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HYPERURICEMIA AND THE METABOLIC SYNDROME IN HIV$^+$ ADULTS

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ABSTRACT: Objective: Hyperuricemia is associated with metabolic syndrome in diabetics and could be a risk factor for coronary heart disease in the general population. However, there is a dearth of information on hyperuricemia and metabolic syndrome in the context of HIV and antiretroviral therapy (ART). The aim of this study was to determine the association between hyperuricemia and metabolic syndrome in HIV-infected patients attending Opportunistic Infections Clinic in Harare, Zimbabwe in 2015. **Methods**: The cross-sectional study (N=186) measured uric acid and markers of metabolic syndrome including total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and blood glucose. Demographic and anthropometric data such as: age, sex, body mass index (BMI), blood pressure, and duration of antiretroviral therapy (ART) were collected from participants and clinic records. **Results**: Of those studied, 80% were female and 20% were ART-naive. There was no difference in all biochemical and anthropometric data between ART-naïve and ART-experienced patients. Prevalence of hyperuricemia was 13% and of metabolic syndrome was 3.8%. About 1% of the population had both hyperuricemia and metabolic syndrome and positive correlation was found between hyperuricemia and BMI, depressed HDL-C and hypertension. However, there was no association between hyperuricemia and metabolic syndrome in all the participants. **Conclusion**: Though there was no association between hyperuricemia and metabolic syndrome, significant association was found between hyperuricemia and BMI, hypertension and depressed HDL-C, respectively. Hyperuricemia may be a risk factor for coronary heart disease via obesity, depressed HDL-C and hypertension.

KEYWORDS: Hyperuricemia; metabolic syndrome; HIV; ART; Zimbabwe

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1. INTRODUCTION

Metabolic syndrome is a cluster of interrelated metabolic factors that are associated with increased risk of developing coronary heart disease. It has been suggested that hyperuricemia be included as a biochemical marker for metabolic syndrome along with the traditional lipids, glucose, hypertension and obesity [1]. Metabolic syndrome is also a common feature in HIV positive patients although, it is not very clear as to the association between HIV infection, and metabolic syndrome due to contradicting information [1, 2]. Of late, hyperuricemia has gained increasing importance as it has been found by some researchers to be associated with coronary heart disease risk and to play a role in the development metabolic syndrome in diabetics [3]. Hyperuricemia has also been associated with increased risk of coronary heart disease in the general population, in people with hypertension, in people already with coronary heart disease and in those with metabolic syndrome [4]. Some studies have documented a positive correlation between hyperuricemia and coronary heart disease, while others have stated a negative correlation. Those that state a negative correlation suggest that hyperuricemia is not an independent risk factor for coronary heart disease but will increase the risk if there is already a risk for coronary heart disease [5, 6, 7]. Disturbances in uric acid metabolism have prior been associated with HIV infection [1]. Though hyperuricemia is observed, prevalence of gout has been reported to be very low (less than 1%) in patients on antiretroviral therapy (ART) [1, 8]. On the other hand, the introduction of ART has changed the clinical picture of HIV infection by reducing morbidity and mortality rates in the population. However, long-term use of ART has led to toxicities and metabolic changes that have become challenges to the successful management of HIV infection [9, 10]. Hence, up to 25% of patients may stop taking their initial ART partly due to adverse side effects [10]. Physiologic disorders associated with long term ART use include dyslipidemia, insulin resistance, glucose metabolism abnormalities, osteoporosis, hypertension, changes in fat distribution and hyperuricemia among others [11, 12]. With respect to uric acid metabolism, ART drugs used in HIV treatment affect serum uric acid concentration differently. Didanosine, stavudine and ritonavir-containing antiretroviral regimens have been known to cause acute hyperuricemia and gout. Tenofovir is associated with hypouricemia and abacavir has been observed to have a neutral effect on uric acid concentration. Abacavir and tenofovir could therefore be considered to be good drug choices for HIV-infected people with hyperuricemia [1, 8, 13]. In the context of coronary heart disease risk, studies have shown that hyperuricemia directly stimulates the production of inflammatory mediators, like C-reactive protein (CRP) in vascular cells [14]. The findings suggest that uric acid is an endothelium-injuring factor and it is therefore justified to consider hyperuricemia as an important risk factor for hypertension and vascular disease [14]. Uric acid also causes a decreased production of adiponectin, a plasma protein secreted from adipose tissue with anti-inflammatory, anti-oxidative, and vasodilator effects. Hence hyperuricemia causes both vessel injury and an adiponectin deficiency, increasing risk of artherosclerosis and coronary heart disease [15]. This study focussed on HIV patients, both ART-

