Changes in Serum Uric Acid andC-Reactive Protein in Menopausal HIV Seropositive with Osteoartritisin NAUTH, Nnewi, Nigeria

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Abstract

Reports of increased in musculoskeletal manifestations in human immunodeficiency virus (HIV) is common since the existence of the global HIV pandemic. Various aspects of bone problems have also been associated with HIV including osteoarthritis. The aim of this study is to assess the impact of osteoarthritis on serum C -reactive protein (CRP) and uric acid among pre-menopausal and post-menopausal HIV infected women in NnamdiAzikiwe University Teaching Hospital (NAUTH), Nnewi. A total of eighty-eight (88) HIV positive women on antiretroviral therapy and control participants between the age of 18 and 65 years were randomly recruited from HIV clinic of NAUTH, Nnewi and grouped thus; Group A (25 premenopausal HIV infected women with osteoarthritis), Group B (21 premenopausal HIV infected women without osteoarthritis) both within the age range of 18-39. Group C (21 post-menopausal HIV infected with osteoarthritis), Group D (21 post-menopausal HIV infected without osteoarthritis), both within the age range of 44-63 years. Blood sample was collected using plain tubes and CRP and uric acid levels were determined using standard techniques. The study observed significantly increased CRP and uric acid levels in pre and post menopausal HIV women with osteoarthritis compared to their corresponding controls. CRP level was significantly increased in post-menopausal HIV women with osteoarthritis compared to premenopausal HIV women with osteoarthritis. No significant correlation was observed in CRP and uric acid when correlated with age and BMI. This suggests significant degree of inflammation in the affected individuals which may have been the reason for osteoarthritis

Keywords HIV, menopause, uric acid, C-reactive protein, osteoarthritis Nigeria.

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INTRODUCTION

Human Immunodeficiency Virus is recognized as a disease that affects both men and women. Nigeria has the second largest HIV epidemic in the world [1] and 58% of these people living with HIV are women [2]. Women are increasingly at high risk of becoming HIV positive due to their biological vulnerabilities (Women's vagina have larger mucosal surfaces also the fragile tissues of the vagina can tear slightly during sex and let the virus enter the body, thus increasing risk of infection), low socio-economic status, dominant sexual practice of males and epidemiological factors [3]. Women suffer from the same complications of HIV infection as men, but also suffer gender-specific manifestations. Gynecological complications are critically important because they are the most commonly reported conditions of women living with HIV and can be more serious and difficult to treat. In earlier stages of the HIV pandemic, the principal concerns surrounding HIV infection in women centered on sexual and reproductive health, largely due to the high rates of HIV infection among women of reproductive age and the risks of vertical transmission. However, in the current era of increasingly accessible and efficacious Anti-Retroviral Therapy, and longer life expectancies, HIV in the context of increased age becomes a key clinical consideration [4, 5]. Consequently, issues pertaining to age-related comorbidities and other life events, including menopause, represent an emerging aspect of HIV care [6]. HIV infected women were reported to lose ovarian follicular function earlier in life than uninfected women leading to an early onset of menopause among them [7].

Menopause specifically, refers to a period of amenorrhea of at least 12 months due to the loss of ovarian function, which occurs in the absence of any other physiologic or pathologic process. This is however, contrary to other forms of menopause that can result from other pathological conditions [8]. In women living with HIV, an intricate relationship between HIV and menopause appears to exist in that HIV may influence the natural history, experience, and complications of menopause, while menopause itself could potentially influence the course of HIV infection [9]. This bidirectional relationship between HIV infection and menopause confers an additional layer of complexity to the ongoing management of HIV-infected women as they age, and presents new and vaguely understood challenges for clinicians. The onset of menopause has been associated with an increased risk for many medical illnesses, including Osteoarthritis, cardiovascular disease, hypertension, diabetes, and osteoporosis, and an earlier age at the onset of menopause increases the risk for these diseases [10]. A large epidemiological study was conducted in Italy, gave epidemiological support to the hypothesis that estrogen deficiency seen in postmenopausal women living with HIV may increase the risk of Osteoarthritis [11]. Inflammation may also have a contributive role in the development and progression of Osteoarthritis. The role of inflammation in the pathophysiology and progression of early osteoarthritis is supported by the observation that C-reactive protein levels are raised in women with early knee osteoarthritis, and higher levels predict those whose disease will progress [12]. C-reactive protein is an acute phase inflammatory protein whose levels are known to increase dramatically in response to injury, infection, and inflammation. Furthermore, uric acid levels are strongly associated with the severity of osteoarthritis and linked to disease progression over time [13].

