

Serum selenium and skin diseases among Nigerians with human immunodeficiency virus/acquired immune deficiency syndrome

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Background: The role of selenium as an antioxidant micronutrient has garnered the unprecedented focus of researchers in recent times. No clinical study has related serum selenium concentration to skin diseases in human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients.

Methods: In this study, 134 newly diagnosed HIV patients that satisfied the inclusion criteria were included. Skin diseases were clinically diagnosed and fasting venous blood was taken for assessment of serum selenium using an atomic absorption spectrophotometer.

Results: The mean age of HIV subjects with and without skin disease were not significantly different: 32.72 ± 9.21 versus 35.86 ± 8.55 years, $P = 0.077$, respectively. The mean of serum selenium (0.51 ± 0.48 versus 0.81 ± 0.39), CD4+ count (228.06 ± 212.89 versus 446.41 ± 182.87), and body mass index (BMI; 21.09 ± 3.58 versus 23.53 ± 3.35) were significantly lower ($P < 0.001$) for HIV/AIDS participants with skin disease than those without skin disease. We found significant clustering of symptoms and signs: fever ($P = 0.037$), weight loss ($P = 0.009$), oral candidiasis ($P = 0.038$), pallor ($P = 0.037$) among HIV/AIDS subjects with skin diseases than those without. Low serum selenium concentration was significantly associated with primary skin disease of HIV/AIDS, such as pruritic papular eruption of AIDS ($P = 0.003$), xeroderma ($P = 0.030$), fluffy hair ($P = 0.021$), blue-black nail hyperpigmentation ($P = 0.033$) and secondary skin disease, such as oral candidiasis ($P = 0.002$). There was a significant association between low serum selenium concentration and increasing frequency of skin diseases ($P = 0.002$), but serum selenium was not significantly related to extents of distribution of skin diseases ($P > 0.05$).

Conclusion: serum selenium concentration was lower among HIV subjects with skin diseases than those without skin disease. Pruritic papular eruption, xeroderma, fluffy hair, blue-black nail hyper pigmentation, and oral candidiasis were significantly associated with low serum selenium concentration.

Keywords: serum selenium, HIV/AIDS, skin disease, Osogbo, Nigeria

Introduction

The skin as an interface organ between the internal and external environments is plagued by oxidative radicals generated from both exogenous and endogenous environments as a result of ongoing pro- and anti-oxidant disequilibrium.¹ The human immunodeficiency virus (HIV) is a known oxidative stress inducer that depletes its host of selenium.² As the virus replicates it incorporates selenium into its own human-like glutathione peroxidase enzyme,²⁻⁴ therefore depleting its host of selenium and anti-oxidant glutathione peroxidase enzyme.²⁻⁴ The resulting reduction in the level of human glutathione peroxidase enzyme which is a scavenger thiol, and activation of nuclear factor kappa light chain enhances the activation of B-cells (NF-kB) by reactive oxygen species and tumor

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necrosis factor- α (TNF- α) consequently results in unabated HIV replication.²⁻⁴ The HIV replication consequently leads to progressive depletion of immune cells and its associated HIV disease progression.²⁻⁵ The consequences of the loss of immune cells in HIV/acquired immunodeficiency disease syndrome (AIDS) include the manifestations of opportunistic infections of which skin diseases form a large portion. Some of these skin manifestations are well recognized as early markers of HIV infection or disease progression.⁶

