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Original Research Article

Prognostic values of adiponectin and leptin in assessment of osteoarthritis in menopausal HIV women in Nauth Nnewi Nigeria

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ABSTRACT

Background: Human immune deficiency virus (HIV) has progressively been implicated with development of inflammatory disease including osteoarthritis. This study evaluated serum levels of adiponectin and leptin in women living with HIV with/without osteoarthritis who have been placed on highly active anti-retroviral therapy (HAART) in NAUTH, Nnewi, Nigeria.
Methods: Eighty eight participants aged between 18 and 65 years attending HAART unit of NAUTH, Nnewi were randomly selected and grouped thus: Group A (premenopausal HIV seropositive women with osteoarthritis), group B (postmenopausal HIV seropositive women with osteoarthritis), group C (premenopausal HIV seropositive women) and group D (postmenopausal HIV seropositive women). Five milliliters of blood sample collected from each of participants for determination of adiponectin and leptin using enzyme linked immunosorbent assay (ELISA) technique.
Results: Adiponectin level was significantly higher in postmenopausal HIV seropositive women with osteoarthritis compared with pre and postmenopausal HIV seropositive women without osteoarthritis ($p<0.05$ respectively). Similarly, leptin level was significantly higher in pre and post-menopausal HIV seropositive women with osteoartritis compared with their counterparts without osteoarthritis ($p<0.05$ respectively). A positive significant correlation was observed between Leptin and age in premenopausal HIV seropositive women with osteoarthritis. Also, a significant negative correlation was observed between adiponectin, age in pre and postmenopausal HIV seropositive women without osteoarthritis.
Conclusions: The significant increases in adiponectin and leptin levels in pre and postmenopausal HIV seropositive women can be linked to severe inflammatory reaction due to osteoarthritis which might have been aggravated by combined effects of menopause and HIV infection.

Keywords: HIV, Osteoarthritis, Menopause, Inflammation, Adipnectin, Leptin

INTRODUCTION

Human immunodeficiency virus is a virus that attacks cells that help the body fight infection, making a person more vulnerable to other infections and diseases including osteoarthritis. Long-term consequences of HIV infection and antiretroviral therapy, particularly disturbances of bone metabolism, are emerging concerns given the growing numbers of older adults living with HIV. Many people with HIV have problems of the

musculoskeletal system (joints, muscles and bones). HIV infection can lead to rheumatic (joint and muscle) illness, including joint pain, arthritis, muscle pain, weakness and fatigue.

Osteoarthritis is a heterogeneous group of diseases that can be differentiated by the risk factors (ageing, obesity and trauma). Each factor has specific pathophysiological pathways, all leading to joint destruction.[1,2] Obesity-associated osteoarthritis is one of the most-studied phenotypes characterized by the association of obesity or overweight with osteoarthritis on weight-bearing joints due to mechanical overload.[3] However, recently, the demonstration of an association between obesity and hand osteoarthritis has shed light on a potential role of systemic metabolic disturbances in the pathophysiology of osteoarthritis.[4] Indeed, several studies have raised the possibility of an association of metabolic syndrome and osteoarthritis, but which did not persist after adjustment on body mass index or weight in some of them.[5,6] In addition to accelerated ageing, patients with HIV infection frequently have metabolic syndrome because of HIV infection, via chronic inflammation and immune activation, which contributes to dyslipidaemia and insulin resistance.[7] Moreover, antiretroviral therapy, especially protease inhibitors, can induce a lipodystrophic syndrome characterized by altered body fat composition, dyslipidaemia and Insulin resistance and subsequent metabolic syndrome development.[8]

Osteoarthritis strikes women more often than men and it increases in prevalence, incidence, and severity with increased hand and knee osteoarthritis after menopause. The effects of age on both hip and knee osteoarthritis risk in women follow similar patterns, increasing rapidly between the age of 50 and 75 years. Conversely, risk of hand osteoarthritis peaks in women after menopause with ≥3.5-fold higher rates in women aged 50-60 years when compared to men of similar age.[9] Therefore the menopause is associated with the onset and progression of osteoarthritis in women.

While the etiology of osteoarthritis is still not clearly understood, the evidence suggested that osteoarthritis is a systemic disorder with a multifactorial origin. The systemic risk factors include obesity, gender, injury, age and a genetic bias.[10,11] However, Gabay et al indicated that the obesity induced high metabolic and inflammatory environments play crucial roles in the onset of osteoarthritis.[12] Furthermore, several early studies have indicated that there is an association between osteoarthritis and some adipokines in serum or synovial fluid.[13,14] One of these mediators of interest is adiponectin, which has been shown to be in relation to osteoarthritis.[15]

Arita et al.[16] discovered the adiponectin in obese subjects were significantly lower than that in non-obese one, although adiponectin was secreted only from adipose tissue. Which compound the controversial connection of obesity, adiponectin and osteoarthritis and might further accept the hypothesis of modulatory mechanism of adiponectin in the osteoarthritis patient.

