Serum Reproductive hormone levels in male symptomatic HIV/AIDS patients on Antiretroviral therapy negative to Malaria parasite in Nnewi, Anambra State, Nigeria

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ABSTRACT

Background: AIDS is an endemic disease that causes death among young adults worldwide especially in Nigeria. **Aims and Objectives:** This study investigated the serum reproductive hormone levels in symptomatic HIV/AIDS male subjects on ART who are negative to malaria parasite in Nnewi, Anambra State, Nigeria. **Materials and Methods:** A total of 274 adult male participants aged between 18 and 60 years were randomly recruited, and grouped into: symptomatic HIV (stage 11) infected male participants on ART (A: n = 69), Symptomatic HIV subjects not on ART (B: n = 69), Asymptomatic HIV positive subjects (C: n = 68) and HIV seronegative subjects (D: n = 68). Serum was used to assay for PSA, LH, FSH, Estrogen, Testosterone, Progesterone and Prolactin levels. Analysis of variance and student t-test were used for data analyses. **Results:** The serum levels of PSA, FSH, Estrogen, Testosterone, Progesterone and Prolactin were significantly different amongst the groups at $p < 0.05$ respectively. There were significantly higher levels of PSA, Estrogen, Progesterone but lower levels of Testosterone and Prolactin in subjects on ART compared with control at $p < 0.05$ respectively. There were significantly higher levels of PSA, FSH, Estrogen,Progesterone but lower levels of Testosterone in subjects not on ART compared with control at $p < 0.05$ respectively. **Conclusion:** The reduction on serum levels of Testosterone and higher levels in FSH, PSA, Estrogen, and Progesterone may reveal presence of hypogonadism, primary testicular failure, prostate abnormalities such as cancer and hyperprogesteronaemia, in symptomatic HIV positives.

Key words: HIV; AIDS; Malaria negative; male subjects; reproductive hormones; ART

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is an endemic disease that causes death among young adults worldwide.[1] AIDS is caused by two lenti-viruses, human immunodeficiency viruses (HIV) types 1 and 2,[2] with HIV type 1 strains classified into M, O and N groups.[3] However, the majorities of HIV-1 viral strains are classified as group M which has various subtypes (A to K)[3] and are distributed worldwide; with subtype C infections endemic to sub-Saharan Africa, India and Brazil. HIV-1 primarily infects CD4^{+} T cells and macrophages.[4] HIV transmission occurs through exposure to contaminated body fluids, such as blood,[5] or breast milk;[6] with possible routes of

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transmission including blood transfusions, intravenous drug use, mother-child transmission and during sexual intercourse.[5-8] Indeed, the United Nations has termed HIV and AIDS the greatest overwhelming public health problems that the world has ever encountered.[9,10] In fact, Nigeria has the second largest HIV epidemic in the world.[11] Although HIV prevalence among adults is much less (2.9%) than other sub-Saharan African countries such as South Africa (18.9%) and Zambia (12.4%), the size of Nigeria's population means 3.6 million people were living with HIV in 2016.[11] However, recently, the global health sector strategy on HIV/AIDS 2011-2015[12] has galvanized global and country action that has helped halt and reverse the AIDS epidemic. During this period, HIV treatment coverage was expanded rapidly with well over 17million people living with HIV on antiretroviral therapy by the end of 2015; with new HIV infections and deaths declined.[13] However, there is no need for complacency as more work is needed in order to bring to minimal the menace of the HIV/AIDS invasion on the human population.

Reproductive endocrinology encompasses the hormones of the hypothalamic-pituitary-gonadal axis and the adrenal glands.[14] The endocrine reproductive system produces reproductive hormones such as FSH, LH, Testosterone, Estrogen, Progesterone, Prolactin and Cortisol into general circulation.[15,16] These hormones are crucial for proper reproductive function.[14] However, many alterations in endocrine functions have been reported in association with human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) in both early and late stages of HIV infection.[17] These changes may be as a result of the systemic effects of HIV, opportunistic infections, infiltration by a neoplasm or as a complication of treatment. Hypogonadism has been reported to increase in HIV disease[18], and gonadal dysfunctions are common among men as compared to women.[19] Also, HIV infected person has been reported to have increased serum LH and FSH levels.[20] Therefore, this study investigated the serum reproductive hormone levels in male symptomatic HIV/AIDS patients on antiretroviral therapy negative to malaria parasite in Nnewi, Anambra State, Nigeria.