Serum selenium has been variously demonstrated to be lower in people living with HIV/AIDS (PLWHA) than among the normal population.^{2,3} Selenium has been shown to be depleted progressively with the stages of HIV infection,^{2,3} and correlate with low CD4+ cell count and disease progression.²⁻⁵ Low levels of selenium have been associated with about a 20-fold risk of opportunistic infections,⁷ increasing mycobacterium disease, poor quality of life,⁸ and a predictor of HIV associated mortality.⁷ In relation to skin diseases, selenium and other oxidant markers have been correlated with certain inflammatory skin diseases.⁹⁻¹¹ Studies have also related pemphigus vulgaris to antioxidant status of patients,⁹ while low serum selenium and associated oxidative stress induction have been implicated in the pathogenesis of psoriasis.^{10,11} Low selenium status has been associated with up to a 4-fold increased risk of developing skin cancers including malignant melanoma and epidermotropic cutaneous T cell lymphomas.^{12,13} Studies have also confirmed the existence of local oxidative stress in some infectious skin diseases, such as viral wart and tinea pedis.^{14,15} However, selenium has not been studied in relation to skin manifestations of HIV which are known correlate of extents of immune involvement.

In resource poor settings, skin manifestations of HIV are important because they aid prompt recognition of disease and contribute significantly to morbidity, mortality, and quality of life impairment.¹⁶ Studying serum selenium in relation to skin manifestations of HIV/AIDS is also relevant in this era of highly active anti-retroviral therapy (HAART) because certain lesions are resistant to treatment, while others are re-emerging as immune reconstitution syndrome with HAART.¹⁶ As studies to improve treatment outcome and survival of HIV patients continues, we investigated the relationship between serum selenium, the primary and secondary skin manifestations among the PLWHA.

Patients and methods

This cross-sectional study involved 134 newly diagnosed HIV positive subjects who were recruited between December 2009 and March 2011. The setting of this study

was Lakoko Akintola University of Technology Teaching Hospital (LTH), Osogbo, Osun State, Nigeria. After counseling and explanation of the aim and objectives of the study, patients were included and informed written consent was obtained. We set out to include every third newly diagnosed HIV subject who satisfied the inclusion criteria and was willing to participate in the study until the sample size was completed. The included participants were non-smokers, non-diabetic, and adults within age bracket of 18 to 64 years. Furthermore, the study participants were not on selenium-containing supplements prior to onset of the study and agreed not to take selenium containing supplements throughout the study period. We excluded patients that did not meet the inclusion criteria, or who had acute medical or surgical illness requiring hospital admission or surgery. HIV positive subjects on selenium supplements and those who refused to participate in the study were excluded. The ethical committee of the institution reviewed and approved the study.

We obtained socio-demographic data related to age, gender, marriage status, and occupation from the subjects. We noted current history of fever, weight loss, diarrhea, and cough. Fever was noted when temperature was $>38.5^{\circ}\text{C}$, weight loss was defined as unexplained weight loss of at least 5% of presumed weight in the past 1-month. Chronic diarrhea was defined as daily passage of at least three or more motions in the past 1-month. Chronic cough was recorded if symptom persisted for 2 weeks or more.¹⁷ Other complaints noted were pruritus and the presence of skin rash. With the aid of a weighing scale, the weights of all the study subjects (in kilograms) were obtained in light clothing and the participants' heights (in meters) were obtained using the stadiometer. Body mass index (BMI) was calculated using the formula $\text{weight (kg)}/\text{height}^2 (\text{m}^2)$. We carefully examined subjects for pallor, jaundice, and oral candidiasis.

We set out to diagnose skin diseases clinically, and to do skin scrapping and skin biopsy when diagnosis seemed difficult. Skin diseases were broadly classified into primary and secondary skin diseases of HIV/AIDS. We estimated extent of skin diseases by using the Wallace rule of nines for calculating the body surface area (BSA) involved in burns in adults for extensive skin diseases and the rule of palm for limited dermatoses. The extent of skin disease was classified as major when $>15\%$ BSA or minor if $>15\%$ BSA was involved.¹⁸ The number of digits involved was also counted as an index of severity of those skin diseases that disproportionately involved the digital nails; major nail disease was defined as involvement of >2 nail digits, while minor nail disease involved >2 digits. All examinations

were conducted under clear day light. All subjects were screened for tuberculosis using careful chest examination, chest X-ray, and sputum tests on three occasions using the Ziehl-Neelsen method. Other investigations were done as a patient's condition required.