A variety of risk factors have been identified in the initiation and/or progression of osteoarthritis including age, gender,

traumatic injury, obesity, metabolic dysfunction, and environmental and genetic factor [14]. Despite extensive research over the past 20 years to delineate the pathogenic mechanisms of osteoarthritis, a full understanding of the initiators of the disease and the factors that accelerate osteoarthritis progression are yet to be achieved. Furthermore, there is no clinical diagnosis for early osteoarthritis seen in HIV infected women and no effective disease-modifying treatment of late osteoarthritis other than pain-relieving medication or the replacement of damaged joints [14]. This work may therefore provide valuable information on the early diagnosis and management of the affected individuals.

MATERIALS AND METHOD

Study Area

This study was carried out at Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria. The study participants that are within the age range of eighteen to sixty-five years were recruited from HIV clinic of Nnamdi Azikiwe University Teaching Hospital, Nnewi. Analysis of samples was performed at Chemical pathology laboratory, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria.

Study design

This is a case control study designed to evaluate the serum levels of C-reactive protein and Uric acid in premenopausal and postmenopausal HIV infected women with Osteoarthritis in Nnewi, Anambra state, Nigeria. Subjects within the age of eighteen to sixty-five years were randomly recruited from the HIV Clinic, Nnamdi Azikiwe University Teaching Hospital, Nnewi. Written consent was obtained from participants and questionnaire was administered to obtain their bio-data. A total of 88 subjects were randomly recruited for the study. These includes twenty five (25) premenopausal HIV positive women with Osteoarthritis, twenty one (21) postmenopausal HIV positive women with Osteoarthritis, twenty one (21) premenopausal HIV positive women without Osteoarthritis, and twenty one (21) postmenopausal HIV positive women without Osteoarthritis.

Inclusion criteria

Premenopausal HIV positive women with osteoarthritis, Postmenopausal HIV positive women with osteoarthritis, Premenopausal HIV positive women without osteoarthritis and postmenopausal HIV positive women without osteoarthritis, who fell within the age limit of eighteen(18) to sixty-five (65) years were included in this study. All the test participants used in the present study were stage two HIV and have been on ART for not less than six months.

Exclusion criteria

Women with a known history of liver and cardiovascular diseases, high blood pressure (hypertension), and diabetes mellitus were excluded. Also pregnant women, nursing mothers, women undergoing hormone therapy, alcoholics, smokers and those outside the age bracket were excluded.

Collection of samples

Five milliliters (5ml) of venous blood was collected aseptically from each of the subjects, dispensed in a plain container (serum container) and was allowed to clot undisturbed. The serum sample was then separated by centrifugation at 5000 rpm for 5minutes for evaluation of serum C-reactive protein and uric acid levels.

Determination of C-reactive protein

The serum level of C-reactive protein was determined by sandwich Enzyme Linked immunosorbent assay as described by Macy *et al* [15].

Principle of the Assay

The hsCRP ELISA is based on the principle of a solid phase enzyme linked immunosorbent assay. The assay system utilizes a unique monoclonal antibody directed against a distinct antigenic determinant on the CRP molecule. This mouse monoclonal anti-CRP antibody is used for solid phase immobilization (on the microtitre wells). A goat anti-CRP antibody is in the antibody enzyme (horseradish peroxidase) conjugate solution. The test sample is allowed to react simultaneously with the two antibodies, resulting in the CRP molecule being sandwiched between the solid phase and enzyme linked antibodies. After 45 minutes incubation at room temperature, the wells are washed with water to remove unbound labeled antibodies. A tetramethylbenzidine (TMB) reagent is added and incubated for 20 minutes, resulting in the development of blue color. The color development is stopped with the addition of 1N HCL changing the color to yellow. The concentration of CRP is directly proportional to the color intensity of the test sample. Absorbance is measured spectrophotometrically at 450nm.

Determination of Uric Acid

Serum uric acid was determined by quantitative fluorometric method as described by Shani *et al* [16].

Principle of the Test

Uric acid reacts with water and oxygen in the presence of the enzyme uricase to produce allantoin and hydrogen peroxide (H2O2). In the presence of HRP (Horseradish peroxidase), a Fluorescence Probe reacts with H2O2 in a 1:1 stoichiometry to produce a highly fluorescent product. This fluorescent product can be easily read by a fluorescence microplate reader with an excitation of 530-560 nm and an emission of 590 nm. Fluorescence values are proportional to the uric acid within the samples. The uric acid content in unknown samples is determined by comparison with its respective standard curve.