MATERIALS AND METHODS

Subjects

This is a case controlled study designed to evaluate the serum hormonal levels in malaria uninfected symptomatic HIV (Stage II) male subjects on antiretroviral therapy in Nnewi, South Eastern Nigeria. A total of 274 adult male participants aged between 18 and 60 (42 ±13) years were randomly recruited at the Voluntary Counseling and Testing (VCT) Centre in Nnamdi Azikiwe University Teaching

Hospital (NAUTH), Nnewi, Nigeria. Based on World Health Organisation (WHO) criteria for staging HIV, the participants were grouped as follows: symptomatic HIV (stage 11) infected male participants on ART (n=69). Lamivudine, 150 mg twice daily, Stavudine, 40mg twice daily and Nevirapine, 200 mg twice daily: this was administered to the symptomatic HIV stage 11 subjects on ART. Symptomatic HIV subjects not on ART (n= 69), Asymptomatic HIV positive subjects (n= 68) and HIV seronegative subjects (n= 68). The subjects were given informed consent, while the study design was approved by the ethical committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria. 5 ml of blood sample were collected from each of the participant in the groups. The participants were screened for HIV infection using Immunoassay and Immunochromatographic method. The serum was used for the estimation of PSA, FSH, LH, Testosterone, Estrogen, Progesterone, and Prolactin levels. The serum samples were stored at -20°C until analyzed.

Antibodies to HIV-1 and HIV-2 in human plasma were determined using Abbott determine TM HIV -1 andHIV-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). Determination of PSA, LH, FSH, Testosterone, Estradiol, Progesterone and Prolactin were done using Enzyme Linked Immunosorbent assay (ELISA) kits (Randox Laboratories Limited, U.K) respectively.

Statistical analysis

The data obtained was statistically analyzed using Statistical Package for Social Sciences (SPSS) version 16.0. One of way analysis of variance (ANOVA) and students't-test were used to compare means. The results were expressed as mean ±SD and confidence limits was chosen at 95% ($P < 0.05$). $P < 0.05$ was considered statistically significant while $P > 0.05$ was insignificant.

RESULTS

The result of analysis of variance showed that the mean serum levels of PSA, FSH, Estrogen, Testosterone, Progesterone and Prolactin were significantly different amongst the group (F=12.07, 5.79, 22.69, 18.03, 14.03 AND 8.04) ($P < 0.05$) respectively, whereas, LH did not differ significantly amongst the group (F=1.94; $P > 0.05$) (Table 1).

The mean serum PSA (ng/ml) level did not differ significantly in HIV seropositive participants on ART (7.414.24) compared with HIV seropositive participants

not on ART (7.91±5.17) (p=0.93). Also the mean serum PSA level in HIV seropositive participants on ART did not differ significantly compared with Asymptomatic HIV positive subjects (P>0.05). However, the serum PSA value in HIV seropositive participants on ART was significantly lower than the value in control group (p=0.000).

The mean serum LH (miu/ml) and FSH levels was not significantly different in HIV seropositive participants on ART compared with HIV seropositive participants not on ART, Asymtomatic HIV positive subjects and control group (p>0.05) respectively.

There was no significant difference in the mean serum Estrogen (pg/ml) levels in HIV seropositive participants on ART compared with HIV seropositives not on ART (P>0.05), but significant statistical increases in the mean serum levels of Estrogen in HIV seropositive participants on ART than in Asymptomatic HIV positives and control subjects (p<0.05) respectively.

The mean (±SD) of serum Testosterone (ng/ml) levels in HIV seropositive participants on ART was significantly lower compared with the corresponding value in the control group (2.58±1.58 Vs 4.80±1.75; p=0.00). However, no significant mean differences were observed between values in HIV seropositive participants on ART and not on ART (P>0.05).

The mean (±SD) of serum progesterone (ng/ml) level did not differ significantly in HIV seropositive participants on ART compared with HIV seropositive participants not on ART and Asymptomatic HIV positives (P>0.05),

whereas the mean (±SD) of serum progesterone level was significantly higher in HIV seropositive participants on ART than in control group (2.42±1.73 Vs 1.09±1.19; p=0.00).

The mean (±SD) of serum Prolactin (ng/ml) levels in HIV seropositive participants on ART was significantly lower compared with the corresponding value in the HIV seropositive participants not on ART (7.15±5.33 Vs 10.33±3.90; p=0.00), while the mean (±SD) of serum Prolactin level in HIV seropositive participants on ART did not differ significantly than in Asymptomatic HIV positive subjects (p=0.20).

DISCUSSION

Human Immunodeficiency Virus (HIV) infection has been convincingly shown to increase opportunistic infection, risk of prostatitis,[21] and several malignancies including testicular cancers, lymphomas, penile cancers[22] and prostate cancers.[23,24]

The present study revealed a significantly elevated PSA levels in HIV/AIDS seropositive subjects on ART than in the HIV seronegative participants. Also, there was a significant difference in the mean value of PSA levels between the HIV/AIDS seropositive participants on ART compared with HIV/AIDS seropositive participants not on ART. Again, comparison of PSA level between HIV/AIDS seropositive subjects on ART and asymptomatic HIV positive participants revealed no significant statistical difference. These findings may suggest a link between

