction in the $CD4^+$ T-cells, $CD8^+$ T-cells, and $CD4^+/CD8^+$ T-cells ratio in newly diagnosed HIV patients.

More research should be undertaken, to actually establish the precise role of IL-8 in HIV disease progression and pathogenesis.

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