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Assessment of Serum Copper and Zinc Status in Patients Receiving Highly Active Antiretroviral Therapy in A Tertiary Health Institution in Southwest Nigeria

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Abstract

Background: The poor prognosis and mortality in HIV infection has been associated with deficiency of micronutrients such as zinc and copper. This study aimed to investigate the level and deficiency of some trace elements in HIV-seropositive subjects receiving HAART treatment.

Methods: A cross-sectional study was conducted among a randomly selected hundred and fifty adults with a confirmatory diagnosis of the human immunodeficiency virus (HIV) and currently receiving HAART at the clinic. Questionnaires were administered to subjects after signing a written informed consent. The concentration of serum levels of zinc and copper after sample collection was analyzed using the spectrometric method and CD4+T-cell count using a flow cytometer. Prevalence was obtained using simple percentages. Mann Whitney U nonparametric test and Chi-square test of independence were used to explore the relationship between Zinc, Copper deficiencies, and CD4 and viral load.

Results: The prevalence of copper and zinc deficiency among subjects was 59% and 16.7% respectively. While CD4 count and Viral load did not differ by copper level among subjects, a significant difference in median CD4 count and Viral load was observed across Zinc levels, p-value < 0.05. Further, zinc level was associated with immune suppression among subjects, p-value < 0.05.

Conclusion: This study showed that the HAART treatment does not complement micronutrients status rather than the CD4+T-cell count levels. HAART treatment centers on boosting the immune system, while the subjects may still suffer micronutrients deficiency amid improved CD4+T-cell count.

Keywords

Zinc, Copper, Antiretroviral therapy, Micronutrients, HIV/AIDS, Trace elements, Immunosuppression, Copper deficiency, Zinc deficiency, CD4+T-cell

Introduction

The Human Immunodeficiency Virus (HIV) infection is one of the greatest challenges of the 21st Century [1,2]. It was estimated that about 36.7 million people were living with HIV/AIDS globally, about 25.5 million infected people in Sub-Saharan African [3]. The introduction and use of highly active antiretroviral therapies (HAART) have revolutionized the management and treatment of HIV/AIDS globally [4-8].

Research has shown that some biochemical abnormalities accompany infection with Human Immunodeficiency Virus. These changes occur as a result

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of the complications of the disease itself as the body's normal response to infection depletes nutritional stores. Also, metabolic stress responses cause the catabolism of protein stores. Undernourishment and micronutrient deficiencies exacerbate immunosuppression, oxidative stress, acceleration of Human Immunodeficiency Virus (HIV) replication, and CD4 T-Cell depletion in HIV-infected individuals [9-11].

Malnutrition is one of the major complications of HIV infection and a significant factor in the progression of the infection into AIDS [11]. Micronutrients which comprise essential trace elements (e.g. Zinc, Copper, and Selenium) and vitamins (e.g. Vitamin A, C and E) are nutrients needed in minute specific quantities in the body. Most micronutrients are not generated in the body but are derived from food intake [10-12].

Zinc and copper are minerals required by the body as necessary components of many enzymes. Levels of zinc and copper in the body are regulated by a protein called metallothionein. As a result of this regulation, copper levels decrease as zinc levels increase and vice versa thus people living with HIV/AIDS who are placed on zinc will probably supplement copper as well [13].

Zinc is an integral part of more than 200 enzymes (metalloenzymes) and plays a crucial role in nucleic acid metabolisms, cell replication, tissue repairs, and growth. Its deficiency leads to severe alteration of the thymic function and subsequent loss of T-cell-mediated responses and increased susceptibility to infectious diseases [14,15]. While copper functions as a scavenger of free radicals in biological membranes and structures via its presence in cytosolic erythrocyte superoxide dismutase [16].

Deficiencies of these micronutrients may result in fatigue, depression, and widespread abnormalities in connective tissue, such as inflamed gingivae, petechiae, perifollicular hemorrhages, and impaired wound healing, coiled hairs, hyperkeratosis and bleeding into body cavities [17]. It may also lead to damage to the cell membrane and leakage of cell contents to the extracellular fluid compartment, cardiac or skeletal myopathies, neuropathies, and liver necrosis, muscle and neurological problems [18,19]. Deficiencies of some micronutrients have been associated with impaired immunological functions [20,21].