Selenium was measured in serum by hydride generating atomic absorption spectrometry (Model 210 VGP, Buck Scientific, East Norwalk, CT, USA) using procedures and methods previously described by other workers.^{19,20} The analyst made two measurements for each sample and the average of the observations was recorded as research data. Standard laboratory selenium solutions containing certified selenium content were used as reference materials to control for the quality of the analysis. The CD4+ cell count was estimated using FAC Scan flow Cytometer, (CyFlow SL Green, Partec GmbH, Münster, Germany).

Data analysis

Data analysis was done using the Statistical Package for Social Sciences software, version 16 (SPSS, IBM Corporation, Armonk, NY, USA). Continuous data were expressed as means \pm standard deviation (SD) and categorical data as percentages. The Student *t*-test and analysis of variance (ANOVA) were used to assess differences between two means or more than two means respectively. Differences between categorical variables were analyzed using chi square with the Fisher's test applied when appropriate. A *P*-value < 0.05 was considered statistically significant.

Results

One hundred and two (76%) participants had skin disease while 32 (24%) participants had no skin disease. There were no significant statistical differences in the age, gender, marital status, occupation, route of transmission, and height of HIV patients with or without skin diseases (Table 1). Patients with skin diseases had significantly higher prevalence of fever, weight loss, oral candidiasis, pallor, and pulmonary tuberculosis when compared to those without skin diseases (Table 1). The participants with skin diseases had significantly lower mean weight (55.3 ± 9.3 versus 61.6 ± 12.3 kg, $P = 0.002$) and lower mean BMI (21.1 ± 3.4 versus 23.5 ± 3.6 kg/m², $P = 0.001$) when compared to those without skin diseases. Also, participants with skin diseases had significantly lower CD4 count (228.06 ± 182.87 versus 446.41 ± 212.89) and lower serum selenium (0.51 ± 0.39 versus 0.81 ± 0.48) when compared to those without skin diseases ($P < 0.001$). The participants who presented with skin diseases were also noted to be significantly at severe and advanced

Table 1 The socio-demographic and clinical characteristics of the patients with and without skin disease

Clinical characteristics	HIV patients with skin diseases (N = 102)	HIV patients without skin diseases (N = 32)	P-value
Mean age \pm SD	35.9 \pm 8.6	32.7 \pm 9.2	0.077
Gender			
Male (%)	34 (33.3)	7 (21.9)	0.275
Female (%)	68 (66.6)	25 (78.1)	
Marital status			
Within family system	77 (75.5)	24 (75.0)	0.955
Not within family system	25 (24.5)	8 (25.0)	
Occupation			
Predominantly traders	51 (50.0)	17 (53.1)	0.840
Non traders	51 (50.0)	15 (46.9)	
Route of transmission			
Heterosexual mode	88 (86.3)	26 (81.2)	0.205
Non heterosexual mode	14 (13.7)	6 (18.8)	
Fever	13 (100.0)	0 (0.0)	0.037
Diarrheal	17 (94.4)	1 (5.6)	0.057
Weight loss	43 (89.6)	5 (10.4)	0.009
Cough	26 (83.9)	5 (16.1)	0.291
Pruritus	24 (88.9)	3 (11.1)	0.097
Oral candidiasis	24 (92.3)	2 (7.7)	0.038
Pallor	33 (89.2)	4 (10.8)	0.037
Jaundice	1 (100.0)	0 (0.0)	0.582
Tuberculosis	24 (82.8)	5 (17.2)	
Mean height \pm SD (meter)	1.62 \pm 0.08	1.61 \pm 0.07	0.716
Mean weight \pm SD (kg)	55.29 \pm 9.25	61.59 \pm 12.28	0.002
Mean BMI \pm SD (kg/m ²)	21.09 \pm 3.35	23.53 \pm 3.58	0.001
Mean CD4 \pm SD count (cells/mm ³)	228.06 \pm 182.87	446.41 \pm 212.89	< 0.001
Mean serum selenium \pm SD (μ mol/L)	0.51 \pm 0.39	0.81 \pm 0.48	< 0.001
Combined WHO laboratory and clinical staging (%)			
Stage 1	17 (16.7)	26 (81.2)	< 0.001
Stage 2	25 (24.5)	1 (3.1)	
Stage 3	4 (3.9)	0 (0.0)	
Stage 4	56 (54.9)	5 (15.6)	