experienced and ART-naïve, to assess the effects of ART on uric acid levels, and find out if there is association with metabolic syndrome in this group of patients.

2. MATERIALS AND METHODS

Setting

This study was a cross sectional study done on HIV infected patients attending treatment at an Opportunistic Infections Clinic in Harare, Zimbabwe.

Ethical considerations

The study was ethically cleared by the Joint Research Ethics Committee of the University of Zimbabwe and Parirenyatwa Group of Hospitals (JREC). Participants were informed about the study, its risks and benefits before giving written consent. To keep the confidentiality of the participants, no names or other personal details were used and participants were assigned unique codes as identifiers.

Participants

HIV^+ adults (ART-experienced and ART-naive), aged 18 years and above who met inclusion criteria were recruited into the study.

Inclusion criteria

HIV^+ adults (ART-experienced and ART-naïve) who are able to give written informed consent

Exclusion criteria

Patients on anti-TB drugs, with hepatic disorders, with renal disease, those who are documented alcoholics and those taking uric acid lowering drugs

Sample and data collection

Blood was collected into EDTA tubes and plasma was separated within 12 hours and stored at -80^0C until assay. Uric acid levels and markers of metabolic syndrome including total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and glucose were measured on the Mindray BS120 analyser. Height and weight measured were used to calculate body mass index (BMI). Weight was measured in kilograms and height in meters. BMI was calculated as: $mass/height^2$ (kg/m^2). Blood pressure was measured using a clinical sphygmomanometer.

Statistical analysis

Statistical analysis was done using STATA® version 13 (Texas, USA). Categorical data were analyzed using chi-square tests. Continuous variables were compared using student's t-tests. Univariate linear regression analysis was used to assess associations of hyperuricemia with individual markers of metabolic syndrome and metabolic syndrome, respectively.

Definition of Metabolic Syndrome

Using the National Cholesterol Education Program (NCEP) Adult Treatment Plan (ATP) definition, metabolic syndrome was defined as a condition where a person has 3 or more of the following (1):

i. Glucose > 6.0 mmol/L or on anti-diabetic treatment

ii. Triglycerides >1.69 mmol/L or on treatment

iii. HDL-C: <1.04 mmol/L in men and 1.29 mmol/L in women

iv. Body Mass Index (BMI) > 30kg/m2 (or waist circumference ≥ 102 cm in men and ≥ 88 cm in women)

v. High Blood Pressure/Hypertension: SBP>130mmHg and DBP>85mmHg or on anti-hypertension medication

3. RESULTS AND DISCUSSION

Table 1 shows the demographic and clinical data of all the participants, including age, sex, BMI and blood pressure. The average age for both males and females was 40.1 ± 10.1 years.

Table 1: Demographic and clinical data of participants

Characteristic	**Number (%)**
Number of participants	186 (100)
Sex: male (%) female (%)	38(20.4) 148 (80.6)
Smoking history (%)	5 (2.7)
History of heart disease (%)	10 (5.4)
History of stroke (%)	9 (4.3)
Characteristic	**Mean ± SD**
Age (years)	40.1 ± 10.I
BMI (kg/m^2)	24.5 ± 4.9
SBP (mmHg)	125.4 ± 18.9
DBP (mmHg)	81.4 ± 15.7

SD, standard deviation; BMI, body mass index; n, number; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

The age distribution of participants by males and females is shown in Figure 1.

