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Increased Aldosterone Among HIV-Infected Women with Visceral Fat Accumulation

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Abstract

Increased aldosterone has been associated with obesity and the metabolic syndrome in non HIV-infected patients, but aldosterone has not been investigated among HIV-infected patients with increased visceral adipose tissue (VAT). 24-hour urine aldosterone was assessed among age and BMI-matched HIV-infected women with increased VAT, HIV-infected women without increased VAT and healthy controls. 24-hour urine aldosterone was higher in HIV-infected women with increased VAT and was associated with systolic blood pressure, VAT, and hemoglobin A1c. Increased aldosterone may contribute to the detrimental effects of excess visceral adiposity on blood pressure and glucose homeostasis among HIV patients.

Keywords

Aldosterone; Lipodystrophy; HIV; Visceral Fat

Increased aldosterone levels have been associated with the metabolic syndrome [1–3] and visceral adiposity [4] in non HIV-infected patients. Whether aldosterone is increased in association with abdominal adiposity and relates to metabolic dysregulation in HIV-infected patients is unknown. In order to begin to assess whether increased aldosterone may contribute in part to the metabolic derangements among HIV-infected patients with central fat accumulation, we investigated the relationship of aldosterone to measures of visceral fat and metabolic indices in HIV-infected women and healthy control women.

We hypothesized that aldosterone would be increased among HIV-infected women with excess visceral fat accumulation. We therefore selected three groups of patients from a prior study [5], in whom samples of 24 hour urine collections were available, for measurement of 24-hour urine aldosterone levels: 1) a control group (n=20) of non HIV-infected patients, 2) an HIV group with VAT similar to the control group (n=21), and 3) an HIV group with VAT that was increased compared to the control group (n=22), to assess the relationship of urinary aldosterone and HIV *per se* vs. increased VAT. The groups were chosen prior to the performance of the aldosterone assay, and were matched for age and BMI to the control

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group, but with distinct patterns of VAT in the two HIV groups (normal and increased). Aldosterone could not be run in the entire group of original patients due to availability of urine samples. The study was approved by the Massachusetts General Hospital IRB and subjects provided written informed consent. Biochemical testing was performed following an overnight fast.

Urine aldosterone concentration was measured using a radioimmunoassay (Diagnostic Products Corporation) and multiplied by the total volume over 24 hours. Fisher's least significant difference test was used and if statistical significance was met for the three group comparisons by ANOVA, further pair-wise comparisons were performed using Student's T-test. Univariate relationships with aldosterone were assessed using Pearson correlation coefficient. Multivariate linear regression modeling was used to examine the relationship of aldosterone to visceral fat and glucose parameters, adjusting for relevant covariates that might influence aldosterone, including also race and use of anti-hypertensive medications.

Demographics, body composition, metabolic parameters and medication use are shown in Table 1. Age and BMI did not differ between the groups. HIV-infected patients with increased VAT demonstrated increased 24-hour urinary aldosterone (Table 1). Among HIV-infected participants, rates of use of PI's, NRTI's, NNRTI's and immune parameters were similar between participants with and without increased VAT. Antihypertensive use was not different between the groups and none of the participants were taking mineralocorticoid receptor antagonists. Serum and urinary creatinine, urinary volume, dietary sodium and potassium intake were similar in all three groups. Similar results were seen when the 24-hour aldosterone levels were normalized for urine creatinine. Urine free cortisol levels were not increased among those with increased VAT. 24-hour urine aldosterone was not significantly different between HIV patients with NCEP-defined metabolic syndrome (26.7 ± 20.6 nmol/24h) vs. HIV patients without the metabolic syndrome (19.7 ± 22.1 nmol/24h) (p=0.38). Thirty-four patients were on current antiretroviral therapy (ART) and 9 patients were not. Compared to the non HIV-infected control subjects, urinary aldosterone was similar in the HIV group not on ART, but tended to be increased among the HIV group on ART (13.4 ± 12.5 for non HIV-infected control, 13.0 ± 8.5 for HIV not on ART, and 23.3 ± 22.5 nmol/24h (mean ± SD) for HIV on ART)(p=0.11).

In HIV-infected participants, 24-hour urine aldosterone was significantly associated with systolic blood pressure (r =0.36, p=0.01), BMI (r=0.37, p=0.01), total body fat (r=0.31, p= 0.04), VAT (r=0.34, p=0.03), and hemoglobin A1c (r=0.50, p=0.001), but not with subcutaneous adipose tissue (SAT) (r=0.19, p=0.23) (Table 2A). By multivariate regression analyses, in a model including age, race, BMI, PI, NRTI, NNRTI use, VAT, hemoglobin A1c, 24-hour urine sodium and anti-hypertension medications, VAT (β=0.14 nmol/24h per cm^2 change in VAT, p= 0.01) and hemoglobin A1c (β=17.28 nmol/24h per % change in hemoglobin A1c, p= 0.0001) remained significantly related to 24-hour aldosterone, among the HIV-infected patients. Overall model r^2 was 0.79 (Table 2B).

