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Original Research Article

Assessment of serum soluble intercellular adhesion molecule-1 and albumin in human immuno-deficiency virus-infected individuals with or without malaria parasite infection in Nauth, Nnewi, Nigeria

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ABSTRACT

Background: Human immunodeficiency virus (HIV) co-infection with malaria is the main cause of morbidity and mortality in developing countries, including Nigeria. Both infections have impact on the disease severity and progression.
Methods: This was a cross-sectional study aimed to determine the serum soluble intracellular adhesion molecule-1 (sICAM-1) and albumin in HIV/malaria-infected individuals attending the antiretroviral therapy (ART) clinic at Nnamdi Azikiwe Teaching Hospital, (NAUTH) Nnewi, Nigeria. 168 randomly selected individuals aged 18-65 years grouped into 42 HIV-infected individuals on ART, 42 HIV-malaria c-o-infected individuals on ART, 42 malaria-infected individuals, and 42 apparently healthy individuals (control) were included in the study. Serum sICAM-1 and albumin were determined using enzyme linked immunosorbent assay (ELISA) and bromocresol green technique respectively while CD4 T-cell count was obtained from the patients' records.
Results: The mean serum sICAM-1, albumin and systolic blood pressure (SBP) levels were significantly higher in HIV individuals with and without malaria infection when compared with control participants ($p<0.05$) respectively. The mean CD4 T-cell count was significantly lower in HIV/malaria co-infected individuals when compared with HIV infected individuals ($p <0.05$). A significant negative correlation was observed between CD4 count and sICAM-1 both in HIV infected individuals and HIV-malaria co-infection ($p<0.05$).
Conclusions: The increased sICAM-1, SBP with decreased albumin levels suggests inflammatory and vascular changes with reduced hepatic synthesis which may result in endothelial dysfunction, adverse cardiovascular conditions, and disease progression.

Keywords: HIV, Malaria, Co-infection, Inflammation, Endothelial dysfunction, Hypertension

INTRODUCTION

Human immunodeficiency virus (HIV) co-infection with malaria is the leading cause of morbidity and mortality in developing nations including Nigeria, they are the greatest health problems worldwide, which is estimated to account for more than 4 million fatalities annually.[1] The co-infection increases the severity and mortality of both diseases.[2] HIV pathophysiology, clinical, and epidemiological interactions with pathogenic organisms,

particularly malaria parasites, constitute a great concern to public health.[3] Infections caused by both, particularly in the case of plasmodium parasites, cause considerable immune system activation and disturbance. The development, severity, and rate of progression of each other's diseases may all be influenced by the two infections (HIV and malaria).[4] Sub-Saharan Africa is home to the majority of the world's cases of HIV and malaria, which are mostly caused by *Plasmodium falciparum*.[5] HIV infection increases the risk and severity of malaria infection as well as its consequences and also promotes the rate of malaria transmission, which in turn results in significant CD4 cell activation and an increase in the production of pro-inflammatory cytokines, creating the perfect atmosphere for the rapid replication of HIV-1 in CD4 cells.[6] The infections deplete vital cells needed for the body's immunological and hematological function, leading to complications such as severe malaria, increased risk of malaria treatment failure (drug resistance), increased viral load, and increased mortality rate.[7,8] Anemia, thrombocytopenia, neutropenia, and leucopenia are hematological abnormalities that have been associated with HIV and malaria co-infection in Nigeria and were found to be much more prevalent in this population than in HIV-only infections.[9] Recurrent episodes of symptomatic malaria in this individual, results to anemia, an increase in plasma viral load, and a drop in CD4 count.[10]