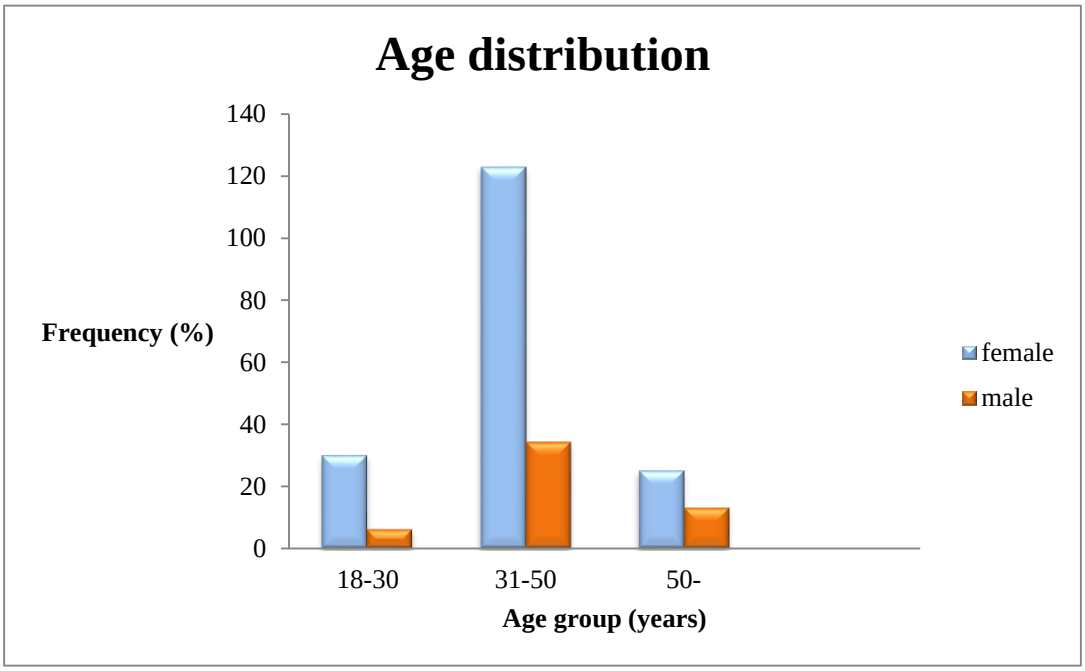

Figure 1: Age distribution of participants, by sex

Most of the participants (80%, n=149) were ART-experienced. Of those on ART, only 5% (n=7) were on protease inhibitor (PI)-based second line ART while the rest were on first line ART comprising lamivudine, tenofovir and either nevirapine or efavirenz. Most reported that the main reason they attended the opportunistic infections (OI) clinic for the first time was to seek treatment for opportunistic infection such as tuberculosis, diarrhoea and severe cough. When participants were compared by ART experience there was no difference in mean levels of glucose, lipids (TC, HDL-C, LDL-C), uric acid and BMI, respectively (Table 2).

Table 2: Comparison between ART-naive and ART-experienced patients

Statistic Mean ±SD	**ART-naïve (n=37,20%)**	**ART-experienced (n=149, 80%)**	**P-value**
RBS (mmol/L)	5.0 ±0.9	5.2 ± 0.9	0.217
TC (mmol/L)	3.69 ± 0.7	4.06 ±1.2	0.115
LDL-C(mmol/L)	2.57 ± 0.7	2.45 ± 1.0	0.563
TC/HDL-C ratio	3.1 ± 1.0	3.5 ±2.4	0.327
HDL-C (mmol/L)	1.30 ±0.4	1.34 ± 0.5	0.657
BMI (kg/m^2)	24.1 ± 4.9	24.5 ± 4.9	0.636
Uric acid(µmol/L)	252.6 ±88.1	246.6 ± 84.1	0.734

SD, standard deviation; ART, antiretroviral therapy; RBS, random blood sugar; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; BMI, body mass index

Mean uric acid concentration for all participants was 248 ±85µmol/L. The proportion of HIV patients with hyperuricemia was 13% (n=24) and proportion of patients with metabolic syndrome was 3.8% (n=7). Approximately 1% (n=2) of patients had both hyperuricemia and metabolic syndrome. Table 3 shows the P-values and r^2 values obtained from univariate regression analysis for association between uric acid and individual markers of metabolic syndrome such as blood glucose, lipids and body mass index. Table 4 shows P-value and r^2 values for association between hyperuricemia and metabolic syndrome.