For instance, zinc deficiency has been reported to decrease lymphocyte concentrations, and copper deficiency reduced cytokine response, while selenium deficiency had a negative impact on the proper functioning of the neutrophils and T- lymphocytes [22,23]. Though HAART has considerably facilitated the management of HIV/AIDS where it is available, correction of micronutrient and electrolytes deficiencies is critical to clinical outcome. And since micronutrient deficiencies may persist in the era of HAART, it is crucial to understand whether initiation of HAART will ameliorate micronutrients and electrolytes deficiencies or to recommend or refute the benefit of providing micronutrient supplements to HIV-positive persons receiving HAART. The scarcity of information in this part of the World necessitates this research. The aim of this study is therefore to determine the prevalence of copper, zinc, and copper-zinc deficiencies and their relationship with markers of HIV/AIDS progression (CD4/Viral load).

Methods

Study site

The study was carried out in Ogbomoso, Oyo Nigeria. It has an area landmass covering about 37,984 square kilometers. It is located in the northern part of Oyo State, at a Latitude of 8° 08' 00" East and a Longitude of 4° 16' 00" North of the Equator. It is the second-largest city in Oyo State after Ibadan, lies within the savannah region, and is a gateway to the Northern part of Nigeria from the West. Ogbomoso is 57 kilometers South West of Ilorin (the Capital of Kwara State) 53 Kilometres North - East of Oyo, 58 Kilometers North - West of Osogbo (Capital of Osun State) and 104 Kilometers North - East of Ibadan (Capital of Oyo State).There are 43 zones with an estimated population of 654,183, and an HIV prevalence of 21.5% [24], while the seroprevalence rate is at 0% [25].

Study design

This study adopted a cross-sectional design and was carried out on subjects receiving HAART at the LAUTECH Teaching Hospital Ogbomoso, Oyo State.

Study population

The study was carried out on patients attending the infectious disease clinic of the Department of Internal Medicine Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital, Ogbomoso, Oyo State.

Sample size determination

The non-probability technique was used to select subjects based on the inclusion criteria among patients attending infectious disease clinics at the Department of Internal Medicine. The clinic runs once weekly, averagely receives up to about 10 patients per clinic. At each clinic, patients who met the inclusion criteria were recruited within a 4 months duration. After this period, a total of 177 subjects were sampled for the study. however, only 150 subjects with completed data were utilized for this study.

Blood specimens were collected. The sera were extracted and stored at -32 °C till day of analysis.

Statistical Analysis

Data entry was done on the computer system and

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subjects with complete data were either contacted or automatically disqualified as the reasons for such step apply. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were expressed in percentages and continuous variables were summarized using mean ± standard deviation. Relationships between categorical variables were analyzed using the chi-square test of independence and means of continuous variables were compared using Man Whitney U test.

Results

Socio-demographic profile of subjects

Table 1, depicts the socio-demographic profile and ART characteristics of subjects in the study population. Subjects were aged between 16 and 78 years, and the majorities (63.3%) were between 30 and 49 years and a mean age of 41.76 ± 11.32. There was a female preponderance with a male to female ratio of 1: 3.69 (Male: 21.3%, Female: 78.7%). The median duration of HAART was 30 months and majorities were placed on Tenofovir Lamivudine Dolutegravir (96.7%).

Table 1: Socio-demographic parameters.

Variables	Frequency (n = 150)	Percentages (%)
Sex		
Male	32	21.3
Female	118	78.7
Age (years)		
Below 29	22	14.7
30 – 34	95	63.3
50 – 69	28	18.7
70 and above	4	2.7
ART		
TLD	145	96.7
Atazanavir/ritonavir	5	3.3
Immuno-suppression	106	70.7
Suppressed	44	29.3
Unsuppressed		

CD4 count (cell/mm^3) ranged between 19 cells/mm^3 and 1910 cells/mm^3 among subjects with a mean of 404.34 ± 365.39 cell/mm^3 and a median of 237 cells/mm^3. Viral load (cp/ml) ranged between of 20 and 682206 cp/ml, a mean of 15810.57 ± 59113.35 cp/ml and a median of 31 cp/ml. More than (68.7%) of subjects were immuno-suppressed (Viral load < 1000 cp/ml).

Prevalence of copper and zinc deficiency among subjects in the study population

Table II shows the prevalence of copper and Zinc Deficiency among subjects in the study population. The prevalence of copper and zinc deficiencies among subjects was 59% and 16.7% respectively. Also, of these values, 69.3% and 36% of copper zinc-deficient subjects were immunosuppressed respectively.

Immuno-suppression was associated with copper deficiency among subjects with a prevalence of 69.3% χ^2 = 0.187, p-value = 0.666. There was no significant association between immunosuppression and zinc levels among subjects, χ^2 = 17.393, p-value = 0.000 (Table 2).

