Hyperuricemia, its Prevalence and Correlation with Metabolic Syndrome in Anti-Retroviral Naïve HIV Cohort: Review of the Literature

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Abstract

Objective: Hyperuricemia is associated with HIV infection. We studied newly diagnosed and Anti retroviral drugs naïve HIV patients. We correlated an association of HIV infection to hyperuricemia and metabolic syndrome (MetS).

Methods: Retrospective study of 283 patients, who had initial uric acid panel, CD4 counts, HIV viral load, triglycerides levels and blood sugar, were selected. Age, gender, ethnicity, BMI, and B.P were also recorded. Our data was analyzed by logistic regression analysis. WHO defined MetS criteria was used.

Results: Among the study population (n=283), the prevalence of uric acid>7 mg/dl was found in 18.4%. HIV patients in our study had mean age of 38.2 yrs (S.D. 11.6 yrs) and included 68.9% males. African American ethnicity predominated by 77.7%. BMI median was 25.2 (range 13.3-63.9). Race, CD4 count and viral load were not significant in univariate analysis. In the multivariate logistic model, uric acid>7 mg/dl was significantly associated with increasing BMI and age, male gender and co-morbidities [Type 2 Diabetes mellitus (DM), Hypertension (HTN) or both]. In a separate model of MetS, 3.2% (n=9) of patients had all 3 variables of MetS and uric acid>7 mg/dl. These 9 patients with all 4 variables had significant ODDS ratio of 12.7 and p=0.002.

Conclusion: Hyperuricemia had a prevalence of 18.4%. Our HIV+MetS model showed a higher association of hyperuricemia with increasing age, BMI, and male gender. Hyperuricemia, when present in HIV population seems to be a harbinger and a marker of MetS. Early therapeutic intervention by detecting this high-risk conundrum of hyperuricemia, HIV infection and MetS will help prevent cardio and cerebro-vascular events, and co-morbidities in this population.

Keywords

HIV infection; Hyperuricemia; Metabolic syndrome

Introduction

In the world, the incidence of HIV infection is rising. In 1990, there were 8 million people infected with HIV, and in 2010, UNAIDS reported the infected population of 34 million with HIV/AIDS worldwide. Since the beginning of the epidemic, racial and ethnic minorities have been disproportionately affected by HIV/AIDS.

Hyperuricemia is associated with HIV infection. It is unclear and data is very scarce as to the exact cause of hyperuricemia, and its relation to MetS in HIV infected patients. Most studies and HIV cohorts with MetS, and hyperuricemia had adverse effects of anti-retroviral or other drugs. This intrigued us to study these HIV+ patients, who were newly diagnosed and anti-retroviral drugs naïve. We were also curious to find an association of hyperuricemia in vulnerable HIV cohort to metabolic syndrome.

With the rise in HIV infected population, association of hyperuricemia and hypouricemia has been observed as well. In advanced HIV infection, hypo- and hyperuricemia can be considered as markers of neoplasia [1]. Despite hyperuricemia, prevalence of gout is very low as found by different groups of authors. 1% prevalence of gout has been reported in a study that had majority of patients on highly active anti retroviral therapy (HAART) [2,3]. Stavudine, Didanosine [4] and ritonavir-containing antiretroviral regimens [3] have been known to cause acute gout. Tenofovir (hypouricemia) and Abacavir (neutral effect) are good choices for hyperuricemic patients [4]. Despite the prevalence of 18.4% with hyperuricemia in our study, only 1 patient had recurrent gout. Low prevalence of gout is not studied very well.

Hyperuricemia in HIV infection has multi-factorial mechanisms. Infections, autoimmune disorders, cachexia resulting from hypermetabolic states [2], drugs such as HAART, chemotherapy, anti-tuberculosis (pyrazinamide) and other drugs, viremia induced cell-turnover [5,6], loss of mononuclear cells [7], oxidative stress [8,9] have been all postulated culprits. Uric acid and HIV-1 virus itself can damage vascular endothelium and lead to atherosclerosis and ischemic stroke [5,8,9]. Uric acid [10] and HIV-1 can also induce NALP3 inflammassome (cytoplasmic, multimolecular protein complex) and IL1β secretion in dendritic cells [11]. Uric acid and Toll-like receptors’ synergism has been known to stimulate IL1β maturation [12]. We wanted to determine the prevalence of hyperuricemia in our newly diagnosed HIV patients. 41% prevalence of hyperuricemia has been reported previously, neoplasia were predominant in their HIV population [1]. We eliminated HAART induced adverse effects and also used newly diagnosed patients to curtail the effect of severity of the infection.