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; SD, standard deviation.

immunosuppression stages than those without skin disease at the time of diagnosis ($P < 0.001$; Table 1).

The leading primary skin lesions among the study participants were pruritic papular eruption (PPE) 25.5%, xeroderma (21.6%), and fluffy hair (18.6%), while the leading secondary skin diseases were oral candidiasis (25.4%), dermatophytosis (24.5%), and pityriasis versicolor (13.7%). Serum selenium was lower among participants with all the documented HIV primary skin diseases than those

without them. Serum selenium was significantly lower among those with PPE ($P = 0.003$) and xeroderma ($P = 0.030$), fluffy hair ($P = 0.021$), and blue-black nail hyper pigmentation, but not significantly among those with seborrheic dermatitis ($P > 0.05$; Table 2).

Similarly, serum selenium was lower among participants with HIV secondary skin diseases than when absent with exception of those participants with viral warts and pityriasis vesicolor who demonstrated statistically insignificant higher concentration of serum selenium when skin disease was present than when absent. However, serum selenium concentration was significantly lower among participants with oral candidiasis than among those without the lesion ($P = 0.028$; Table 2).

In Table 3, we dichotomized the frequency of occurrences of skin diseases into three and the mean \pm SD of serum selenium concentrations were calculated using one way ANOVA for the groups. Eighty seven (64.9%) subjects had none or single skin disease, 33 (24.6%) had 2, and 14 (10.5) had ≥ 3 skin diseases. Participants with multiple skin diseases (≥ 2 and ≥ 3) had significantly lower mean serum selenium than patients without or with single skin disease, ($F = 6.312$ and $P = 0.002$).

PPE, xeroderma, and diffuse post inflammatory skin hyper pigmentation were the extensively distributed skin diseases. The participants with major PPE, xeroderma, and diffuse post inflammatory skin hyper pigmentation had lower mean serum selenium concentration than participants with minor disease. Similarly, patients with major blue-black

hyper pigmentation and tinea unguium nail involvement had lower mean serum selenium concentration than participants with minor digital nail involvements. However, these findings were not statistically significant ($P > 0.05$; Table 4).

Discussion

In the present study, HIV positive participants with skin disease had lower mean serum selenium concentration than those without skin diseases. The pattern of skin disease found in our study is similar to the pattern previously documented in our environment.²¹ Oral candidiasis, PPE, and dermatophytosis were the leading skin diseases among PLWHA subjects while lesions such as Kaposi's sarcoma and deep mycosis were not documented in the present study.

The significant presence of many skin diseases when selenium was low among HIV positive participants in this study was found in association with increasing clustering of symptoms and signs of HIV disease progression such as weight loss, oral candidiasis, tuberculosis, diarrheal disease, pruritus, pallor, and low CD4 count. It has been documented that adequate concentration of selenium inhibits in vitro HIV replication, prevents development of viral virulence,²⁻⁵ and therefore prevents disease progression.^{7,8} Adequate selenium concentration may therefore be of importance in preventing clustering of symptoms including skin manifestations and retarding the progression of HIV disease. Low serum selenium concentration was significantly associated with PPE, xeroderma fluffy hair, blue-black nail hyper pigmentation and oral candidiasis. These skin diseases are common among

Table 2 The presence or absence of representative primary and secondary skin diseases in relation to serum selenium