In this study, we demonstrate increased 24-hour urine aldosterone in HIV-infected women with increased visceral fat accumulation, compared to age and BMI-matched healthy controls and HIV-infected subjects without visceral fat accumulation. To our knowledge this is the first report to suggest that aldosterone may be increased among the subgroup of HIV-infected patients who experience increased visceral fat accumulation and to suggest an independent relationship between increased aldosterone and hemoglobin A1c, an index of overall glucose homeostasis.

Our findings relating aldosterone to adiposity are consistent with prior studies in non-HIV populations and extend these results for the first time to a human model with acquired

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visceral adiposity that differs from a model of more generalized obesity. Rossi et al. found plasma aldosterone correlated with BMI in overweight-obese patients with primary hypertension and Bentley-Lewis et al. showed 24-hour urine aldosterone correlated with BMI in normotensive overweight and obese participants [6,7]. To our knowledge, there is only one prior study relating aldosterone to VAT in humans, demonstrating that plasma aldosterone correlated with VAT in non HIV-infected, normotensive women[4].

Among HIV-infected patients, both loss of subcutaneous fat and increases in visceral fat have been found, though these changes may not be linked physiologically and may result from different mechanisms [8]. In a recent study among the Swiss HIV Cohort, approximately 22% were shown to have clinically significant abdominal lipohypertrophy[9], and treatment strategies to treat the metabolic abnormalities among these patients are needed. Our data demonstrate that 24-hour urine aldosterone is associated with VAT, but not with SAT in HIV-infected women. Urinary aldosterone measures were used to obtain an integrated measure of aldosterone throughout the day, as in prior studies relating aldosterone to adiposity[6,10]. Dietary sodium, urinary creatinine, urinary volume and serum creatinine were equivalent in all three groups. Fat, protein and carbohydrate intake were also similar among the groups.

We found a strong association of aldosterone with hemoglobin A1c, independent of BMI or visceral adiposity. Other studies have found correlations between aldosterone and markers of insulin resistance in overweight and obese patients without HIV [4,6,11]. We did not find an association of aldosterone with HOMA-IR or other measures of short-term glucose homeostasis; however, this may be due to differences in our study population. For example, the mean BMI in our study (25.6 kg/m^2) was not as high as in the other studies[4,6,11]. Prior *in vitro* studies suggest that aldosterone can negatively affect insulin action [12] and animal studies have shown that mineralocorticoid blockade can improve indices of insulin resistance [10]. Further studies are necessary to determine if increased aldosterone mediates, in part, dysregulation of the glucose axis in HIV-infected patients with increased visceral adiposity and the effects of mineralocorticoid blockade on glucose and other metabolic parameters in these patients.

The study was conducted in women only and thus the results may not be generalizable to men. Future studies in larger number of HIV patients, including men, are needed to confirm these findings. Moreover, the cross-sectional nature of our study does not allow us to answer questions of causation, for example as to whether altered adipogenesis contributes to increased aldosterone, as suggested in prior *in vitro* studies[13].

Our data may have potential cardiovascular and metabolic implications for the subgroup of HIV-infected patients with increased visceral fat accumulation[14], in whom increased aldosterone could also contribute to cardiovascular risk through effects on blood pressure, renal function and glucose homeostasis. Moreover, manipulation of the aldosterone axis could potentially be useful as a novel treatment strategy among HIV patients with increased visceral fat accumulation. These data suggest the need for future studies to confirm the relationship of aldosterone and visceral adiposity in HIV-infected patients and to investigate the effects of mineralocorticoid receptor blockade in HIV patients with excess visceral adiposity. Further studies are also needed to determine whether increased aldosterone is related in part to ART, immune, viral or host factors among HIV-infected patients with increased visceral fat accumulation.