Serum soluble intracellular adhesion molecule-1 (sICAM-1) represents the circulatory form of cellular adhesion molecule-1 (CAM-1), intercellular adhesion molecule-1 (ICAM-1) - a transmembrane protein expressed on the surface of various types of cells in the body, such as endothelial cells. It serves as a counter-receptor for lymphocyte function-associated antigen (LFA-1). And plays a role in the immune system's response to inflammation and infection.[11] The interaction between sICAM-1 expressed on the surface of epithelial cells and LFA-1 facilitates leucocyte adhesion and migration across the endothelium. When inflammation occurs, ICAM-1 is upregulated and released into the bloodstream yielding the sICAM-1.[12] Elevated levels of sICAM-1-1 have been seen in certain inflammatory and autoimmune conditions, including rheumatoid arthritis, systemic erythematosus, multiple sclerosis, cardiovascular disease, HIV, and malaria and it plays critical roles in generating inflammatory responses and boosting HIV infectivity.[13] The levels of sICAM-1 are considerably raised during HIV infection and may be higher in the co-infection, indicating a more severe inflammatory response and potentially higher risk of complications.[14] sICAM-1 has been proposed as a potential marker for disease severity and prognosis in malaria infection.[15] Increased sCAM-1 levels reflect endothelial cell damage and contribute to the development of complications such as cerebral malaria and acute respiratory distress syndrome.[16] Measuring sICAM-1 levels in the blood can therefore provide an indication of the severity of these infections and the risk of associated complications.

Albumin which is a transport protein that is produced by the liver plays a critical role in maintaining proper fluid balance in the body. Infections such as HIV and malaria may cause a decrease in albumin levels in the blood, which can lead to malnutrition and other complications.[17] Measuring albumin levels in the blood can therefore provide an indication of the severity of these infections and the risk of associated complications. Assessing serum sICAM-1 and albumin levels can be used in conjunction with other clinical assessments to monitor the progression of HIV and malaria infections and guide treatment decisions, hence, the design of this study.[14]

METHODS

Study site

This study was conducted at Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra state, Nigeria.

Study design

This was a cross-sectional study conducted to evaluate the serum levels of sICAM-1 and albumin in HIV-malaria-infected adult participants and HIV-infected individuals on ART attending the Institute of Human Virology, Nigeria (IHVN) clinic in NAUTH, Nnewi, Nigeria between October, 2022 and January, 2023. Participants within the age range of 18–65 years were randomly selected for the study. Written consent was obtained from each participants and a questionnaire was administered to obtain their bio-data. The patient's record was used to obtain the CD4 count. A total number of 168 adult participants were involved; these comprised 42 malaria-infected HIV individuals, 42 non-malaria-infected HIV individuals, 42 malaria-infected individuals, and 42 individuals without malaria or HIV infection which served as control.

Inclusion criteria

HIV seropositive individuals (both male and female) with or without malaria parasite infection who have been placed on antiretroviral therapy for not less than six months and HIV seronegative individuals with or without malaria were included in this study. Participants were within the age range of 18–65 years.

Exclusion criteria

HIV seronegative individuals and HIV seropositive individuals with other known underlying health conditions such as cardiovascular diseases, kidney diseases, liver diseases autoimmune diseases, inflammatory diseases, and those outside the age bracket were excluded.

Informed consent

Consent of the participants was obtained prior to the study.

Ethical approval

The ethical approval for this research was obtained from the board of ethics committee of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Nigeria.

Sample collection

About four (4 ml) of venous blood was collected for the study. The blood was dispensed into a plain container and centrifuged at 4000 rpm for 10 minutes to extract serum which was used for the analysis.

Screening for malaria

The participants were screened for malaria using the Abbot malaria rapid test kit as described by (Abbot Laboratories). The test qualitatively detects *Plasmodium* antigen in human whole blood samples. This test applies lateral flow immunochromatography and is a tool to assist in the diagnosis of malaria. Malaria positivity was confirmed using the Giemsa staining technique.

HIV screening

Antibodies to HIV-1 and HIV-2 in human serum were determined immunochromatographically using Abott determine TM HIV-1 and HIV-2 kit, which is an in vitro read immunoassay, and HIV-1 and 2 Statpak assay kit, which is an immunochromatographic test for the quantitative detection of antibodies to HIV-1 and HIV-2 in human serum.