Statistical analysis

Statistical Package for Social Science (SPSS) version (2000), Student's t-test and Analysis of Variance (ANOVA) were used for statistical analysis of data. Data was presented as mean ± Standard deviation (SD). Values were deemed significant at $P< 0.05$. Correlation of parameters was determined using the Pearson's Correlation Coefficient.

RESULTS

Table 1: Shows the characteristics of the pre-menopausal study group. Its shows the frequency distribution based on age ranges and BMI of the pre-menopausal study group. Forty six (46) pre-menopausal HIV infected women were recruited and 54.7% have osteoarthritis (test group) while 45.7% are without osteoarthritis (control group). For the test group, 64.0% are within the age range of 29-39 years and 88.0% have normal weight. For the control group, 66.7% are within the age range of 29-39 years and 89.1% have normal weight.

Table 1: Characteristics of the pre-menopausal study group

Parameters	With osteoarthritis	Without osteoarthritis	Total
No. of participants	25(54.3%)	21(45.7%)	46(100%)
Age range			
18-28	9(36.0%)	7(33.3%)	16(34.7%)
29-39	16(64.0%)	14(66.7%)	30(65.2%)
Body Mass Index (BMI)			
Underweight	1(4.0%)	0(0.0%)	1(2.2%)
Normal weight	22(88.0%)	19(90.5%)	41(89.1%)
Over weight	2(8.0%)	2(9.5%)	4(8.7%)
Obese	0(0.0%)	0(0.0%)	0(0.0%)
Age average	30.60±5.16[a]	30.38±4.74[a]	
BMI average(kg/m^2)	22.76±1.63[a]	22.91±1.74[a]	

"a" = value reported in mean and standard deviation.

Table 2: Shows the characteristics of the post-menopausal study group. Its shows the frequency distribution based on age ranges and BMI of the post-menopausal study group. Forty two (42) post-menopausal HIV infected women were recruited and equal percentage (50%) of those with osteoarthritis (test group) and those without osteoarthritis (control group) were able to be recruited. For the test group, 61.9% are within the age range of 44-53 years and 76.20% have normal weight. For the control group, 66.7% are within the age range of 44-53 years and also 76.20% have normal weight.

Table 2: Characteristics of the post-menopausal study group

Parameters	With osteoarthritis	Without osteoarthritis	Total
No. of participants	21(50.0%)	21(50.0%)	42(100%)
Age range			
44-53	13(61.9%)	14(66.7%)	27(64.3%)
54-63	8(17.4%)	7(33.3%)	15(35.7%)
Body Mass Index (BMI)			
Underweight	0(0.0%)	0(0.0%)	0(0.0%)
Normal weight	16(76.2%)	16(76.2%)	32(76.2%)
Over weight	5(23.8%)	5(23.8%)	10(23.8%)
Obese	0(0.0%)	0(0.0%)	0(0.0%)
Age average	52.90±4.74[a]	51.42±4.17[a]	
BMI average(kg/m^2)	24.05±1.54[a]	24.08±1.32[a]	

"a" = value reported in mean and standard deviation.

Table 3: Shows the association of C-reactive protein and uric acid between pre-menopausal with osteoarthritis (test group) and without osteoarthritis (control group) determined via independent sample – T test. The means and standard deviations with significant levels (P-values) are also presented. There was no significant difference in the level of C-reactive protein between premenopausal HIV infected women with osteoarthritis (test group) and without osteoarthritis (control group) (P>.05).

There was a significant increase in uric acid level in premenopausal HIV infected women with osteoarthritis (test group) compared with those individuals without osteoarthritis (control group) (P<.05).

Table 3: The association of C-reactive protein and uric acid between pre-menopausal with osteoarthritis and without osteoarthritis

Parameters	Frequency	C-reactive protein(mg/L)	Uric acid (µmol/L)
With Osteoarthritis	25	0.06±0.04	353.24±67.15
Without Osteoarthritis	21	0.04±0.03	256.76±42.87
t-value		1.03	5.68
P-value		0.31	0.00[b]

"b" = Significant at P ≤ .05.

Table 4: Shows the association of C-reactive protein and uric acid between post-menopausal with osteoarthritis (test group) and without osteoarthritis (control group) determined via independent sample – T test. The means and standard deviations with significant levels (P-values) are also presented. There was significant increase in C-reactive protein and uric acid levels in post-menopausal HIV infected women with osteoarthritis (test group) when compared with post menopausal women without osteoarthritis (control group).