Besides its association with hyperuricemia, HIV population is prone to metabolic syndrome (MetS) as well. Metabolic syndrome (MetS) is a constellation of risk factors such as dyslipidemia, increased abdominal obesity, hypertension, glucose intolerance, and a prothrombotic/inflammatory state (triggered by uric acid), that increase the risk of cardio and cerebrovascular disease. In HIV infected patients, MetS can result from sedentary lifestyles, poor nutrition, co-morbidities ([hypertension (HTN), diabetes (DM)]) and HAART therapy (PIs can cause MetS [13,14]). We conducted our study of 283 consecutive newly diagnosed drugs naïve HIV patients, when they were enrolled in outpatient HIV clinics. We correlated our patients’ uric acid levels to BMI, age, co-morbidities (HTN, DM)
triglycerides levels (WHO definition of MetS), CD4 count and HIV viral loads.

Materials and Methods

More than 300 consecutive charts from our HIV clinics were reviewed. All patients chosen were anti-retroviral drugs and other drugs naïve. They were newly diagnosed with HIV infection. Only 283 patients were selected, as they all had uric acid along with CD4 count, HIV viral load, blood sugar (fasting) and triglycerides (fasting) on their initial panel. BMI was calculated using weight (kg) divided by height (meters) squared formula and initial blood pressure readings were recorded. Charts without uric acid and/or other missing data were not included in the study (17 patients). All patients had a record of race, ethnicity, age, BP, BMI, uric acid levels, lipid profile (triglycerides, LDL), fasting blood sugar, CD4 counts and HIV viral load, history of malignancy and concomitant infections.

Analysis of MetS

WHO definition of MetS was used in our study. We determined impaired fasting glucose as an indication of insulin resistance and type 2 diabetes, plus 2 or more of “1) BMI>30 kg/m²; 2) B.P>140/90 mm Hg and 3) triglycerides>150 mg/dl”.

Statistical analysis methods

Univariate and multivariate analysis and logistic regression models were used to determine a p value, odds ratio and confidence interval (CI). Statistical analysis methods: Demographic characteristics of patients with hyperuricemia were compared to those with no hyperuricemia using the two-sample T-test or χ²-test. BMI was compared between groups using the median test.

The relation of hyperuricemia to independent variables like age, gender, race, co morbidities (DM and hypertension), CD4 count, viral load and composite variable MetS (metabolic syndrome) were examined using logistic regression. Variables significant in univariate analysis at p ≤ 0.5 were used in the final models. Odds ratio and confidence intervals along with p value are reported for the significant variables. All analyses were conducted using STATA 7.0 (Stata Corporation). Statistical significance was determined at a P-value of 0.05 or less.

Chart reviews: Charts were reviewed by two independent individuals and then data confirmed by both individuals to avoid any personal errors.

Results

The study population consisted of 283 newly diagnosed HIV+ anti-retroviral naïve patients. Initial panels included uric acid levels. HIV+ patients in our study had mean age of 38.2 yrs (SD11.6yrs) and 68.9% were males. Ethnicities included African Americans 77.7%, Caucasians 18.4%, and unknown 3.9%. Their BMI median was 25.2 (range 13.3-63.9). Uric acid prevalence of >7 mg/dl was found in 18.4% of patients. Race, CD4 count, and viral load were not significant in univariate analysis. In the multivariate logistic model, hyperuricemia of >7mg/dl was significantly associated with increasing BMI and age, male gender and co-morbidities (HTN, DM or both) (Table 1). The graph (Figure 1) demonstrates demographic characteristics comparing normouricemic and hyperuricemic population. In our separate model of MetS, 3.2% of patients had all 3 variables of MetS (dyslipidemia, BMI and increased co-morbidities) and uric acid>7 mg/dl. These 9 patients with all variables (MetS+hyperuricemia) were significantly associated with OR of 12.7 and p=0.002.