Leptin on the other hand, regulates adipose tissue volumes and body mass index through a negative feedback mechanisms.[17] Leptin has been described as a new bone growth regulator as well as skeletal growth factor that stimulates endochondral ossification.[18,19] Because functional leptin receptor has been shown to be expressed in normal human cartilage.[20] It can be speculated that leptin could also act on this particular connective tissue, especially during osteoarthritis, a disease in which great metabolic changes of chondrocytes are observed. The potential role of leptin in osteoarthritis is supported by the relationship between high body mass index and an increased risk of osteoarthritis.[21] This positive association is observed not only for knee joints but also for non-weight-bearing joints such as the hands, suggesting that osteoarthritis may be initiated by metabolic disorders, with progression being worsened by high mechanical stress on abnormal cartilage. The role of leptin and adiponectin in patients with osteoarthritis cannot be ignored. The study therefore, aimed to assess the impact of menopause and osteoarthritis on adiponectin and leptin levels in pre and post-menopausal HIV infected women on highly active antiretroviral therapy.

METHODS

Study area

The study was carried out in NAUTH, Nnewi, Nigeria. The study participants that are within the age range of eighteen to 65 years was recruited from the HIV clinic of NAUTH, Nnewi. Analysis of the samples was performed in the chemical pathology unit of NAUTH, Nnewi, Anambra State, Nigeria.

Study design

This is a case control prospective study designed to evaluate the serum levels of adiponectin and leptin in premenopausal and postmenopausal HIV seropositive women with osteoarthritis attending antiretroviral therapy unit, NAUTH, Nnewi, between February and August, 2022. Participants within the age range of eighteen to sixty-five were recruited. Questionnaire was administered to each participants who have been on highly active antiretroviral therapy for not less than six months to obtain their bio data and medical history. Written consent was obtained from each of the participants. A total of 84 subjects were recruited for the study, which comprise 21 HIV positive premenopausal women who have been diagnosed of osteoarthritis and have been placed on HAART, twenty one HIV positive premenopausal women, twenty one HIV positive postmenopausal women, twenty one HIV positive postmenopausal women

who have been diagnosed of osteoarthritis and have been placed on HAART.

Inclusion and exclusion criteria

HIV positive premenopausal women with osteoarthritis, HIV positive premenopausal women, HIV positive postmenopausal women and HIV positive postmenopausal women with osteoarthritis. Participants that are within the age range of eighteen to 65 years. While women with diabetes, cardiovascular disease, dyslipidemia and hypertension were excluded from the study. Also excluded were pregnant women, nursing mothers, women undergoing hormone and antioxidant therapy, alcoholics and those outside the age bracket, females on contraceptives and smokers and heavy consumer.

Collection of sample

About 5 ml of venous blood was collected for this study. Serum was extracted after centrifugation at 5000 RPM for 4 minutes. Samples was stored at-4 degree centigrade before analysis.

Determination of serum adiponectin and leptin levels

Levels of serum adiponectin and leptin levels were was determined by sandwich Enzyme linked immunosorbent assay (ELISA) technique as described by Ismaill et al and Chavarria-Avila et al respectively.[22,23]

Anthropometric measure

Anthropometric measures of the study participants was obtained according to WHO criteria.[23] Height and weight was measured while participants stood upright, with no shoes, and wearing light clothing. The height was measured to the nearest 0.1m and weight to the nearest 0.1 kg in the upright position. The body mass index (BMI, weight kg/ height^2, m^2) was also recorded.

Statistical analysis

Statistical package for social science and students t-test analysis of variance (ANOVA) was used for the analysis of the result. Frequency distribution of population was determined. Data was presented as mean + standard deviation (SD) Values was deemed significant at $p<0.05$. Correlation of parameters with age and BMI was determined using the Pearson's correlation coefficient.

RESULTS

Socio-demographic distribution of participants

A total of 84 HIV positive women (with osteoarthritis=44, without osteoarthritis=46) participated in the study. Out of the 44 women with osteoarthritis, 22 (50 %) were premenopausal while 22 (50 %) were post-menopausal, likewise in the group without osteoarthritis, 23 (50 %) were premenopausal and 23 (50 %) post-menopausal. The age range for this study was between 18 and 61. Majority of these participants also fell into the normal BMI range (75%) with the mean BMI being 21.147 (Table 1).

Table 1: Respondents with osteoarthritis demographic characteristics.

