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Possible alteration in serum ferritin level in malaria infected HIV seropositive individuals in Nauth, Nnewi, Nigeria

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Abstract

The role of Ferritin in monitoring disease progression in immune compromised HIV individuals with an underlying active infection like malaria is a subject of growing research. Ferritin being an acute phase protein, plays important role in assessing the range of damage due to inflammation in immunosuppressed patients leaving in highly endemic malaria regions. The levels of serum ferritin in malaria infected HIV positive individuals in Nnamdi Azikiwe University teaching hospital (NAUTH), Nnewi, Anambra State, Nigeria, was assessed. Questionnaire was used to obtain the demographic details of the participants, and to rule out other inflammatory infections. 88 participants of the age group 18 - 65 years, comprising 24 with HIV infection, 22 with HIV and Malaria co-infection, 22 with Malaria infection, and a control group of 22 individuals with neither HIV nor malaria infection were randomly recruited. Ferritin level was determined using enzyme linked immunosorbent assay technique and a cross sectional prospective study design was used. A significantly high mean serum ferritin level was observed in HIV infected individuals with and/ or without malaria co-infection than in malaria positive and control group ($p<0.05$ respectively). Serum ferritin level was significantly higher in female participants than in male counterparts ($p < 0.05$). Serum ferritin level was significantly higher in individuals with CD4 count >500 than in CD4 count ≤ 500 ($p < 0.05$). Blood pressure was significantly higher in HIV infected and malaria positive individuals when compared with controls. The increased serum ferritin level and higher blood pressure in HIV infected participants suggests active inflammatory process, reduced immunity and hypertension which may have worsened by malaria co-infection. This may subsequently lead to vascular and endothelia damage causing disease severity.

Keywords: Ferritin; HIV; Malaria; Co-infection; ART

1. Introduction

Malaria and HIV are double-barreled infections of global health concern. *Plasmodium falciparum* infection is a global life-threatening parasitic disease which has remain endemic in sub-Saharan Africa including Nigeria [1, 2]. HIV infection weakens the immune system, making it harder for the body to fight off malaria infection despite the introduction of the highly active anti-retroviral therapy (HAART). However, the regulatory mechanism controlling the interaction between HIV and malaria infection has generated increasing interest in recent years [3].

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HIV is associated with increased evidences of hemochromatosis causing multiple organ damage including the hearts, bone marrow, liver and other organs. This may be due to sequestration of iron in the macrophages because of acute and chronic inflammation [4]. Increased iron stores might favor malaria as well as HIV progression by impairing the key mediators in the host response [5, 6]. One of the clinical problems is the difficulty in differentiating between iron overload and malaria-induced hyperferritinemia, as both conditions can result in elevated ferritin levels. This can be particularly challenging in HIV-infected individuals who may already have elevated ferritin levels due to their underlying condition [7].

Serum ferritin levels has been shown to be strongly involved in iron metabolism and its elevation in malaria and HIV infection causes iron deficiency and adverse health conditions [8]. The human immune response to malaria and HIV infection might influence the clinical course of one another. The regulation of malaria parasitemia is immune mediated leaving some affected individual in endemic areas asymptomatic [1, 9].

Iron is believed to be harmful in HIV infection, a supposition based partly on studies from the pre-Anti retro viral therapy era with findings suggesting that elevated iron status may be associated with an increased risk of disease progression [10]. More recent studies also suggest that replication of the virus is an iron-dependent process and that increased concentrations of non-transferrin bound iron (NTBI) from supplementation may also be associated with the risk of opportunistic infections [11].

Elevated serum Ferritin level has been reported in acute and chronic inflammation, whereas in HIV infection, it has been shown to be enhance disease progression [4]. Malaria infection also, can cause a significant increase in serum ferritin levels due to increased iron release from hemolysis of red blood cells, and it can be difficult to differentiate between iron overload and malaria-induced hyperferritinemia in HIV-infected individuals.

In patients with HIV infection, higher serum ferritin levels have been associated with the presence of opportunistic infections leading to increased morbidity and mortality which might result from severity of the disease [11]. HIV infected population is at increased risk of developing severe and complicated malaria hence, the present study is aimed at investigating the relationship between ferritin levels and disease severity in HIV and malaria co- infection.

2. Materials and methods

2.1. Study Site

This study was conducted on individuals who are HIV positive, malaria infected individuals, HIV/malaria co-infected individuals and those with neither HIV nor malaria at Nnamdi Azikiwe University teaching hospital (NAUTH), Nnewi, Anambra state.

2.2. Study Design

The study was a cross sectional prospective study conducted to evaluate the level of serum ferritin in HIV infected, malaria infected and HIV/malaria co-infected participants attending Institute of human virology Nigeria (IHVN) clinic in Nnamdi Azikiwe University teaching hospital (NAUTH), Nnewi, Anambra State.

