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Microalbuminuria in HIV infection

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Abstract

Objective—Microalbuminuria is associated with increased risk of cardiovascular disease and mortality. The objective of the study was to evaluate if HIV infection was an independent risk factor for microalbuminuria.

Design—Cross sectional.

Methods—The relationship between HIV infection and microalbuminuria was assessed using subjects enrolled in the study of Fat Redistribution and Metabolic Change in HIV Infection, which consists of HIV-positive and control men and women. Participants with proteinuria (dipstick $\geq 1+$) were excluded.

Results—Microalbuminuria (urinary albumin/creatinine ratio, $ACR > 30$ mg/g) was present in 11% of HIV infected, and 2% of control participants ($P < 0.001$); a fivefold odds after multivariate adjustment (odds ratio, 5.11; 95% confidence interval, 1.97–13.31; $P = 0.0008$). Several cardiovascular risk factors were associated with higher ACR in HIV participants: insulin resistance ($HOMA > 4$; 32%, $P < 0.0001$), systolic blood pressure (21%, $P = 0.01$ for 120–140 versus < 120 mmHg, and 43%, $P < 0.06$ for > 140 versus < 120 mmHg), and family history of hypertension (17%, $P = 0.03$). Higher CD4 cell count was associated with lower albumin/creatinine ratio (-24% , $P = 0.009$ for 200–400 versus < 200 cells/ml and -26% , $P = 0.005$ for > 400 versus < 200 cells/ml).

Conclusion—HIV infection had a strong and independent association with microalbuminuria, the severity of which was predicted by markers of insulin resistance, hypertension, and advanced HIV infection. These associations warrant further investigation, as the increased prevalence of microalbuminuria in HIV infection may be a harbinger of future risk of cardiovascular and kidney diseases.

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Keywords

Microalbuminuria; kidney; urine protein; insulin resistance; lipodystrophy

Introduction

Renal disease manifesting as proteinuria or elevated creatinine has been described as a common complication of HIV infection. Among a cohort of women with HIV infection, 39% of African–American and 25% of Caucasian women had clinically significant proteinuria [1]. These levels of proteinuria have subsequently been demonstrated to be associated with poorer outcomes including an increased risk of hospitalization and mortality [2–4]. Risk factors for clinically significant proteinuria include African–American race, higher HIV RNA level, and lower CD4 lymphocyte count [1].

Similar to the data on prevalence of proteinuria, a strikingly high prevalence of microalbuminuria among HIV-infected patients of 19%, 30%, and 34% has been described in three studies [5–7]. One of these reports suggested that patients with 'clinical AIDS' or 'AIDS related complex' may be at greater risk compared with asymptomatic HIV-infected individuals [7]. Since the publication of these studies (1992, 1993, and 1996), the treatment of HIV infection has changed dramatically. With the introduction of protease inhibitors and highly active antiretroviral therapy, survival of patients with HIV infection has improved substantially [8,9]. However, concurrent with this improved survival, changes in fat distribution, worsening lipid profiles, and insulin resistance have also been noted [10–12]. Recent data indicate that the rate of cardiovascular disease is increased in patients with HIV infection on combination antiretroviral therapy, although the role of antiretroviral therapy and abnormalities of body composition is debated [13,14].

Microalbuminuria is a marker of renal damage that is associated with increased risk of cardiovascular disease and mortality in the general population [15–18]. Given these associations, microalbuminuria may be an important early marker of cardiovascular disease risk in persons with HIV infection [19,20]. We hypothesized that HIV infection would be associated with greater prevalence of microalbuminuria compared with similarly aged controls. Using the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) cohort, comprised of both HIV-infected and control participants, this study was undertaken to compare the prevalence of microalbuminuria in each group and explore predictors of microalbuminuria among persons with HIV infection.