Table 4: The association in C-reactive protein and uric acid between post-menopausal with osteoarthritis and without osteoarthritis

Parameters	Frequency	C-reactive protein(mg/L)	Uric acid (µmol/L)
With Osteoarthritis	21	0.16±0.09	332.67±73.15
Without Osteoarthritis	21	0.03±0.02	261.62±42.32
t-value		6.03	3.85
P-value		0.00[b]	0.00[b]

"b" = Significant at P ≤ 0.05.

Table 5: Shows the association of C-reactive protein and uric acid between pre-menopausal and post-menopausal with osteoarthritis (both are test groups) determined via independent sample – T test. The means and standard deviations with significant levels (P-values) are also presented.

There is significant increase C-reactive protein level in post-menopausal HIV infected women with osteoarthritis when compared with their pre-menopausal counterparts (P< .05).

Conversely, there was no significant difference in the level of uric acid between pre-menopausal and post-menopausal HIV infected women with osteoarthritis (both are test groups).

Table 5: The association in C-reactive protein and uric acid between pre-menopausal and post-menopausal with osteoarthritis

Parameters	Frequency	C-reactive protein (mg/L)	Uric acid (µmol/L)
Pre-menopausal	25	0.06±0.04	353.24±67.15
post-menopausal	21	0.16±0.09	332.67±73.15
t-value		-4.72	0.99
P-value		0.00[b]	0.33

"b" = Significant at P ≤ 0.05.

Table 6: Shows the Pearson bivariate correlation of C-reactive protein and uric acid level with age and BMI of pre-menopausal HIV infected women with osteoarthritis. The Pearson correlation values and significant levels (P-values) are also presented.

There was no significant correlation in C-reactive protein and uric acid between age and BMI in pre-menopausal HIV infected women with osteoarthritis.

Table 6: The correlation of C-reactive protein and uric acid level to the age and BMI of pre-menopausal with osteoarthritis

Parameters	Age (P-value)	BMI (P-value)
C-reactive protein (mg/L)	-0.01(0.96)	0.33(0.10)
Uric acid (µmol/L)	-0.16(0.44)	0.29(0.16)

Table 7: Shows the Pearson bivariate correlation of C-reactive protein and uric acid with age and BMI in post-menopausal HIV infected women with osteoarthritis. The Pearson correlation values and significant levels (P-values) are also presented.

Since the p- value for correlation to age and BMI (0.88 and 0.15 respectively) are greater than the α-value (0.05. There is no significant correlation of the level of C-reactive protein to age and BMI in post-menopausal HIV infected women with osteoarthritis. There is no significant correlation between uric acid, age and BMI in post-menopausal HIV infected women with osteoarthritis.

Table 7: The correlation of C-reactive protein and uric acid level to the age and BMI of post-menopausal with osteoarthritis

Parameters	Age(P-value)	BMI (P-value)
C-reactive protein (mg/L)	-0.03(0.88)	0.15(0.52)
Uric acid (µmol/L)	0.18(0.43)	-0.18(0.42)

DISCUSSION

The relationship between HIV infection and osteoarthritis is poorly studied. The virus has widespread systemic effects including the musculoskeletal system which has been linked to osteonecrosis, osteopenia, bone and joint tuberculosis and septic arthritis from unknown origin [17]. It is therefore highly imperative to ascertain if these conditions are associated with age, HIV infection itself or the HAART, as it may give more in sight on the specific diagnostic biomarkers, with more promising treatment options. .

The present study showed that serum level of uric acid in both pre-menopausal and post-menopausal HIV infected women with osteoarthritis is significantly elevated compared to those of pre-menopausal and post-menopausal HIV infected women without osteoarthritis respectively. Our study is similar to previous finding by other researchers [18-20]. The second author reported an independent relationship between menopause and higher serum uric acid levels [19]. However, this finding is contrary to many other studies on uric acid which showed no association between it and osteoarthritis [21]. Felson *et al*., [22] found a positive association between knee osteoarthritis and uric acid but the association was insignificant. This difference might be as a result of the study population or ART used. Some previous studies have implicated some antiretroviral drugs such as stavudine in the as contributory factor for OA in HIV infected individuals [23, 24] though our present study is focusing on menopausal HIV infected women with OA. The present study was based on HIV infected women whereas the previous studies were based on the general population and irrespective of gender. However, the increase observed in this study can be explained with the report of Kono *et al*., [25] who stated that uric acid regulates the inflammation induced by tissue injury. Additionally, other study by Crisan *et al*., [26] attributed the positive effect to chronic hyperuricemia which may trigger inflammatory responses thereby, motivating the release of IL-1β in peripheral blood leukocytes. Some research has shown that estrogen deficiency can result to increased risk of Oetoarthritis [27, 28] though it's regulated through complex molecular pathways [29, 30]. They attributed the OA observed to loss of ovarian function which may perhaps be as a result of menopause.