2.3. Inclusion and exclusion criteria

The study included both male and female confirmed HIV seropositive participants, malaria infected, co-infected participants, as well as HIV seronegative and malaria negative individuals as control participants. Individuals with other known underlying health conditions such as cardiovascular diseases, other inflammatory conditions like tuberculosis, Hepatitis B were excluded from this study.

2.4. Sample Collection

Five milliliters (5 mls) of blood sample was collected from each of the participants and dispensed into plain containers for the determination of serum ferritin level. The serum samples was separated and stored at -20°C until analyzed.

2.5. Methods

- **Screening of HIV infection:** The participants were screened for HIV infection using Immunoassay and Immunochromatographic method. Antibodies to HIV-1 and HIV-2 in human plasma were determined using Abbott determine TM HIV -1 and HIV-2 kit, which is an in-vitro visually read immunoassay (Abbott Japan

Co.Ltd.Tokyo, Japan) and HIV-1 and 2 STAT-PAK Assay kit, which is an Immunochromatographic test for the quantitative detection of antibodies to HIV-1 and HIV-2 in Human plasma (CHEMBIO Diagnostic system, Inc, New York, USA).

- **Screening of Malaria parasitaemia:** The participants were screened for malaria using Abbot Malaria rapid test kit described by Abbot Laboratories. The test qualitatively detects *plasmodium* antigen in human whole blood samples. This test applies lateral flow immuno-chromatography which is a tool in the diagnosis of malaria.

2.6. Determination of Serum Ferritin as was described by (Gupta *et al*., [12].

Principle: Ferritin test is based on simultaneous binding of human Ferritin to two monoclonal antibodies, one immobilized on microwell plates and the other conjugated with horseradish peroxidase (HRP). After incubation the bound/free separation was performed by a simple solid-phase washing. Then the enzyme HRP in the bound-fraction reacts with the substrate (H2O2) and the TMB substrate and develops a blue color that changes into yellow when the stop solution (H2SO4) is added. The colour intensity is proportional to the ferritin concentration in the sample.

2.7. Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the analysis of the results. Data obtained was presented as mean ± standard deviation (SD) and analyzed statistically using one way analysis of variance (ANOVA), pos hoc (LSD) and Pearson correlation. The level of significance was set at $p < 0.05$.

3. Results

3.1. Mean serum ferritin level in HIV infected, HIV/malaria co-infected, malaria positive and control group

The mean serum ferritin level was significantly high in HIV infected (158.79 ± 28.79) and HIV/malaria co-infected individuals (213.21 ± 37.80) when compared with malaria positive (123.33 ± 35.89) and control participants (32.85 ± 7.61) ($P < 0.05$ respectively). The mean serum ferritin level was significantly high in HIV/malaria co-infected individuals (213.21 ± 37.80) when compared with HIV infected (158.79 ± 28.79) and malaria positive (123.33 ± 35.89) individuals ($p < 0.05$ respectively).

Table 1 Mean serum ferritin level in HIV infected, HIV/mal co-infected, malaria positive individuals and control group

Group	Ferritin (ng/ml)
HIV infected (n=22)	158.79 ± 28.79
HIV/mal co-infection (n=22)	213.21 ± 37.80
Malaria positive (n=22)	123.33 ± 35.89
Control (n=22)	32.85 ± 7.61
F(P) value	139.57 (0.000)
A vs B	0.000
A vs C	0.001
A vs D	0.000
B vs C	0.000
B vs D	0.000
D vs C	0.000

Values was considered statistically significant at $p < 0.05$

3.2. Gender comparison of the mean serum ferritin level among all the groups

The mean serum ferritin level was significantly higher Female participants (155.76 ± 76.65) when compared with the male counterparts (120.19 ± 61.58) ($p \leq 0.05$).

Table 2 Gender comparison of mean serum ferritin level among all the groups

Gender	Ferritin (ng/ml)
Male (n=50)	120.19 ± 61.58
Female (n=38)	155.76 ± 76.65
T- value	3.363
P- value	0.020

Values was statistically significant at P < 0.05

3.3. The mean serum ferritin level in HIV infected participants based on CD4 Count ≤ or > 500 cells /µL

The mean serum ferritin level was significantly higher in individuals with CD4 Count >500 (194.83 ± 44.11) when compared to CD4 count ≤500 (100.98 ± 62.46) (p = 0.020).

Table 3 The mean ferritin level in HIV infected participants based on CD4 Count ≤ or > 500 cells/L

CD4 T- cell µ/L	Ferritin (ng/ml)
≤ 500	100.98 ± 62.46
> 500	194.84 ± 44.11
t (P - value)	7.582 (0.000)

Values are statistically significant at P < 0.05

3.4. CD4 T- cell count between HIV infected individuals and HIV/ malaria co- infection.

The mean CD4 T- cell count in HIV/mal co-infected individuals (0.830 ± 0.381) was significantly higher when compared with HIV infected participants (0.540 ± 0.509) (P < 0.05).