Methods

Subjects

Briefly, FRAM is a cross-sectional study with the overall objective to evaluate abnormalities in fat distribution using measurement of regional subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) by magnetic resonance imaging in HIV-infected subjects and control subjects, as well as physical examination and laboratory examination of metabolic parameters. HIV-infected subjects were recruited from 16 HIV or infectious disease clinics or cohorts during 1999. FRAM is representative of patients with HIV infection in the U.S. [21]. Control subjects were recruited from two centers of the Coronary Artery Risk Development in Young Adults (CARDIA) study [22]. CARDIA subjects were originally recruited as a population-based sample of healthy 18–30-year-old white and African–American men and women from four cities in 1985–1986 for a longitudinal study of cardiovascular risk factors. Participants who agreed to the year 15 CARDIA examination were approached to participate in FRAM. Eighty participants with significant proteinuria

(≥ 1 by dipstick) and those identifying as non-White or non-Black were excluded from this analysis. The protocol was approved by institutional review boards at all sites. The methods have been described in detail previously [21,23].

Measurements

Albumin and creatinine concentrations were measured in spot urine specimens obtained in 67% (967/1451) of subjects. Urine albumin excretion was estimated using the albumin to creatinine ratio (ACR) and calculated by dividing the spot urine albumin concentration by the spot urine creatinine concentration [24–27]. Microalbuminuria was analyzed as both a dichotomous variable defined as $ACR > 30 \text{ mg/g}$ and a continuous variable. Prior research from the CARDIA cohort has found that the ability of ACR to approximate 24-h urine albumin excretion differs somewhat by sex and race, due to differences in creatinine production. Within HIV-infected subjects, we used ACR adjustment coefficients for women and African-Americans that were derived by Jacobs and colleagues to reduce sex- and race-related effects on ACR levels [28]. Serum creatinine was measured and creatinine clearance was calculated using the Cockcroft–Gault formula [29]. The homeostatic method of assessment (HOMA) was utilized to assess beta-cell function and insulin resistance using basal (fasting) glucose and insulin concentrations [30]. Simply, HOMA provides a framework to utilize these two parameters to estimate increasing insulin resistance (i.e., a greater insulin level to achieve the same glucose level) and decreased beta-cell function (i.e., a greater glucose level given a degree of insulin sensitivity). Among HIV-infected subjects, blood was drawn for determination of CD4 cell counts and HIV RNA by PCR and measured in a single laboratory (Covance, Indianapolis, IN, USA).

Statistical analyses

Clinical and demographic variables were summarized for HIV-infected and control subjects separately stratified on the presence or absence of microalbuminuria ($ACR > 30 \text{ mg/g}$). Continuous and categorical variables were compared between groups based on the presence or absence of microalbuminuria within cohort defined by HIV infection using Student's t-test or Wilcoxon's rank-sum test and Pearson's chi-square or Fisher's exact test as appropriate.

The first objective of our analysis was to evaluate whether HIV infection was independently associated with a greater prevalence of microalbuminuria ($ACR > 30 \text{ mg/g}$) compared with the control population. Multivariable logistic regression was used with adjustment for other predictors of microalbuminuria that were measured in both HIV-infected and controls. These analyses were repeated using linear regression to evaluate the presence of HIV infection as a predictor of ACR as a continuous variable; because of its skewed distribution, ACR was log-transformed in all linear regression analyses. Variables tested to determine if they confounded the association between ACR and HIV infection include demographics (age, sex, race), medical history (presence of HIV infection, diabetes mellitus, or hypertension; family history of kidney disease or hypertension), physical exam parameters (systolic and diastolic blood pressure), laboratory parameters (the presence of urine glucose, HOMA, social history (self-reported use of illicit drugs), medications (statins, ACE-I, anti-hypertensives), and assessments of visceral and regional subcutaneous adipose tissue (VAT and SAT) volume.