Determination of serum sICAM-1

sICAM-1 was determined using an enzyme-linked immunoassay method as described by Engvall.[18]

Determination of serum albumin

Serum albumin level was determined using the bromocresol green method as described by Doumas et al.[19]

Statistical analysis

The data generated from the study was subjected to statistical analysis using statistical package for the social sciences (SPSS) version 25. Student-independent t-tests and analysis of variance were used to obtain the independent variables. P value was deemed significant at $p<0.05$.

RESULTS

Comparison of the mean value of anthropometric data among the study groups

The mean systolic blood pressure was significantly higher in malaria-infected HIV individuals (148.00±14.44) when compared with HIV-infected individuals (127.92±9.28) ($p<0.05$). A significantly higher mean systolic blood pressure was also observed when malaria-infected individuals (131.75±11.16) were compared with HIV-infected individuals (127.92±9.28) ($p<0.05$).

The mean diastolic blood pressure was significantly higher in malaria-infected HIV individuals (86.67±13.39), HIV-infected individuals (80.42±12.89), malaria-infected individuals (80.00±10.95) when compared with control participants (74.76±7.78). There was no significant difference in body mass index (BMI) among the study groups (Table 1).

Comparison of the mean value of albumin, sICAM-1 level, and CD4 count among the test groups and control participants

Albumin was significantly lower in HIV/malaria co-infected individuals (30.53±4.73), HIV-infected individuals (32.93±4.96), malaria-infected individuals (39.22±6.11) when compared with control participants (40.99±6.51) ($p<0.05$) respectively. The mean albumin level was significantly lower in HIV/malaria co-infected individuals and HIV-infected individuals when compared with malaria-infected individuals ($p<0.05$) respectively.

The mean sICAM-1 was significantly higher in HIV/Malaria co-infected individuals (604.85±64.90), HIV-infected individuals (552.47±90.38), and malaria-infected individuals (559.66±61.82) when compared with control participants (240.92±20.77) ($p<0.05$) respectively. The mean sICAM-1 was significantly higher in HIV/malaria co-infected individuals (604.85±64.90) when compared with other test groups ($p<0.05$) respectively.

There was no significant difference when the mean sICAM-1 level of HIV-infected individuals was compared with that of malaria-infected individuals ($p>0.05$).

CD4 count was significantly lower in HIV/malaria co-infected individuals (630.975±247.73) when compared with HIV-infected individuals (817.58±304.15) ($p<0.05$) (Table 2).

Comparison of serum levels of albumin and sICAM-1 in HIV-infected individuals based on CD4 count grouping

Table 3 compares levels of albumin level and sICAM-1 between CD4 counts grouped below 500 cells/ml and equal or above 500 cells/ml in HIV-infected individuals.

Albumin was significantly lower in HIV-infected individuals whose CD4 count was <500 cells/ml (31.78±3.51) when compared with those whose CD4 count was >500 cells/ml (38.18±4.69) ($p<0.05$).

sICAM-1 was significantly higher in HIV-infected individuals whose CD4 count was <500cells/ml

(647.02±36.71) when compared with those whose CD4 count was >500cells/ml (526.47±72.95) (p<0.05).

Comparison of serum albumin and sICAM-1 levels in HIV/malaria co-infected individuals based on CD4 count grouping

Table 4 compares albumin level and sICAM-1 level between CD4 count grouped below 500 cells/ml and equal or above 500 cells/ml in HIV-malaria co-infected subjects.

Albumin was significantly lower in HIV/malaria co-infected individuals whose CD4 count was <500 cells/ml (29.99±4.41) when compared with those whose CD4 count was >500 cells/ml (36.44±5.51) (p<0.05).

sICAM-1 was significantly higher in HIV/Malaria co-infected individuals whose CD4 count was <500 cells/ml (678.22±27.94) when compared with those whose CD4 count was >500 cells/ml (577.04±60.09) (p<0.05).