Parameters	Frequency (%)
N	45 (100)
Age range (Years)	
18-28	11 (24.4)
29-39	10 (22.2)
40-50	11 (24.4)
51-61	12 (26.7)
Body mass index	
Underweight	13 (28.9)
Normal weight	31 (68.9)
Overweight	1 (2.2)
Obese	0 (0)
Menopause	
Premenopausal	22 (48.9)
Post-menopausal	23 (51.1)
Age (Years)	41.808±12.479[a]
Body mass index (kg/m^2)	21.147±1.091[a]

"a" variables reported as mean ± standard deviation.

While the demographic characteristics of participants without osteoarthritis. The mean ± standard deviation of their age (41.426±12.353), body mass index (20.654±1.831). Also, a majority of the participants were found to have normal weight (75%) (Table 2).

Table 2: Respondents without osteoarthritis demographic characteristics.

Parameters	Frequency (%)
N	45 (100)
Age range (Years)	
18-28	9 (20.0)
29-39	10 (22.2)
40-50	12 (26.7)
51-60	14 (31.1)
Body mass index	
Underweight	10 (22.2)
Normal weight	34 (75.5)
Over weight	1 (2.2)
Obese	0 (0)
Menopause	
Premenopausal	22 (48.9)
Post-menopausal	23 (51.1)
Age (Years)	41.426±12.353[a]
Body mass index (kg/m^2)	20.654±1.831[a]

"a" variable reported as mean ± standard deviation.

Adiponectin levels was found to be significantly lower in premenopausal women (52.092±4.122) with osteoarthritis

than in postmenopausal women with osteoarthritis (64.807±6.592) ($p<0.05$). This significantly lower levels were also seen in Leptin when that of premenopausal women with osteoarthritis (215.125±179.865) was compared to postmenopausal women with osteoarthritis (341.250±212.499) ($p<0.05$). On analysis for women without osteoarthritis, it was found that premenopausal women has lower adiponectin and leptin levels as compared to those of postmenopausal women but the decrease is not significant (Table 3).

Table 3: Adiponectin and leptin levels in HIV premenopausal and post-menopausal women with and without osteoarthritis.

Group	Adiponectin (µ/mL)	Leptin (ng/mL)
Group A (n=22)	52.092±4.122	215.125±179.86
Group B (n=23)	64.807±6.592	341.250±212.49
Group C (n=22)	52.664±5.205	169.074±125.48
Group D (n=23)	55.701±6.122	197.630±131.61
F value	4.732	4.834
P value	0.025	0.000
A vs B	0.012	0.006
A vs C	0.910	0.030
A vs D	0.117	0.029
B vs C	0.029	0.002
B vs D	0.037	0.005
C vs D	0.154	0.008

Group A=Pre-menopausal HIV seropositive women with osteoarthritis, group B=Post-menopausal HIV seropositive women with osteoarthritis, group C=Pre-menopausal HIV seropositive women without osteoarthritis, group D=Post-menopausal HIV seropositive women without osteoarthritis.

The levels of adiponectin and leptin when correlated with age and BMI, shows a positive significant correlation between leptin and age for premenopausal women with osteoarthritis ($r=0.553$, $p=0.006$) whereas none was observed for adiponectin or BMI (Table 4).

When the levels of adiponectin and leptin was correlated with age and BMI of postmenopausal women with osteoarthritis, no significant correlation or association was observed between the parameters (Table 5).

The levels of adiponectin and leptin when correlated with age and BMI in premenopausal HIV positive women without osteoarthritis, it was not significantly correlated (Table 6).

The levels of adiponectin and leptin when correlated with age and BMI in premenopausal women with osteoarthritis, shows a positive significant correlation between adiponectin and BMI for postmenopausal HIV positive without osteoarthritis ($r=0.504$, $p=0.007$). Also, a significant negative correlation was observed between adiponectin in postmenopausal HIV seropositive women without osteoarthritis and age ($r=-0.0400$, $p=0.038$). However, no significant correlation was observed for leptin (Table 7).

Table 4: Correlation between age, BMI, leptin and adiponectin levels in premenopausal women with osteoarthritis, (n=22).

Parameters	Age Pearson (p value)	BMI (kg/m^2), Pearson (p value)
Adiponectin	0.114 (0.595)	0.295 (0.162)
Leptin	0.553(0.006*)	-0.117 (0.587)

*Pearson is significant at $p<0.05$.

Table 5: Correlation between age, BMI, leptin and adiponectin levels in post-menopausal women with osteoarthritis (n=23).

Parameters	Age Pearson (p value)	BMI (kg/m^2), Pearson (p value)
Adiponectin	0.256 (0.188)	-0.196 (0.319)
Leptin	0.347 (0.070)	0.215 (0.271)

*Pearson is significant at $p<0.05$.