The second major objective of the analysis was to evaluate the determinants of ACR among the HIV-infected participants. ACR was analyzed as a continuous variable based on its previously described association with mortality [15]; we incorporated ACR adjustment coefficients, derived by Jacobs and colleagues, to minimize sex and race effects on ACR levels [28]. The first of these two models tested all of the variables listed above plus

including HIV specific parameters [i.e., current HIV RNA level (\log_{10}), current CD4 lymphocyte count (\log_2), duration of HIV infection, and risk behavior for HIV acquisition]. The second of these two models included all variables listed above, HIV specific parameters, and use or duration of individual antiretroviral medications (e.g., stavudine, zidovudine, etc.) as well as classes of antiretroviral medications [nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTI), or protease inhibitors]. Duration or use of each antiretroviral agent, antiretroviral agent class, and HAART as previously defined [22] were added to the model in a forward stepwise manner. These models were fitted to logarithmic transformations of ACR to produce estimated percentage differences in ACR levels. Multivariate regression models were built using stepwise regression, with $P=0.05$ for entry and retention and with gender, age, and ethnicity forced to be included in every model. Confidence intervals were determined using the bias-corrected accelerated bootstrap method [31], with P values defined as the one minus the highest confidence level that still excluded zero. This was necessary both because the outcome appeared to be non-Gaussian, even after log transformation, and to control for multiple important predictors. Model validity was also examined by testing for important interactions, multicollinearity, outliers, etc. (Fig. 1)

Results

Microalbuminuria among HIV-infected and control participants

Characteristics of HIV infected participants and controls with and without microalbuminuria are displayed in Table 1. In general, HIV-infected subjects with microalbuminuria (ACR > 30 mg/g) were more likely to be female ($P = 0.02$), African-American ($P=0.0003$), have an elevated systolic or diastolic pressure or have hypertension ($P=0.0003$, 0.02, and 0.002, respectively), and a lower nadir CD4 lymphocyte count ($P=0.04$) as compared with HIV-infected subjects without microalbuminuria. Additionally HIV-infected subjects with microalbuminuria had a trend toward more insulin resistance (greater mean HOMA) though this was not statistically significant ($P=0.08$). Among control subjects, those subjects with microalbuminuria had greater insulin levels, fasting glucose levels, measures of insulin resistance, (i.e., HOMA) ($P=0.04$, 0.003, 0.01) and greater triglyceride levels ($P=0.06$). There were no apparent associations with regional adipose tissue volumes (P values for association with individual adipose tissue depot volumes were all > 0.49).

Association of microalbuminuria with HIV infection

Microalbuminuria (ACR > 30 mg/g) was present in 83 (11%) of the HIV-infected subjects and 5 (2%) of the controls ($P < 0.001$) (Fig. 1). In the univariate analysis, HIV-infected subjects had a fivefold higher odds than controls of having microalbuminuria (OR=4.95, $P = 0.0002$; 95% CI, 1.98–12.38) (Table 2). After multivariable adjustment for other predictors of micro-albuminuria, the presence of HIV infection remained the strongest predictor of microalbuminuria (OR, 5.11; $P = 0.0008$; 95% CI, 1.97–13.31 for HIV infection) (Table 3). Other predictors of microalbuminuria included African-American race, greater serum triglyceride measurement, greater systolic blood pressure, and female gender. Similarly, when ACR was analyzed as a continuous variable, in the multivariate model of subjects with and without HIV infection, the presence of HIV infection was strongly associated with a higher ACR level (58%; 95% CI, 39–82; $P < 0.0001$) compared to control participants.

Predictors of microalbuminuria among HIV-infected participants

Among participants with HIV infection, older age ($P=0.02$) and African-American race ($P=0.001$) were associated with higher ACR. Interactions between ACR and both gender and race were tested in separate models and were not significant ($P>0.05$). Several traditional cardiovascular risk factors were strongly associated with higher ACR; these

included insulin resistance (HOMA>4; $P<0.0001$), greater systolic blood pressure ($P=0.01$ for 120–140 mmHg versus < 120 mmHg, and $P=0.06$ for > 140 mmHg versus < 120 mmHg), family history of hypertension ($P=0.03$), and urine glucose ($p=0.002$). In contrast, tobacco use ($P=0.57$) was not significantly associated with higher ACR.