Relationship between copper, zinc deficiency, and CD4 and viral load

Table 3, shows the distribution of CD4 and viral load by copper, and zinc levels among subjects. The median CD4 count was similar among subject with copper deficiency (Median: 237 ug/dL) and subjects with normal copper levels (Median: 237.00 ug/dL), Z = -0.766, p-value = 0.444.

Similarly, the median viral load did not differ significantly among subjects with copper deficiency (Median: 57.50 μ mol/L) and subjects that had normal copper levels (Median: 20.00 μmol/L), Z = -1.418, p-value = 0.156.

However, CD4 count and viral load differ significantly by zinc level among subjects, p-value < 0.05.

Subjects with normal zinc levels had a higher CD4 count (Median; 395 cell/mm^3) compared to subjects with zinc deficiency (Median; 132 cell/mm^3) while the viral load was higher among subjects with zinc deficiency (16257 cp/ml) compared to subjects with normal zinc levels (20 cp/ml).

Table 2: Immuno-suppression and copper-zinc deficiency.

Variables	Immuno-suppression			χ^2	p-value
	Suppressed	Unsuppressed	Prevalence		
CU (ug/dl)					
Deficient	61 (69.3%)	27 (30.7%)	88 (59%)	0.187	0.666
Normal	45 (72.6%)	17 (27.4%)	62 (41%)		
Zn (μmol/L)					
Deficient	9 (36.0%)	16 (64.0%)	25 (16.7%)	17.393	*0.000
Normal	97 (77.6%)	28 (22.4%)	125 (83.3%)		

χ^2: Chi square statistics, p-value < 0.05 indicate significance.

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Table 3: CD4 Count and viral load by copper and zinc deficiencies.

Variables	Cu Level				Zn level			
	Deficient	Normal	Z	P-value	Deficient	Normal	Z	P-value
CD4 count (Median)	237.00	237.00	-0.766	0.444	132.00	395.00	-5.438	*0.000
Viral load (Median)	57.50	20.00	-1.418	0.156	16257.00	20.00	-4.105	*0.001

*Z statistic, p-value < 0.05 indicates significance.

Discussion

In this study, the prevalence of copper and zinc deficiency among subjects was 59% and 16.7% respectively. Zinc deficiency has often been described in HIV infection [26]. And that HIV-infected subjects had significantly lower zinc concentrations. This observation is in agreement with previous reports [27,28]. Zinc deficiency is associated with impaired immune function [29,30] and increased susceptibility to infection. More so, zinc deficiency may result due to malnutrition. One of the factors responsible for malnutrition in an HIV-infected person is reduced appetite. In addition, poor dietary intake, absorption and diarrhea which are common in HIV infection may also have contributed to the reduced levels of micronutrients in the HIV subjects [31]. About 30–50% and 90% of HIV patients in developed and developing countries respectively, complain of diarrhea and malabsorption [32] which in most cases are responsible for low levels of these HIV-infect persons.

This study recorded a zinc deficiency prevalence of 16.7%. This finding is lower than the previous report of 23% and 20% from studies in Germany [33] and South Africa [34] respectively and far lower than 53% zinc deficiency among HIV subjects earlier reported in Addis Ababa, Ethiopia [35]. Regional disparity in zinc intake may account for these differences. The mean ± SD Pre-HAART Zinc levels of the HIV-infected subjects were found to be significantly lower (p < 0.05) than the controls. This is consistent with the findings of Eley, et al. [36] Bobat, et al. [37] and Ogunroet, al. [38] However, it was observed that zinc levels increase in HAART subjects compared to pre-HAART Zinc levels.

Serum copper in this study did differ between the HIV-infected subjects and the HIV seronegative subjects. This finding is in contrast with another study in Ethiopia [15]. However, this observation agrees with previous reports [39,40] that found significantly higher serum copper in HIV-seropositive subjects than in controls but considerably lower than in pre-HAART levels. The mean ± SD serum copper levels of the pre-HAARHIV-infected Patients in this study were found to be significantly higher (p < 0.05) than that of the controls. This is in accordance with the findings of previous studies done by Lawal, et al. [41] and Nwegbu, et al. [42] both reported a significant increase in the mean plasma copper concentration of HIV-infected Subjects when compared with the control group. Copper is required for immune complex formation, blood and coagulation factors formation. It is a major micronutrient required by the body in HIV infection [21].