Table 4 CD4 T- cell count between HIV infected individuals and HIV/ malaria co- infection

Group	CD4 T cells/µL
HIV infected	0.540 ± 0.517
HIV/mal co-infection	0.830 ± 0.381
t (P - value	2.248 (0.029)

Value was considered statistically significant at P < 0.05

3.5. The mean value of age and anthropometric parameters among HIV infected, HIV/mal co-infection, malaria positive and control group

Table 5 Comparison of mean value of age and anthropometric parameters among HIV infected, HIV/mal co-infection, malaria positive and control group

Groups	Age (years)	SBP (mmHg)	DBP (mmHg)	BMI (kg/m^2)
HIV infected (A)	26.00 ± 10.50	127.92 ± 11.16	80.42 ± 12.39	24.58 ± 4.24
HIV/mal co-infection (B)	26.38 ± 8.52	131.00 ± 14.44	86.67 ± 14.89	24.79 ± 4.99
Malaria positive (C)	24.05 ± 2.35	113.24 ± 9.28	80.00 ± 10.78	24.32 ± 4.08
Control (D)	24.05 ± 5.95	108.75 ± 7.88	74.76 ± 7.95	26.31 ± 3.51
F – value	1.036	4.936	4.126	0.923
p-value	0.987	0.003	0.343	0.433

A vs B	0.948	0.006	0.000	0.866
A vs C	0.069	0.000	0.909	0.845
A vs D	0.085	0.000	0.000	0.178
B vs C	0.731	0.000	0.002	0.722
B vs D	0.682	0.000	0.000	0.236
C vs D	0.408	0.002	0.001	0.141

Value was considered significant at $p < 0.05$

The mean value of SBP and DBP were significantly higher in HIV/mal co-infected individuals (121.00 ± 14.44, 131.00 ± 14.44), HIV infected (117.92 ± 11.16, 80.42 ± 12.39) and malaria positive participants (113.24 ± 9.28, 113.24 ± 9.28) when compared with control group (108.75 ± 7.88, 74.76 ± 7.95) ($P < 0.05$ respectively). The mean SBP was significantly higher in HIV/mal co-infected (121.00 ± 14.44) and HIV infected (117.92 ± 11.16) individuals when compared with malaria positive participants (113.24 ± 9.28) ($p < 0.05$ respectively). The mean DBP was significantly higher in HIV/mal co-infected (121.00 ± 14.44) when compared with HIV infected individuals (80.42 ± 12.39) and malaria positive participants (80.00 ± 10.78) ($p < 0.05$ respectively).

4. Discussion

Infectious diseases especially HIV and malaria persists as important public health problem worldwide. Both diseases are characterized by acute and chronic inflammation with further consequences of cellular damage and disease progression.

In this study, the mean serum ferritin level was significantly higher in HIV infected and HIV/malaria co-infected individuals when compared with malaria positive and control groups. This may suggest excess iron accumulation and may be attributed to some degree of inflammatory reaction, anaemia and immunosuppression which may have resulted from HIV and/or malaria parasite infection. This finding is consistent with other research done previously [13, 14, 15]. Barffour *et al*., [16] noted significant relationship between malaria infection and increased ferritin levels. HIV as well as malaria parasite infections are two important inflammatory diseases which can worsen in the presence of excess accumulation of iron in the body of affected individuals [17]. According to some previous studies, ferritin levels may be increased in the presence of HIV infection or other chronic diseases including malaria parasite infection, atherosclerosis, vascular and endothelial dysfunction [18, 19]. Ferritin is an important iron storage protein which is very useful in the body iron hemostasis and immune regulation [20]. Iron plays significant roles in the body energy metabolism, cell proliferations and in various disease condition. Its alterations in the body metabolism can disrupt the immune response, induce cellular and organ damages leading to anaemia, iron deficiency and adverse health conditions [17, 19]. Elevated ferritin levels in HIV infection can lead to inflammation and anaemia which can increase viral replication, mortality and proliferation of opportunistic infections [21, 22]. Studies conducted by Matheson *et al.*, [23] indicated that HIV infection could alter the iron status of infected cells, by increasing ferritin accumulation and causing iron overload. Hemochromatosis is a syndrome of dysregulated iron homeostasis leading to excess accumulation of iron and this has been increasingly reported in people leaving with HIV infection as well as malaria parasitaemia [13, 22, 24]. This may be attributed to excess iron or inflammatory process due to disease severity. Aneamia is an important risk factor of disease progression in both malaria and HIV infections which can be caused by poor dietary intake, malnutrition, infections, ART and other environmental and genetic factors [25, 26, 27]. Reports have shown that increased ferritin levels can result from ART administration and iron supplementation in HIV infected individuals [22, 28]. Iron supplementation may adversely affects HIV-infected patients, due to the routine administration to treat iron deficiency anemia. However, the exact interactions between ferritin, ART and iron supplementation in HIV infected individuals have not been fully elucidated [21, 22]. According to the study done by Armitage *et al*. [14]. Elevated serum ferritin level has been reported in early development of HIV infection, in parallel with other inflammatory cytokines. Another study done by Selvam *et al*. [29], showed that HIV seronegative infants born from HIV-positive mothers had significantly elevated ferritin levels in cord blood. This was not correlated with alterations in iron or transferrin and was instead attributed to a possible hyper-inflammatory state during pregnancy.