We had 52 patients with hyperuricemia of >7 mg/dl (normal range 3.5-7 mg/dl), with mean age of 43.8 years. 44% were males and 42% were of African American ethnicity and 24% had high BMI and co-morbidities (HPT, DM) as shown in table 2.

In current study, only 1 patient had uric acid level <2 mg/dl and 1/9 patient had got associated with MetS (having all 4 variables).

We had 6 cases of malignancy- Kaposi’s sarcoma-1, GI cancer-1, lymphoma-2, ovarian cancer-1 and prostate cancer-1 (none with uric acid>7 mg/dl). We had 3 patients with chronic renal failure (1/3 with uric acid of 7.2 mg/dl).

Discussion

The prevalence of hyperuricemia of 18.4% in the anti-retroviral naïve HIV infected population is significant, and it can be used as a marker of metabolic syndrome (MetS).

Table 1: Variables associated with hyperuricemia.

<table>
<thead>
<tr>
<th>Hyperuricemia</th>
<th>Odds ratio</th>
<th>P value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1.09</td>
<td>&lt;0.0001</td>
<td>1.04-1.15</td>
</tr>
<tr>
<td>AGE</td>
<td>1.04</td>
<td>0.003</td>
<td>1.01-1.07</td>
</tr>
<tr>
<td>GENDER</td>
<td>4.95</td>
<td>0.001</td>
<td>1.94-12.63</td>
</tr>
<tr>
<td>HTN/DM</td>
<td>2.20</td>
<td>0.032</td>
<td>1.06-4.55</td>
</tr>
</tbody>
</table>

Figure 1: Demographic clinical characteristics: BMI, co-morbidities were higher in males and AA race in hyperuricemic population when compared to normouricemic population.

Table 2: Demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Hyperuricemia</th>
<th>Normouricemia</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients N (%)</td>
<td>52 (18.4%)</td>
<td>231* (81.6%)</td>
</tr>
<tr>
<td>Age (mean yrs) (SD, CI)</td>
<td>43.8 (11.7, 40.5-41.1)</td>
<td>36.9 (11.2, 35.5-38.4)</td>
</tr>
<tr>
<td>Gender Male (N, %)</td>
<td>44 (84.6)</td>
<td>151 (65.1)</td>
</tr>
<tr>
<td>Race AA (N, %)</td>
<td>42 (80.7)</td>
<td>178 (77.1)</td>
</tr>
<tr>
<td>BMI (median)</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>HTN/DM (N, %)</td>
<td>24 (46.2%)</td>
<td>44 (19.05%)</td>
</tr>
<tr>
<td>CD4 count mean (SD)</td>
<td>263 (211)</td>
<td>294.6 (259.4)</td>
</tr>
</tbody>
</table>

*1/231 patient had uric acid of 2 mg/dl


doi: http://dx.doi.org/10.4172/2329-9541.1000108
We incorporated BMI, triglyceride levels, and co-morbidities correlating with hyperuricemia to analyze the pattern of metabolic syndrome in our HIV+ cohort.

Our MetS model showed high association with an older age, BMI, males and African American ethnicity. Prevalence of MetS in HIV infection has been variable (25%-96%) [15,16]. Inter-twinning mechanisms of hyperuricemia, MetS and HIV infection are interesting and have not been explored in detail. Lipodystrophy (lipodatrophy, hypertrophy or both) can occur in HIV infection alone (21%) as reported in large Australian cohort of 1348 patients [17]. In this study, protease inhibitors (PIs) demonstrated lipodystrophy of 62%. MetS and its relevant risk factors are thus prevalent in HIV infected population.