HIV-specific risk factors associated with higher ACR were lower CD4 lymphocyte count ($P=0.009$ for 200–400 versus <200 cells/ml, and $P=0.005$ for >400 versus <200 cells/ml), current HIV RNA level ($P=0.05$), and current use of NNRTI ($P=0.01$). Current use of NNRTI was the only ARV selected into the model (entrance criterion $P<0.05$) among candidate predictors that included duration or use of each individual ARV, class of ARV, and use of HAART regimens. Co-infection with hepatitis C virus ($P=0.58$) was not significantly associated with higher ACR.

Discussion

This analysis demonstrated that HIV infection is a strong risk factor for the presence of microalbuminuria, independent of other risk factors for the presence of renal disease. Among HIV-infected individuals, risk factors for microalbuminuria included traditional HIV specific markers such as CD4 lymphocyte count and HIV RNA level. The association of HIV infection with albuminuria and proteinuria was reported in an earlier era of the HIV epidemic in the USA with a prevalence of between 19 and 34% [5–7]. One of these prior studies demonstrated associations between the presence of microalbuminuria and 'stage' of HIV-infection [7]. A more recent study also found that HIV RNA level, CD4 lymphocyte count, and African–American race were important determinants of overt proteinuria [1]. In the study described in this report, decreased CD4 cell count, increased viral load, and African–American race were all associated with higher ACR.

However, higher albumin excretion rate in this study was also strongly associated with several traditional renal and cardiovascular risk factors such as higher systolic blood pressure, insulin resistance, and glycosuria [32,33]. The importance of these renal and cardiovascular risk factors as determinants of albumin excretion rate in HIV-infected individuals may mark a shift in the significance of microalbuminuria in the current era of HIV in the USA. Rather than a marker of the severity of HIV infection and HIV-related renal disease, the increased prevalence of microalbuminuria among HIV infected patients may signal an increase in their cardiovascular risk.

Our findings indicate that within the HIV-infected population, non-HIV factors may be more important predictors of microalbuminuria than HIV severity in the current era of HIV in the USA. In particular, the cardiovascular risk factors of increased systolic blood pressure, insulin resistance, and older age (risk factors previously noted in the general population) were strongly associated with microalbuminuria in our HIV-infected cohort. These results suggest that microalbuminuria may be a sign of current endothelial dysfunction and microvascular disease rather than of advanced HIV infection in this cohort, and may thus portend substantial risk of future cardiovascular disease events. Possible contributing factors include early kidney disease such as HIV-associated nephropathy, a marker of end organ damage related to comorbidities of diabetes mellitus or hypertension, or more diffuse endothelial cells dysfunction. Nevertheless, after adjustment for non-HIV factors, HIV itself is a major risk factor.

A relationship between microalbuminuria and current use of NNRTI was noted but was not as strong as the association of microalbuminuria with other measures, such as HOMA and CD4 lymphocyte count. While the potential for an indication bias related to the prescription of a class of antiretroviral medications such as NNRTI is not intuitive, it does remain a

possibility. However, clearly, the limited strength of the relationship in the setting of multiple hypothesis-testing with dozens of individual and classes of medications should be reflected in its interpretation. While certain antiretroviral medications have been associated with acute renal failure and nephrolithiasis [34–37], glomerular damage has not previously been reported with those medications and they were not apparently associated with microalbuminuria in this study. Tenofovir use was very low at the time of study; indinavir use was not associated with microalbuminuria.

Given the recent findings that even a very low ACR is a predictor of cardiovascular disease and death [38], a similar correlation of these findings with outcomes in HIV-infected persons as well as assessments of therapeutic interventions will be essential. Given the analogous clinical scenario of a decrement in microalbuminuria with agents that disrupt the renin–angiotensin axis among patients with diabetes mellitus [38], a similar therapeutic use among HIV-infected persons with microalbuminuria is plausible.