Copper has been established as an acute phase reactant and its serum level has been shown to change significantly in a range of acute and chronic infective, inflammatory and neoplastic processes owing to increased reproductive of ceruloplasmin [43,44]. Serum copper has been shown to return to normality after overcoming the initial acute phase of the associated disease [39]. The present study observed a high copper deficiency among subjects (59%) in contrast with previous study [45]. HAART treatments significantly affect the copper status of the HIV subjects. This finding is in contrast as well with a previous study [46]. However, the findings herein agree with the work of Akinola, et al. [28] who observed that Patients on HAART had significantly (p < 0.05) higher levels of zinc, but a lower level of copper compared to control subjects.

The CD4 count from this study varied largely among subjects with a minimum of 19 (cell/mm³), a maximum of 1910 (cell/mm³), and a mean of 404.34 ± 365.39 (cell/mm³), and a median of 237 (cells/mm³). As expected, this study observed a significantly lower CD4+T-cell count in the HIV-infected subjects when compared with the control. This finding is consistent with older reports [45,46]. The hallmark of HIV infection and subsequently AIDS pathogenesis is progressive depletion of CD4+T-cell populations in close association with progressive impairment of cellular immunity and increased susceptibility to opportunistic infections [47,48].

Similarly, Viral load varied largely among respondents with a minimum of 20 (cp/ml), maximum of 682206 (cp/ml), a mean of 15810.57 ± 59113.35 (cp/ml) and a median of 31 (cp/ml). Majority (68.7%) of the subjects were immuno-suppressed (Viral load < 1000 cp/ml)

The median CD4 count was similar among subject with copper deficiency (Median: 237 ug/dL) and subjects with normal copper levels (Median: 237.00 ug/dL), Z = -0.766, p-value = 0.444.

The median viral load did not differ significantly among subjects with copper deficiency (Median: 57.50 µmol/L) and subjects that had normal copper levels (Median: 20.00 µmol/L), Z = -1.418, p-value = 0.156.

However, CD4 count and viral load differ significantly among subjects with zinc deficiency and subjects that had normal zinc levels, p-value < 0.05. Subjects with

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normal zinc levels had a higher CD4 count (Median; 395 cell/mm^3) compared to subjects with zinc deficiency (Median; 132 cell/mm^3) while the viral load was higher among subjects with zinc deficiency (16257 cp/ml) compared to subjects with normal zinc levels (20 cp/m), which signify treatment failure among subject with zinc deficiency.

Immuno-suppression was not associated with copper deficiency among subjects with a prevalence of 69.3% and 72.6% among subjects with copper deficiency and normal copper levels respectively, χ^2 = 0.187, p-value = 0.666. There was a significant association between immunosuppression and zinc levels among subjects, χ^2 = 17.393, p-value = 0.000

In line with this study, Rousseau, et al. [49] he observed a significant decrease in the percentage of persons with zinc deficiency (from 77% to 10%) and copper overload (from 98% to 43%) after HAART initiation. Their findings show that selenium, copper and zinc levels were neither significantly improved after HAART initiation nor higher in those receiving HAART at follow-up. They, therefore, conclude that HAART may reduce zinc deficiency and not necessarily increase its level. A zinc deficiency is dependent on the immune status of HIV/AIDS patients. On the other hand, copper does not seem to be influenced by the immune status in those patients. HAART probably reduces zinc deficiency even in patients with low CD4 cell count AART may help avoid bodyweight loss.

Conclusion

In conclusion, this study demonstrated a high level of copper deficiency, 59%. More so, the zinc status of the HIV-infected subjects on HAART treatment was comparable with HIV-infected subjects that are HAART naïve. This showed that the HAART treatment does not complement micronutrients status rather than the CD4+T-cell count levels. HAART treatment centers on boosting the immune system, while the subjects may still suffer zinc or copper deficiency amid improved CD4+T-cell count. Hence micronutrients supplementation should be considered while offering HAART treatment.

The decrease in micronutrients that accompanies HIV infection suggests a potentially important role of nutritional supplementation and good nutrition in the proper management of HIV/AIDS. We, therefore, recommend that HIV-infected Patients should be investigated and treated for micronutrients deficiency, to reduce the morbidity and mortality associated with HIV infection.

This research work adopted a cross-section design whereas a longitudinal approach could have been employed to follow up and study the pattern of micronutrients over a given period. Other hematological parameters include meaning corpuscular volume MCV, mean corpuscular hemoglobin MCH, etc which have revealed other nutritional deficiencies. Furthermore, convenient sampling was used limiting the generalization of our findings. We believe more can be achieved in the nearest future with more resources and funding.

Conflict of Interests

The authors declared no conflict of interest for this study

Ethical Approval

Ethical approval for the study was obtained from the ethical review committee of the LAUTECH Teaching Hospital Ogbomoso, Oyo State Nigeria.

Ethical Clearance Number: *LTH/OGB/ET/214*

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