The serum level of uric acid between pre-menopausal and post-menopausal HIV infected women with osteoarthritis appeared to be higher in pre-menopausal HIV infected women but was not statistically significant. This is contrary to the findings of Hak and Choi [31] and Aung *et al*., [32]. Both reported uric acid serum elevation in post-menopausal women compared to pre-menopausal women. The difference may be due to the beneficial effect of highly active antiretroviral therapy (HAART). Also the increase in serum level of uric acid in pre-menopausal HIV infected women may be attributed to the facts in literature that osteoarthritis in post-menopause is mainly primary osteoarthritis with no cause other than aging effect whereas osteoarthritis in pre-menopause is due to secondary arthritis involving a known reason such as joint instability, congenital, or mal-positioning of the joints [33]. The later appear to have more inflammatory injury than the former, hence the high serum uric acid level which is as a result of its anti-inflammatory regulatory function.

Also, this present study assessed the association of serum level of C-reactive protein (CRP) in both pre-menopausal and post-menopausal HIV infected women with osteoarthritis to those of pre-menopausal and post-menopausal HIV infected women without osteoarthritis respectively. It was observed that pre-menopausal and post-

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menopausal HIV infected women with osteoarthritis have significantly higher CRP level compared to those of pre-menopausal and post-menopausal HIV infected women without osteoarthritis respectively. Our study is supported by the findings of Jin *et al*., [34] and Perruccio *et al*., [35] who reported significantly higher CRP concentration in women with osteoarthritis.

The serum level of CRP between pre-menopausal and post-menopausal HIV infected women with osteoarthritis appeared to be higher in post-menopausal HIV infected women and was statistically significant. This is in consistent with the report of Aung *et al*., [32] and Suguna and Mary, [36] who also observed high serum CRP level in post-menopausal women compared to pre-menopausal women. Menopause has been associated with inflammation and CRP and uric acid have also been implicated [37, 38], hence the increases in CRP and UA in post menopausal HIV infected women. Increased levels of CRP and uric acid in some other patients with cardiac syndrome X have also been reported elsewhere Eroglu *et al*., [39]. Further study has reported associated increased risk of cardiovascular and metabolic diseases to hyperuricaemia and this form its basi in the induction of systemic inflammation [40].

Inflammatory disorders generally in the body have been implicated in increasing blood pressure while diminishing the presence of nitric oxide in the endothelial cells thereby resulting in vasocontriction [39]. Vasoconstriction on the other hand, have been reported to reduce blood supply to the joints and other parts of the body resulting in hypoxia and compromised joint function that may lead to the development of osteoarthritis [41].

However, this study observed no statistically significant correlation in CRP and uric acid with age and BMI in pre-menopausal and post-menopausal HIV infected women with osteoarthritis. Our study was in consistent with the previous findings by [42] but contrary to the study reported by Oluboyo *et al*., [43]. The difference may be as the result of the study population which involved general women population with no regards to osteoarthritis. Also, our study did not observe significant result in BMI across the group of individuals studied. Obesity has been strongly associated with increased CRP [42], which can result to significant degree of systemic inflammation in menopausal women.

CONCLUSION

Based on the result of this study, CRP and uric acid levels increases in HIV infected women with osteoarthritis than those without osteoarthritis irrespective of their menopausal status. Also, CRP was observed to increase in menopausal HIV infected women with osteoarthritis than those without osteoarthritis but has no effect on their uric acid level. However, high serum CRP and Uric acid are strongly associated with inflammation which must have been the reason for osteoarthritis. Further neglect to these conditions may predispose the affected women to gout and other cardiovascular and metabolic diseases. These parameters should be employed by clinicians as modules for routine diagnosis of bone problems in HIV management.

Ethics statement

The ethical approval for this study was obtained from the board of ethics committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria, while, the informed consent was sought and obtained prior to the study

Availability of data and material

The authors confirm that the data supporting the findings of this study are available within the article

Competing interest

Authors declare no conflict of interest.

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Authors' contributions
Conceptualization, N RU; Data curation, OAM, GEU,and BCU; Formal analysis, OAM, GEU and BCU; Investigation, OAM and OAK; Methodology, NRU and ACI; Project administration, OAM; Resources, OAM and OAK; Software, OAM, ACI and OAK; Supervision, NRU and ACI; Validation, NRU and ACI; Visualization, NRU and ACI; Writing – original draft, NRU and OAM; Writing – review & editing, NRU, ACI, OAK, OAM, GEU, BCU.

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