While the strengths of this study include recruitment of subjects from 16 geographically diverse centers, with subject demographics similar to those of HIV infected subjects in the USA [21], this study does have important limitations. With respect to study design, it is important to note that cross-sectional studies such as this may be affected by a survival bias. Additionally, causation and whether treatment of predictors such as systolic blood pressure and insulin resistance would decrease albuminuria in HIV cannot be determined from these data.

In summary, the presence of HIV infection was independently associated with a fivefold risk of micro-albuminuria as compared with an age-matched cohort without HIV infection. Cardiovascular risk factors appeared to be stronger predictors of microalbuminuria than markers of HIV severity. Persons with HIV infection and microalbuminuria therefore appear to potentially bear the burden of two separate pathologic processes: microvascular end organ damage related to known vascular risk factors, and HIV specific processes such as the direct viral infection of kidney cells [39]. The high prevalence of microalbuminuria among the HIV infected could be a harbinger of future increased risks of both kidney and cardiovascular disease. Further study defining the prognostic significance of microalbuminuria among HIV-infected persons will be essential.

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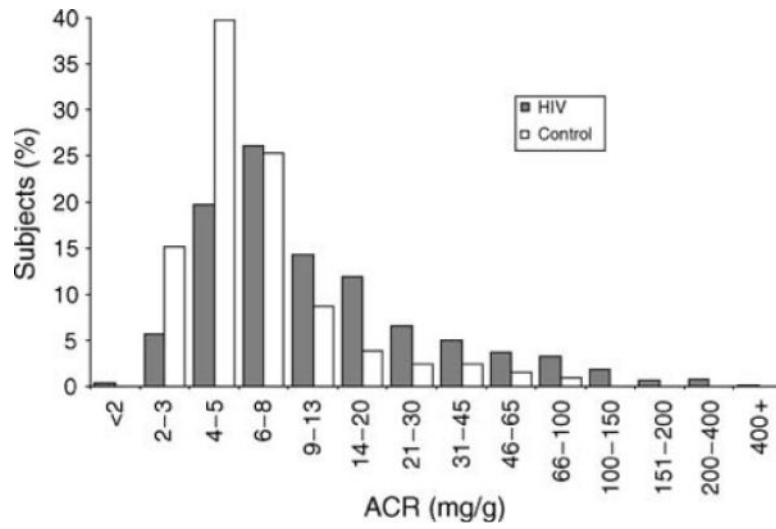


Fig. 1.
Distribution of ACR among HIV-infected and control participants.

Table 1

Clinical and demographic variables for HIV-positive patients and controls based on the presence or absence of microalbuminuria.