Table 6: Correlation between age, BMI, leptin and adiponectin levels in premenopausal women without osteoarthritis, (n=22).

Parameters	Age Pearson (p value)	BMI Pearson (p value)
Adiponectin	0.062 (0.759)	0.078 (0.699)
Leptin	0.305 (0.122)	0.046 (0.819)

*Pearson is significant at $p<0.05$.

Table 7: Correlation between age, BMI, eptin and adiponectin levels in post-menopausal women without osteoarthritis, (n=23).

Parameters	Age Pearson (p value)	BMI Pearson (p value)
Adiponectin	-0.400 (0.038*)	0.504 (0.007*)
Leptin	-0.313 (0.122)	-0.249 (0.211)

*Pearson is significant at $p<0.05$.

DISCUSSION

Postmenopausal women living with HIV are at particularly risk of osteoarthritis as a result of the additive effects of estrogen-depletion and the virus itself. This study was set up with the aim of assessing the impact of menopause and osteoarthritis on adiponectin, leptin and lipid profile in HIV infected women on highly active antiretroviral therapy.

From the analysis of differences in the levels of adiponectin and leptin in premenopausal and post-menopausal HIV positive women suffering from osteoarthritis, it shows that there exists a significant difference in the level of adiponectin and leptin in pre- and post-menopausal HIV positive women suffering from osteoarthritis with post-menopausal HIV positive women

with osteoarthritis having a higher level of adiponectin and leptin than premenopausal HIV women with osteoarthritis. This may be attributed to some degree of inflammation which may have contributed to the osteoarthritis in the HIV infected women. The result might support those of a previous study that indicated that the break down of adipose tissue can evolve osteoarthritis.[24] and the adiponectin might possibly enhance osteoarthritis which increases in postmenopausal women as they enter the menopausal phase. Documented evidences have shown that HIV positive individuals with HIV related metabolic complications experiences a pre-inflammatory changes that can dysregulate the generation of adiponectin and leptin compared with the in some general population.[25,26] A previous study by Otero et al held the opinion that the increased levels of adiponectin in patients with arthritis usually shows some form of homeostasis.[27] Increased serum adiponectin levels was also reported in female patients with inflammatory compared with non-inflammatory osteoarthritis.[28] Additionally, previous report on early introduction of anti-retroviral therapy implicated both protease inhibitors and nucleoside reverse transcriptase inhibitors in the downregulation of adiponectin level from subcutaneous adipose tissue cells.[29] On the other hand, adiponectin levels between pre- and post-menopausal HIV positive women without osteoarthritis shows no significant difference in comparison. Adiponectin on its own has also been known to play roles in some metabolic processes, as well as, in inflammation and anti-inflammation.[30] A significant association between higher serum adiponectin level and lower bone mineral density (BMD) in pre and post-menopausal women have earlier been reported.[31] A strong negative correlation has also been reported between adiponectin and obesity by Arita et al.[32]

There was a significant difference in leptin level between pre- and post-menopausal HIV positive women with/ without osteoarthritis. This in fact agrees with the work by Illiopoulos et al.[33] Who stated that a genetic correlation exists between osteoarthritis and leptin. In further attempt to establish a relationship between adiponectin and leptin levels in premenopausal HIV infected women with osteoarthritis, age and BMI of these women, a positive correlation was observed in the level of leptin as it pertains to age. This states that age as a factor plays a role in the level of leptin in women with HIV associated osteoarthritis. This finding agrees with previous work by Greene and Loeser. [34] A strong correlation was however found between adiponectin, BMI and age of post-menopausal HIV positive women without osteoarthritis. This relation to BMI can be attributed to the role adiponectin plays in decreasing muscular lipid content[35] or its relation to atherosclerosis.[36]

HIV-infected individuals are known to always be at a high risk of developing several inflammatory and degenerative diseases.[37] This is the leading cause of several age-related inflammatory diseases in HIV-patients and general population which is likely to get worse as an individual moves into the later times of their life, accompanied by the immense hormonal imbalance that accompanies the postmenopausal phase in women. Osteoarthritis is the most common type of arthritis and has been known to be closely associated with age, obesity, sex, hormonal and metabolic imbalance. With menopause being a product of aging it can be clearly seen as to why it is most likely for postmenopausal women to have osteoarthritis Ukibe et al.[38] According to Imai et al.[39] who stated that osteoarthritis is eminent especially in post-menopausal HIV infected women due to effects of oestrogen-depletion and the virus itself.

CONCLUSION

The significant increases observe in adiponectin and leptin levels in postmenopausal HIV seropositive women can be linked to severe inflammatory reaction due to osteoarthritis which might have been aggravated by combined effects of menopause and HIV infection and may subsequently progress to bone loss and adverse cardiovascular injuries in the affected individuals.

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