Table 3: Association between hyperuricemia and markers of metabolic syndrome using univariate linear regression analysis

Hyperuricemia	**r^2 value**	**P-value**
RBS	0.0092	0.1960
TC	0.0117	0.1474
LDL-C	0.0000	0.9447
TC/HDL-C	0.0198	0.0570
HDL-C	0.0360	0.0104
BMI	0.0314	0.0161
Hypertension		
SBP	0.0759	0.0002
DBP	0.0311	0.0167

r^2, coefficient of determination; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 4: Association between hyperuricemia metabolic syndrome using univariate linear regression analysis

Hyperuricemia	**r^2 value**	**P-value**
Metabolic syndrome	0.00017	0.5460

r^2, coefficient of determination

Most of the 186 participants were women (80%) (Table 1), young adults (<50 years) (Figure 1) and were mostly ART-experienced (80%). The demographic and biochemical data for the ART-naive and ART-experienced participants (Table 2) showed little significant difference between the two groups (P>0.05). In contrast, many earlier studies report differences due to ART exposure, as ART is thought to cause metabolic syndrome [16]. The reason for the difference obtained in this study might be due

to the small number of ART-naïve participants as opposed to the ART-experienced participants (Table 2). This can be explained by the fact that most participants at the study site had to be introduced to ART as soon as they started attending the OI clinic due to opportunistic infections. A larger study group may however be needed in future to increase the power of the study. The prevalence of hyperuricemia was 13% in HIV-infected individuals. The results showed that 3.8% of the participants had metabolic syndrome, and only 1.1 % had both hyperuricemia and metabolic syndrome. From the results obtained, for association between hyperuricemia and individual markers of metabolic syndrome, univariate regression analysis showed association between hyperuricemia with some metabolic syndrome components (HDL-C, BMI, SBP and DBP) but no association for some (RBS, TC, LDL-C and TC/HDL-C) (Table 3). These results are in contrast to many earlier studies which reported an association between hyperuricemia and metabolic syndrome [17]. Different mechanisms have been suggested to link the association between hyperuricemia and hypertension (high SBP and DBP). Hyperuricemia has been suggested as either the cause of hypertension or the result of hypertension. Other studies suggest that hyperuricemia could both be a cause and a consequence of hypertension [18]. Traditionally, metabolic syndrome has been defined to include low HDL-cholesterol, high triglycerides, hypertension, and hypergylcemia or diabetes mellitus [19]. Studies done over the years have brought forward increasing evidence that uric acid levels play a role in metabolic syndrome, stroke and coronary heart disease. The role of uric acid in these diseases is not very clear and currently under debate, and whether hyperuricemia should be included in the definition for metabolic syndrome [3, 20]. This is because it is usually accompanied by other risk factors such as hypertension, obesity, dyslipidemia, dietary factors and lack of exercise [21, 22, 23]. There was no association between hyperuricemia and metabolic syndrome in HIV-infected individuals in the current study, ($p=0.5460$) (Table 4). The main limitation of this study was the fact that fasting glucose and triglycerides were not measured. This is because some patients were not fasting as required for the two biochemical measurements. These two are important in identifying metabolic syndrome in participants. Instead, three components were used to define metabolic syndrome (hypertension, BMI and low HDL-cholesterol) and the participant had to have all of them. This may explain the low percentage of metabolic syndrome as compared to the prevalence found in other studies. Another limitation of the study was the small number of the ART-naive participants as most participants had already started ART. A higher number of ART-naïve participants is needed to increase the power of study.

4. CONCLUSION

In conclusion, no significant association was found between hyperuricemia and metabolic syndrome, but significant associations were found between hyperuricemia and BMI, hypertension and low HDL-cholesterol in the group of HIV-infected adults studied. Hyperuricemia is therefore a risk factor for coronary heart disease due to its association with factors known to increase risk of coronary heart

disease in the general population.

CONFLICT OF INTEREST

No conflict of interest to declare

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