Skin diseases	Mean serum selenium \pm SD ($\mu\text{mol/L}$)		t-value	P-value
	Skin diseases present	Skin diseases absent		
Primary skin diseases of HIV/AIDS				
Pruritic papular eruption	0.36 \pm 0.28	0.63 \pm 0.44	-3.055	0.003
Xeroderma	0.40 \pm 0.27	0.58 \pm 0.47	-2.192	0.030
Fluffy hair	0.37 \pm 0.24	0.62 \pm 0.45	-0.235	0.021
Blue-black nail hyperpigmentation	0.38 \pm 0.35	0.61 \pm 0.43	-1.997	0.033
Seborrheic dermatitis	0.50 \pm 0.31	0.55 \pm 0.47	-0.668	0.505
Secondary skin diseases of HIV/AIDS				
Oral candidiasis	0.35 \pm 0.27	0.63 \pm 0.44	-3.179	0.002
Dermatophyte infection ^a	0.54 \pm 0.39	0.59 \pm 0.44	-0.546	0.586
Pityriasis vesicolor	0.59 \pm 0.42	0.58 \pm 0.43	0.068	0.946
Folliculitis/furuncles	0.54 \pm 0.45	0.55 \pm 0.46	0.565	0.573
Herpes zoster	0.43 \pm 0.34	0.55 \pm 0.46	-0.289	0.289
Candida intertrigo	0.48 \pm 0.40	0.58 \pm 0.43	-0.681	0.497
Viral wart	0.60 \pm 0.33	0.58 \pm 0.43	0.090	0.928
Herpes simplex	0.46 \pm 0.16	0.58 \pm 0.44	-0.568	0.571
Molluscum contagiosum	0.34 \pm 0.33	0.58 \pm 0.43	-0.989	0.324

Note: ^aTinea unguium, corporis, pedis, and cruris.

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; SD, standard deviation.

Table 3 Serum selenium concentration in relation to frequencies of HIV/AIDS skin disease occurrences

Skin diseases	Frequency (%)	Mean serum selenium \pm SD ($\mu\text{mol/L}$)	t-value	P-value
None or one skin disease	87 (64.9)	0.68 \pm 0.47	6.312	0.002
Two skin diseases	33 (24.6)	0.41 \pm 0.29		
Three skin diseases and above	14 (10.5)	0.42 \pm 0.26		

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; SD, standard deviation.

PLWHA in Africa, and are a recognized marker of advanced immune involvement in HIV/AIDS.^{22–24} Previous studies have also established associations between low selenium, oral candidiasis, depressed T-cell function and abnormal phagocytic activities both in animal and human studies.^{4,25–27} The association between low CD4 count and low selenium concentration has been previously documented.^{7,8,27} Adequate selenium concentration is required for proper functioning of both cell mediated and humoral immunity²⁷ of which the cutaneous immune system forms a continuous network.²⁸ Low levels of serum selenium will therefore prevent proper functioning of the skin immune system giving way to opportunistic infections, such as oral candidiasis and skin malignancy. It is also known that HIV induces the loss of functional immunocompetent cells²⁷ (including impairment of the skin immune system) leading to the manifestation of a

Table 4 Serum selenium concentration in relation to extent of occurrences of HIV/AIDS skin diseases

Skin diseases (major or minor)	Frequency	Mean serum selenium ($\mu\text{mol/L}$) \pm SD	t-value	P-value
Xeroderma				
< 15% BSA	6	0.38 \pm 0.32	0.069	0.945
\geq 15% BSA	17	0.37 \pm 0.30		
Pruritic papular eruption				
< 15% BSA	9	0.39 \pm 0.33	0.061	0.938
\geq 15% BSA	18	0.38 \pm 0.31		
Hyperpigmentation				
< 15% BSA	6	0.51 \pm 0.52	1.104	0.295
\geq 15% BSA	6	0.20 \pm 0.45		
Blue-black nail pigmentation				
< 2 nails	4	0.41 \pm 0.28	0.272	0.788
\geq 2 nails	13	0.36 \pm 0.33		
Tinea unguium				
< 2 nails	9	0.58 \pm 0.40	1.540	0.146
\geq 2 nails	6	0.28 \pm 0.31		