Correlation of CD4 count, albumin, and sICAM-1 in HIV infection and HIV/malaria co-infection

There was a strong negative correlation between sICAM-1 with CD4 count in HIV-infected individuals (r=-0.792, p<0.05). There was a strong negative correlation between sICAM-1 with CD4 count in HIV/Malaria co-infected individuals (r=-0.719, p<0.05). There was no correlation between Albumin and CD4 count, same with Albumin and sICAM-1 (Table 5).

Table 1: Comparison of the mean value of anthropometric data among the study groups.

Groups	Age (years)	SBP (mmHg)	DBP (mmHg)	BMI (kg/m^2)
Co-infection (A) n= 42	26.38±8.52	148.00±14.44	86.67±13.39	24.79±4.99
HIV only (B) n=42	26.00±6.50	127.92±9.28	80.42±12.89	24.58±4.24
Malaria only (C) n=42	24.05±4.35	131.75±11.16	80.00±10.95	24.32±4.08
Control (D) n=42	24.05±5.95	110.24±7.88	74.76±7.78	26.31±3.51
F value	1.036	4.936	5.126	0.923
P value	0.987	0.003*	0.003*	0.433
A versus B	0.948	0.006*	0.001*	0.866
A versus C	0.731	0.010*	0.004*	0.722
A versus D	0.085	0.000*	0.000*	0.236
B versus C	0.069	0.031*	0.909	0.845
B versus D	0.682	0.005*	0.017*	0.178
C versus D	0.408	0.002*	0.025*	0.141

Table 2: Comparison of the mean value of albumin, sICAM-1 level, and CD4 count among the test groups and control participants.

Groups	Alb (g/dl)	sICAM-1 (ng/ml)	CD4 count (cell/mm^3)
Co-infection (A) n= 42	30.99±4.73	604.85±64.90	630.975±247.73
HIV only (B) n=42	32.93±4.96	552.47±90.38	817.58±304.15
Malaria only (C) n=42	39.22±5.11	559.66±61.82	-
Control (D) n=42	40.53±6.51	240.92±20.77	-
F value	7.202	140.133	11.668
P value	0.000*	0.000*	-
A versus B	0.298	0.027*	0.003*
A versus C	0.005*	0.007*	-
A versus D	0.000*	0.000*	-
B versus C	0.013*	0.718	-
B versus D	0.000*	0.000*	-
C versus D	0.689	0.000*	

sICAM-1=soluble intercellular adhesion molecule-1, Alb=albumin, p value is significant at p<0.05

Table 3: Comparison of mean serum albumin and sICAM-1 level among HIV-infected individuals based on CD4 count grouping.

Group (42)	Alb (g/dl) Mean±SD	t value	P value	sICAM-1(ng/ml) Mean±SD	t value	P value
CD4<500 (14)	31.78±3.51	4.458	0.006*	647.02±36.71	3.183	0.004*
CD4≥500 (28)	38.18±4.69			526.47±72.95		

sICAM-1=soluble intercellular adhesion molecule-1, Alb=albumin, p value is significant at p<0.05

Table 4: Comparison of albumin and sICAM-1 levels among HIV/malaria co-infected individuals based on CD4 count grouping.

Group (42)	Alb (g/dl) Mean±SD	t value	P value	sICAM-1(ng/ml) Mean±SD	t value	P value
CD4<500 (18)	29.99±4.41	3.957	0.000*	678.22±27.94	4.488	0.000*
CD4≥500 (24)	36.44±5.51			577.04±60.09		

sICAM-1=soluble intercellular adhesion molecule-1, Alb=albumin, p value is significant at p<0.05

Table 5: Correlation of CD4 count, albumin and sICAM-1 in HIV infection and HIV/malaria co-infection.