Hyperuricemia mediates adipocyte specific pro-inflammation and increases insulin resistance as studied in the murine model of MetS [18]. Viremia induced increased cell turnover [5,6], loss of mononuclear cells [7], concomitant infections and increased oxidative stress [8,9] and catabolic states [2] can all be implicated factors for hyperuricemia in HIV patients. Increased oxidative stress leads to HIV replication and transcription through activation of nuclear factor κB [9]. Anti-retroviral drugs [protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTI)] can cause mitochondrial dysfunction, lactic acidosis, and hyperuricemia. PI’s have been implicated in causing premature atherosclerosis and MetS [13]. Intermittent use of anti-retroviral therapy can result in higher incidence of cardio-vascular events [19]. We studied patients, who were newly diagnosed and were never placed on any therapy for HIV infection.

Hyperuricemia can produce monocyte chemotactic protein-1 (MCP-1), an adipokine that plays an essential role in inducing proinflammatory state in adipocytes in obesity. Uric acid also causes a decrease in production of adiponectin, an anti-inflammatory agent and adipocyte-specific insulin sensitizer [18]. Adipokines biomolecules are adipocyte secreted cytokines with expanding list. They include leptin, adiponectin, resistin, visfatin, apelin, acylation stimulating protein, vaspin and omentin. TNF α, acute phase reactants, adipose derived interleukins are included in adipokines. Some researchers coined the term adipose derived hormones to reactants, adipose derived interleukins are included in adipokines.

We incorporated BMI, triglyceride levels, and co-morbidities correlating with hyperuricemia to analyze the pattern of metabolic syndrome in our HIV+ cohort.

According to Mangili et al. [25], HIV infected patients with MetS, had greater internal and common carotid intimal thickness (c-IMT) and cardiac calcium scores (HRCT). Hypertriglyceridemia and HIV patients had greater intimal thickness in their study. Prevalence of MetS was 23% in their group, and had most patients on HAART. There was no co-relation to MetS and PI’s.

The role of MetS in HIV infected patients with stroke was studied by Ances et al. [26]. Other causes of stroke due to HIV infection and concomitant infections were eliminated. 11 cases from a large cohort (2346 patients) were diagnosed with cryptogenic stroke associated with MetS. 82% of these cryptogenic strokes were ischemic, as observed by others as well [27,28]. Patients with strokes had higher uric acid levels (range 6.3+/- 2.2) [29]. Mean arterial pressure (HPT) and hyperuricemia were significant in their MetS and cryptogenic stroke strata. Elevated uric acid levels were associated with sub-clinical strokes as seen in white matter hyperintensities on MRI [29]. Combined triggers of uric acid and HIV-1 infection resulting in MetS can be due to production of IL1β and induction of inflammasome.

To our knowledge, our cohort is one of its kinds, where HIV patients were evaluated for hyperuricemia and MetS in a drug-naive population. We postulate that as the HIV infected population ages, MetS will become more prevalent in the future. Along with this, cardio- and cerebrovascular risks and morbidity will be on rise. In our MetS model, hyperuricemia co-existed with BMI, age and male gender. Despite hyperuricemia, incidence of gout is very low, as observed by us and others as well. Further studies need to delineate this low incidence and its mechanisms. Early treatment of dyslipidemia, co-morbidities along with, life style modifications such as exercise, diet and smoking cessation are recommended to prevent MetS in this vulnerable HIV population. Therapeutic strategies using adipokines mediated mechanisms; perhaps IL1β blockade (inflammasome-blockade) may ameliorate MetS in the future. Hydroxychloroquine through its blockade of HIV replication [30] and TLR mediated lipopolysaccharides/immune activation [31] may ameliorate MetS and is a useful immunomodulon and recommended option. Elevated uric acid levels should be used as a marker and included in early diagnosis of MetS. Larger cohort studies are needed to determine specific causes of hyperuricemia, its relation to MetS in drug-naive HIV population, where early therapeutic interventions will culminate in better life style and reduced morbidity.

Acknowledgements

We would like to thank Dr. Lynne Besch and Dr. Rebecca Clark for allowing us to use patient population from their HIV outpatient clinics.

Author’s Contribution

All authors were involved in drafting and revising the article for its final contents, and all authors approved its final version for its publication. Nirupa Patel. MD had full access to all the data, and takes the responsibility for the integrity of all contents.

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