Abbreviations: AIDS, acquired immunodeficiency syndrome; BSA, body surface area; HIV, human immunodeficiency virus; SD, standard deviation.

plethora of skin diseases.^{29–31} The destruction of CD4+ vector and effector cells has been recognized as an important contributor to the pathogenesis of most of the cutaneous manifestations of HIV.^{29–31} Nail hyper pigmentation has significant association with low serum selenium in this study; the same has been associated with low CD4 count in a previous African study.²⁴

Meanwhile, certain viral, bacterial, and fungal infections tend to occur early in the course of HIV disease. These lesions did not demonstrate significant association with low serum selenium concentration in the present study. The higher concentration of serum selenium among patients with pityriasis vesicolor and viral warts than those without the lesion is not unusual because these lesions can also occur early and can be seen among immunocompetent adults, and therefore cannot signify low serum selenium.

Although the presence of representative skin diseases such as PPE and xeroderma was associated with low selenium concentration, the extent of their distribution showed no such association. Further studies may be required to determine other immunological and non-immunological factors that contribute to the extent and or severity of cutaneous distribution of skin diseases among HIV positive patients. Skin hyper pigmentation extents also demonstrated insignificant association with low serum selenium concentration. This can be attributed to the fact that hyper pigmentation is usually a post inflammatory lesion representing old skin inflammatory diseases and may not correlate with present immunological status. The frequency of skin disease has been associated with decreased skin immunity in the early phase, total number of skin diseases correlated with CD4 count, survival time, and time to development of AIDS in studies.^{29–31} The number of skin diseases reflects immune status of patients, therefore, severe and multiple skin diseases are not unusual as the disease progresses and serum selenium becomes low.^{6,16,21,31,32} It must be mentioned that certain factors contribute to the variation of selenium concentration in humans.

Selenium status and function may reflect biochemical markers such as the selenoenzymes concentration, biological or molecular markers such as blood Gpx1 mRNA levels, as well as the extent of induced oxidative stress.^{33,34} Other recognized factors that may determine variation in selenium concentration between individuals, is the genetic polymorphism of selenoenzymes genes. This polymorphism of individual selenoprotein genes determines human response to selenium supplementation, the types or isoforms of selenium in plasma during selenoprotein synthesis,³⁴ and gender differences in susceptibility to cancer and survival.^{35,36} Studies

are needed to examine genetic variation or polymorphism status of these selenoenzymes genes among HIV patients in early disease and in the advance stage of HIV disease in relation to oxidative stress in Africa. In the present study, other determinants of serum selenium like the patient age, presence of sepsis or the acute phase response, cigarette smoking, alcohol ingestion, and selenium intake in oral medications were corrected for.

In this study, we observe the following limitations: the stigma attached to HIV infection in this part of the world has been a limiting factor that restricts studies like this to the source of care, therefore limiting the extrapolation of research findings. Since most PLWHA present when HIV disease is in advanced stage having developed skin disease(s) and other opportunistic infections, it will be difficult in our environment to document the pre-morbid skin status of most patients before infection and relate this to skin changes due to oxidative stress induced by HIV.

Summarily, serum selenium is lower among PLWHA with skin diseases than those without skin lesions. Low serum selenium was significantly associated with primary HIV skin diseases like PPE, fluffly hair, blue-black nail hyperpigmentation, xeroderma, and secondary HIV skin disease like oral candidiasis. Serum concentration of selenium decreases significantly as frequency of skin diseases is increasing but not significantly with the extent of cutaneous distribution of the skin diseases. We therefore advocate rational supplementation of oral selenium as an adjuvant therapy for HIV patients with skin diseases in sub-Sahara Africa.

Disclosure

The authors report no conflicts of interest in this work.

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