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Table 1

Clinical Characteristics of Study Participants

	Controls	HIV without Excess VAT Accumulation	HIV with Excess VAT Accumulation	*p*-value
	n=20	n=21	n=22	
Demographics				
Age (years)	40 ± 7	42 ± 5	41± 6	0.45
Race (%)				0.47
Caucasian	35%	38%	50%	
African-American	50%	43%	32%	
Hispanic	5%	5%	9%	
Asian	10%	5%	0%	
Other	0%	10%	5%	
Antihypertensive Medication Use (%)	0%	10%	14%	0.25
Markers of HIV Disease and Antiretroviral Medications				
CD4 count (cells/mm^3)	823 ± 316	291 ± 148*	385 ± 196*	<0.0001
Viral load (copies/mL)	NA	3724 ± 6088	7268 ± 14052	0.35
% Patients with Undetectable Viral Load	NA	44%	43%	0.96
Duration of HIV Diagnosis (months)	NA	90 ± 56	115 ± 50	0.12
PI (%)	NA	33%	36%	0.83
NRTI (%)	NA	81%	77%	0.77
NNRTI (%)	NA	43%	32%	0.45
Duration of PI (months)	NA	12 ± 21	22 ± 20	0.11
Duration of NRTI (months)	NA	31 ± 36	54 ± 36	0.05
Duration of NNRTI (months)	NA	11 ± 15	9 ± 12	0.63
Body Composition				
BMI (kg/m^2)	25.5 ± 3.9	25.5 ± 3.4	25.7 ± 3.2	0.97
Total Body Fat (kg)	23.6 ± 8.8	23.8 ± 8.2	21.2 ± 6.8	0.50
Visceral abdominal fat (cm^2)	54 ± 25	55 ± 24	118 ± 38*†	<0.0001
Subcutaneous abdominal fat (cm^2)	257 ± 144	223 ± 109	258 ± 116	0.58
Cardiovascular Parameters				
SBP (mm Hg)	112 ± 14	107 ± 10	116 ± 14	0.12
DBP (mm Hg)	70 ± 10	70 ± 12	74 ± 11	0.18
Metabolic and Endocrine Parameters				
Hemoglobin A1c (%)	5.2 ± 0.4	5.1 ± 0.6	5.0 ± 0.9	0.55
HOMA-IR	1.1 ± 0.7	1.5 ± 0.8	2.8 ± 3.2*	0.03
2h OGTT glucose (mmol/L)	5.3 ± 1.3	6.3 ± 0.9*	6.7 ± 1.8*	0.01
Total cholesterol (mg/dL)	169 ± 26	184 ± 26	185 ± 54	0.35
LDL-cholesterol (mg/dL)	92 ± 22	110 ± 27	109 ± 48	0.20
HDL-cholesterol (mg/dL)	63 ± 18	54 ± 11	43 ± 12*†	0.0002
Triglycerides (mg/dL)	69 ± 26	101 ± 40*	175 ± 103*†	<0.0001
Creatinine (μmol/L)	70.7 ± 26.5	79.6 ± 8.8	79.6 ± 8.8	0.27

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	Controls	HIV without Excess VAT Accumulation	HIV with Excess VAT Accumulation	*p*-value
	n=20	**n=21**	**n=22**	
24hr urine creatinine (mmol/24h)	8.0 ± 4.4	7.3 ± 3.3	7.9 ± 3.4	0.77
24hr urine cortisol (nmol/24h)	119 ± 55	89 ± 41	90 ± 57	0.11
24hr urine aldosterone (nmol/24h)	13.3 ± 12.5	14.7 ± 10.0	27.2 ± 26.1*†	0.03
24hr urine aldosterone/Creatinine (nmol/mmol)	1.6 ± 1.0	2.3 ± 1.7	3.3 ± 2.7*	0.02
24hr urine sodium (mmol/24h)	116 ± 35	100 ± 56	105 ± 56	0.58
Total urine volume (L)	1.8 ± 0.8	1.5 ± 0.7	1.5 ± 0.7	0.25
Dietary Intake				
Average daily sodium (mmol/day)	141 ± 52	135 ± 46	138 ± 31	0.93
Average daily potassium (mmol/day)	60 ± 15	70 ± 30	59 ± 18	0.28
Average daily fat (g/day)	69 ± 28	72 ± 29	74 ± 26	0.86
Average daily carbohydrate (g/day)	236 ± 74	257 ± 97	240 ± 41	0.64
Average daily protein (g/day)	72 ± 27	73 ± 25	70 ± 22	0.91

Results are reported as mean ± SD for continuous variables. For race, percentages are reported in parentheses.

P-values reported for ANOVA F test for continuous variables. For race, *P*-values are reported for chi-square test.

* *P*-value <0.05 vs. controls,

† *P*-value <0.05 vs. HIV without excess VAT accumulation.

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Table 2

Table 2A: Univariate Correlations with 24 hr Urine Aldosterone in HIV Patients

Variable	r	*p*-value
Systolic BP	0.36	0.02
Diastolic BP	0.26	0.09
BMI	0.37	0.01
Total Body Fat	0.31	0.04
Visceral abdominal fat area	0.34	0.03
Subcutaneous abdominal fat area	0.19	0.23
Hemoglobin A1c	0.50	0.001
2h OGTT glucose	0.21	0.22
Total cholesterol	0.20	0.22
LDL-cholesterol	0.06	0.71
HDL-cholesterol	0.16	0.34
Triglycerides	0.22	0.19
24 hour urine potassium	0.12	0.44
Duration HIV infection	0.02	0.88
CD4 count	−0.12	0.48
Viral load	0.15	0.37
Duration of PI use	0.15	0.35
Duration of NRTI use	−0.08	0.61
Duration of NNRTI use	−0.18	0.27

Table 2B: Relationships between Adjusted Covariates and 24-Hour Urine Aldosterone (nmol/24h) in Multivariable Regression Modeling

Parameter	Estimate (β)	Standard Error	*P*-value
VAT (cm2)	0.14	0.05	0.01
Hemoglobin A1c (%)	17.28	3.74	0.0001
Age (y)	−1.33	0.45	0.007
Race	−12.98	5.12	0.02
BMI (kg/m2)	0.53	0.86	0.54
PI Use	−6.79	2.87	0.03
NRTI Use	−3.98	3.66	0.29
NNRTI Use	−2.42	2.74	0.39
24-hour Urine Sodium (mmol/24h)	0.06	0.04	0.20
Antihypertensive Medication Use	−4.16	3.86	0.29