Our study also observed significantly higher ferritin level in HIV infected individual with CD4 T-cell count greater than 500 cells/μL. This is an indication of sever inflammatory reactions which can be due to ART administration and iron supplementation. This finding is similar to the report by Kharb et al., [18]. The author noted increased ferritin levels in advance HIV infection, which was attributed to the underlying infections. A significant correlation between increased

serum ferritin and insulin resistance in HIV infected individuals on ART has been previously reported, indicating an association between increased ferritin levels, reduced immunity, lipid and glucose metabolism and disease progression [30, 31]. Ana *et al*., [32] shows a correlation between high serum ferritin, decreased CD4 T cell numbers and mortality. Whereas, persistently high serum ferritin levels was reported in HIV infected individuals not on ART at the chronic phase of the infection [14, 16]. Another report by Obirikorang *et al*., [33] noted no significant difference in serum ferritin levels in HIV infected individuals with varying levels of CD4 count.

Malaria parasite infection on the other hand, is an iron dependent disease condition which also devastates the iron status and body immune response causing inflammation, anaemia and worsening the disease condition of the affected individuals. Some reports have noted the protective effects of iron deficiency against childhood mortality in malaria endemic areas [34], which can be reversed and worsened by iron supplementation [35, 36]. This finding was further supported by the study of Zhang *et al*., [37]. The authors reported increased iron export in mice model during *plasmodium* malaria infection from the red blood cells through ferroportin which when reversed enhances iron storage, immune dysfunction and hence, disease progression. Increased ferritin levels have been previously reported in malarial infected individuals [38]. However, the protective and susceptibility mechanisms following iron metabolism in various human disease conditions still remains an important topic of investigations.

The mean serum ferritin level was significantly higher in HIV infected female participants when compared with the male counterparts. This is consistent with the study done by Kamagate *et al*., [39]. However, some researcher reported increased ferritin levels in males than in females [40, 41].

The results of this study revealed significantly higher SBP and DBP in HIV infected individuals irrespective of malaria parasitaemia when compared with the control. This is suggestive of hypertension which is an important risk factor of cardiovascular disease. Our study agrees with the reports of previous studies which noted elevated blood pressure in HIV infected individuals [42, 43, 44]. While, some reported lower blood pressure [45, 46], others noted no significant difference [47, 48]. Some studies reported increased serum ferritin in hypertensive individuals [49, 50, 51]. Hypertension is identified as having an SBP ≥130 mm Hg or DBP ≥80 mm Hg or self-reported use of antihypertensive medications [52]. Malaria infection may have contributed to the increased blood pressure observed in HIV infected individuals in the present study. This is supported by our previous study which shows that malaria infection can increase blood pressure leading to hypertension [53, 54]. This may also become worse in chronic disease condition such as HIV infection leading to disease severity. Previous research has also reported increased blood pressure level in ART than those not on ART [43, 55]. The authors attributed their findings to the use protein inhibitors (PIs) which has been shown to increase blood pressure levels leading to hypertension and subsequent cardiovascular and metabolic complications. Additionally, there has been a recent reports of significant association between increased serum ferritin and higher risk of hypertension in young adult HIV infected populations [50]. The author noted indiscriminate relationship between serum ferritin and SBP, as well as DBP.

5. Conclusion

In conclusions, increased serum ferritin and blood pressure levels in HIV infected individuals with and without malaria co-infection suggests active inflammatory process with reduced immunity which can predispose the individuals to vascular and endothelia activation with subsequent disease severity. Further longitudinal studies are crucial with more sample size to unravel the proper mechanisms and effects of altered ferritin levels in HIV infection especially in malaria endemic areas vis-avis co-infections.

Compliance with ethical standards

Acknowledgment

Authors wish to acknowledge all the HIV infected individuals who voluntarily agreed to participate in this study

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The ethical approval was obtained in accordance with the principles of declaration of Helsinki from the board of ethics committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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