Table 1: Reproductive Hormone Levels in Malaria Negative Adult Male Subjects on ART						
Variables	PSA (ng/ml)	LH (miu/ml)	FSH (miu/ml)	Estrogen (pg/ml)	Testosterone (ng/ml)	Progesterone (ng/ml)	Prolactin (ng/ml)
HIV/AIDS on ART (A) (n=69)	7.41±4.24	12.02±7.45	14.38±7.96	58.99±45.58	2.58±1.58	2.42±1.73	7.15±5.33
HIV/AIDS not on ART (B) (n=69)	7.91±5.17	9.72±6.93	12.53±8.53	66.79±19.83	2.07±2.14	2.63±1.57	10.33±5.33
Asymptomatic HIV+ve subjects (C) (n=68)	9.34±5.77	10.72±5.57	16.71±7.14	39.67±22.25	3.22±2.28	2.10±1.31	8.57±2.71
Control (D) (n=68)	4.66±2.92	9.56±7.16	11.53±7.58	31.14±18.20	4.80±1.75	1.09±1.19	9.39±3.34
p-value	0.000	0.124	0.001	0.000	0.000	0.000	0.000
F-value	12.07	1.94	5.79	22.69	18.03	14.03	8.04
A V B	0.93	0.23	0.56	0.56	0.38	0.89	0.00
A V C	0.12	0.64	0.28	0.01	0.23	0.60	0.20
A V D	0.00	0.20	0.14	0.00	0.00	0.00	0.02
B V C	0.42	0.79	0.01	0.00	0.01	0.15	0.10
B V D	0.00	0.99	0.01	0.00	0.00	0.00	0.43
C V D	0.00	0.72	0.00	0.07	0.00	0.00	0.40

Fp=HIV on ART subjects, HIV not on ART subjects, Asymptomatic HIV subjects and HIV seronegative control group compared using ANOVA;
A V B=HIV on ART subjects compared with HIV not on ART subjects (using student's t-test);
A V C=HIV on ART subjects compared with Asymptomatic HIV subjects (using student's t-test);
A V D=HIV on ART subjects compared with HIV seronegative control subjects (using student's t-test);
B V C=HIV not on ART subjects compared with Asymptomatic HIV subjects (using student's t-test);
B V D=HIV not on ART subjects compared with HIV seronegative control subjects (using student's t-test);
C V D=Asymptomatic HIV subjects compared with HIV seronegative control subjects (using student's t-test)

HIV/AIDS and prostate cancer risk. However, the underlying mechanism behind this increase is not clear. This finding is in consonance with the report of Vianna et al.[25] Several other authors have reported the occurrence of prostate carcinoma in HIV-positive men,[26,27] although Julia et al. had earlier reported a lower incidence of prostate cancer among HIV-positive men than in HIV-Negative Men.[28]

In this study, the mean serum testosterone level was significantly decreased in the HIV/AIDS seropositive subjects on ART compared with the control (2.42±1.73 Vs 4.80±1.75; P=0.000). This decrease may be indicative of hypogonadism among the studied population. This is in line with previous studies.[29-32] Hypogonadism is a clinical condition characterized by low serum testosterone levels occurring in association with any of the signs and symptoms including sexual dysfunction, weight and muscle mass loss, fatique, depressed mood and anemia.[33,34] This decrease may be as a result of the effect of HIV on the gonads,[35] or due to cytokine effect; as HIV infection is known to upregulate tumour necrosis factor and interleukin-1[36], resulting in decreased testicular steroidogenesis.

However, both LH and FSH levels were raised, although not statistically significant in HIV/AIDS seropositive participants on ART than in the control subjects (p>0.05). This increase may be suggestive of subnormal or primary hypogonadism. This increase may be attributed to the severity of the infection. This finding is in agreement with other similar reports.[37] Also, the mean FSH levels in the asymptomatic HIV positive subjects was significantly higher than in control group (16.71±7.14 Vs 11.53±7.58; p=0.00), whereas the mean serum LH level did not differ significantly (p=0.99) between the asymptomatic HIV positive subjects and seronegative participants.

The present study showed a significant increase in the mean value of Estrogen concentration in HIV/AIDS seropositive participants on ART than in the control subjects. Also, this study revealed a significant decrease in the mean serum Estrogen levels in the asymptomatic HIV positive participants compared with the value obtained in the HIV/AIDS seropositive participants on ART (p=0.01). This confirms the fact that the stimulatory effects of elevated serum LH and FSH concentrations on the testis increases conversion of testosterone to estradiol.[38] Estrogenic effect is a peripheral conversion of testosterone to Estrogen by Aromatase and Enolase.[39] Also, the abnormal androgen metabolism which results in increased aromatization of testosterone to estradiol had earlier been reported in HIV positive men.[40]

Furthermore, there was a significant statistical increase in the mean serum progesterone concentrations in HIV/AIDS seropositive participants on ART than in the control subjects (p=0.00). This may be due to the stimulatory effect of HIV infection on the endocrine glands to release progesterone.

This study also observed that the serum prolactin level was significantly elevated in HIV/AIDS seropositive participants not on ART than in those on ART and control subjects respectively. This could be the resultant effect of the disease burden on the pituitary which causes an increase stimulation and secretion of prolactin into the circulation. The reduced prolactin level observed in participants on antiretroviral drugs may be due to the health recovery effect resulting from ART therapy.

CONCLUSION

This study revealed a stimulatory effect of HIV infection on the endocrine glands to release LH, FSH, Progesterone, Prolactin and Estrogen, with a concomitant inhibitory effect on the release of testosterone from the gonads.

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