Correlation	HIV infection (n=42)		HIV/malaria-co-infection (n=42)	
	R	P value	R	P value
sICAM-1 versus CD4 count	-0.792*	0.000	-0.719*	0.000
Alb versus CD4 count	0.106	0.621s	0.193	0.367
Alb versus sICAM-1	0.396	0.065	0.022	0.919

sICAM-1=soluble intercellular adhesion molecule-1, Alb=albumin, p value is significant at p<0.05

DISCUSSION

HIV and malaria are both significant global health problems, both are inflammatory in nature and co-infection with both can lead to worse outcomes than either infection alone. This study was designed to evaluate serum levels of albumin and sICAM-1 in HIV-malaria co-infected individuals in order to explore their potential as biomarkers for disease progression and prognosis. Soluble ICAM-1 is released from cell-surface ICAM-1 by proteolytic cleavage in response to inflammatory cytokines and endothelial damage, it is a marker of endothelial activation.[20] Albumin, on the other hand, is an important inflammatory marker and a carrier protein in the body that can assess the kidney and liver condition as well as nutritional status.

This study revealed significantly elevated serum sICAM-1 in HIV infection, malaria Infection, and HIV-malaria co-infection, with co-infection showing a significantly higher sICAM-1 level compared to the individual infections. The raised serum s-ICAM-1 concentrations may result from tissue damage due to inflammation and vascular changes caused by malaria and HIV infections. sICAM-1 has been shown to be released by immune cells during the binding and infiltration of infected tissues. Both infections can lead to endothelial cell activation and damage to the lining of the blood vessels causing disease progression and severity.[21] Some previous reports done in Kenya and elsewhere also showed significantly increased levels of s-ICAM-1 in HIV-infected individuals, while, reports in Cameroon and Gambia showed similar observation in malaria-infected patients.[22-24] A similar report was also made in Uganda in HIV-malaria co-infected patients.[25] Contrastingly, a study carried out in Malawi recorded a decreased sICAM-1 level in HIV and malaria co-infection.[26] Enhanced soluble intracellular adhesion molecules have been implicated in the risk of cardiovascular diseases due to increased endothelial activation.[27]

Furthermore, results based on CD4 count level showed significantly higher serum sCAM-1 concentration in individuals with CD4 counts less than 500 cells/ml compared to those with higher CD4 counts. This indicates a negative relationship which was later revealed in the work. A negative association was observed between serum sICAM-1 concentration and CD4 count both in co-infection and HIV mono-infection. The negative correlation between sICAM-1 and CD4 count in HIV infection is likely as a result of the complex interplay between immune activation, inflammation, and CD4 T-cell depletion. This is in line with previous reports on the negative association between serum sICAM-1 and CD4 count, in a study carried out in Africa in HIV infection.[22,23,28] Contrastingly, some other studies carried out elsewhere, reported no association between sICAM-1 and CD4 count.[21,29] Traditionally, CD4+ T-cell count has been used to define the stability of HIV-infected individuals, with numbers below 200 being considered an indication of immunosuppression, poor prognosis, and disease progression. This means that a significantly higher serum sICAM-1 in HIV-malaria co-infection is a sign of favorable prognosis because there is a negative correlation between serum sICAM-1 concentration and CD4+ T-cell count.

The co-infected individuals showed a significantly lower mean CD4 count value compared to HIV-infected individuals without concurrent malaria infection. This shows that HIV-malaria co-infection may result to more immune dysfunction and disease severity such as cerebral malaria and acute respiratory distress syndrome. This finding corresponds to the previous studies on HIV-malaria co-infection in Calabar Nigeria, and in Mozambique.[30,31] The authors reported more co-infection in individuals with lower CD4 count.

The mean albumin level was significantly lower in HIV-infected individuals and HIV-malaria-co-infected individuals. This is similar to our previous studies reported in Jos, Nigeria, and Tanzania respectively.[32,33] The latter reported significantly lower serum albumin in HIV

seropositive females during their menstrual cycle. It has been earlier noted that as HIV/AIDS progresses, the CD4+ T cells become increasingly depleted with other important health indices including albumin and other micronutrients due to reduced intake and reduced hepatic synthesis.[34] Onyenekwe et al reported increased serum albumin levels in HIV-malaria co-infection which may have been attributed to enhanced nutritional intake at the time of the study.[35] The authors, however, noted that at a certain stage of HIV infection, malaria has a way of moderating the hepatic synthesis of albumin in HIV-infected individuals in malaria-endemic areas irrespective of heart conditions. Albumin was observed to be significantly lower among HIV/malaria co-infected individuals and HIV-infected individuals whose CD4 count was <500 cells/ml and was higher among those with higher CD4 count (>500 cells/ml). This indicates a positive association. This is in line with some previous studies that reported a positive association between serum albumin concentration and CD4 count.[34,36] Contrary to a study carried out in Tanzania which reported that no association exists between albumin and CD4 count.[32]

Furthermore, in this study, the systolic blood pressure was observed to be normal among all the study groups except in HIV/malaria co-infected individuals. The significantly higher systolic blood pressure levels in HIV co-infection is an indication of possible inflammatory reactions due to the synergistic effects of the two infections. This can subsequently lead to hypertension with progressive adverse cardiovascular conditions which is evidenced by the observed differences in serum sICAM-1 and albumin in this study. Increased burden of hypertension in HIV-infected individuals on ART has been previously reported.[37,38] The mechanisms behind the possible elevation of blood pressure in HIV-infected individuals have not been properly elucidated, however, CD4 T-cell count may be implicated in these findings. Previous reports have associated major organ T cells with enhanced inflammation and hypertension.[37,39] Some authors attributed it to late onset of ART when the CD4 count is low with aberrant reconstituted immunity and immunosuppression.[40] This may explain the increased blood pressure observed in individuals with CD4 counts below 500 cells/ml in the present study. Other researchers also attributed the cause to the type of ART used and the long duration of ART usage.[41] Another study carried out in Uganda reported low systolic blood pressure in HIV infection.[42] However, the elevated blood pressure levels as observed in malaria-infected individuals in this study indicates hypertension. This shows that malaria parasite infection and hypertension may have tripled the burden of HIV-infected individuals thereby leading to disease severity and complications. Malaria infection alone exacerbates inflammatory reactions and endothelial activation.[43] The increased blood pressure may also result from the genetic mutation of the human renin-angiotensin system (RAS) in malaria-endemic regions. This enhances the angiosystem 11 levels thereby raising the blood pressure in the affected individuals.[44] This is further worsened by co-morbidity with HIV infection causing disease progression and severity.[45] A more longitudinal study is needed to explain the consequences of these variations in blood pressure in HIV-infected individuals especially in endemic regions of co-infections.

Limitations

The limitations observed during our study include the short duration of the study. The study was a prospective cross-sectional study which involved short period of sample collection within three months. A follow up and longitudinal study with large sample size is needed to ascertain a clearer picture of the relationship of sICAM with CD4 count in HIV infected individuals as well as in co-infection. Viral load of the patients was not available at the time of the sample collection thus, limiting study. Further study is necessary to compare our findings with viral load to confirm the relationships observed in the study. Other biomarkers of cardiovascular disease were not tested. It is important that lipid profile, fasting blood glucose and other biomarkers of cardiovascular disease are tested to confirm the strength of sICAM with endothelial dysfunction vis- avis cardiovascular disease.

CONCLUSION

The study observed increased inflammatory reaction, reduced hepatic synthesis and some degree of vascular changes in HIV-infected individuals with or without malaria co-infection. This may subsequently degenerate to increased endothelial dysfunction, cerebral malaria and worsening disease progression.

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