	HIV positive patients			Control subjects		
	Microalbuminuria (N = 83)	No microalbuminuria (N = 677)	P	Microalbuminuria (N = 5)	No microalbuminuria (N = 202)	P
Age (years) (mean ± SD)	44 ± 10	44 ± 9	0.52 ^a	41 ± 4	40 ± 4	0.49 ^d
Sex [n (%)]						
Male	52 (63)	508 (75)	0.02 ^b	2 (40)	108 (53)	0.67 ^c
Female	31 (37)	168 (25)		3 (60)	94 (47)	
Race/ethnicity			0.0003 ^b			0.38 ^c
African-American	52 (63)	282 (42)		4 (80)	108 (54)	
White	31 (37)	395 (58)		1 (20)	94 (47)	
Creatinine (mg/dl) (mean ± SD)	0.9 ± 0.2	0.9 ± 0.2	0.80 ^a	0.8 ± 0.3	0.9 ± 0.2	0.58 ^d
Creatinine clearance (cc/min) (mean ± SD)	117 ± 49	116 ± 365	0.48 ^a	159 ± 34	133 ± 35	0.10 ^d
HDL-C (mg/dl) (mean ± SD)	46 ± 19	45 ± 17	0.85 ^a	51 ± 10	52 ± 15	0.95 ^d
Cholesterol (mg/dl) (mean ± SD)	204 ± 63	198 ± 52	0.90 ^a	227 ± 40	201 ± 38	0.14 ^d
LDL-C (mg/dl) (mean ± SD)	106 ± 48	110 ± 42	0.26 ^a	149 ± 47	123 ± 32	0.15 ^d
Triglycerides (mg/dl) (mean ± SD)	288 ± 400	210 ± 204	0.16 ^a	159 ± 78	113 ± 87	0.06 ^d
Insulin resistance (mean ± SD)						
Insulin (mg/dl)	23 ± 30	19 ± 16	0.08 ^a	21 ± 3.2	15 ± 7	0.05 ^d
Fasting glucose (mg/dl)	104 ± 45	96 ± 24	0.94 ^a	120 ± 35	95 ± 20	0.003 ^d
HOMA (mean ± SD)	7 ± 19	5 ± 4	0.08 ^a	6 ± 2	4 ± 2	0.01 ^d
Blood pressure (mmHg) (mean ± SD)						
Systolic	122 ± 16	116 ± 14	0.0003 ^a	116 ± 17	118 ± 16	0.60 ^d
Diastolic	80 ± 12	77 ± 10	0.02 ^a	80 ± 15	78 ± 9.8	0.89 ^d
Hypertension (≥ 140/90 mmHg)	19 (23)	76 (11)	0.002 ^c	1 (20)	28 (14)	0.54 ^d
Hepatitis C (positive)	20 (24)	156 (23)	0.88 ^c	0 (0)	1 (0.5)	1.0 ^d

	HIV positive patients		Control subjects		P
	Microalbuminuria (N = 83)	No microalbuminuria (N = 677)	Microalbuminuria (N = 5)	No microalbuminuria (N = 202)	
HAART/ARV Status					0.50 ^c
Never	6 (7.2)	77 (11)	-	-	-
Ever	11 (13)	79 (12)	-	-	-
Current	66 (80)	520 (77)	-	-	-
Years since HIV test (mean ± SD)	9 ± 4	8 ± 4	-	-	0.42 ^a
Nadir CD4 (cells/ml) (mean ± SD)	159 ± 157	207 ± 195	-	-	0.04 ^d

^a Nonparametric Wilcoxon rank sum test.

^b Chi-square test.

^c Fisher's exact test. HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol. HOMA, homeostatic method of assessment; ARV, antiretroviral therapy.

Table 2

Microalbuminuria among HIV-infected patients and control subjects [urinary albumin/creatinine ratio (ACR) > 30 mg/gm].

	HIV positive patients (n = 760)	Control subjects (n = 207)	<i>P</i>
Median ACR ^a	5 (IQR, 8.5)	4 (IQR, 2.0)	
With microalbuminuria [n (%)]	83 (10.9)	5 (2.4)	
Unadjusted OR	4.95 (95% CI, 1.98–12.38)		< 0.0001 ^b
Adjusted OR ^c	5.11 (95% CI, 1.97–13.31)		0.0008

^aContinuous form of ACR.

^bChi-square test.

^cAdjusted for race, serum triglyceride measurement, human insulin and systolic blood pressure, via logistic regression. IQR, Interquartile range; OR, odds ratio; CI, confidence interval.

Table 3

Results of multivariate model assessing association of HIV-related and non-HIV-related factors with urine ACR in HIV-infected subjects.

Variable	Effect [% (95% CI)]	P
Age (per decade increase)	10.5 (1.7 to 20.4)	0.02
Sex		
Female versus male	-14.8 (-28.0 to 3.3)	0.10
Race		
African-American versus Caucasian	33.0 (13.0 to 54.7)	0.001
HOMA > 4	32.4 (15.2 to 53.3)	< 0.0001
Systolic blood pressure		
120–140 versus < 120 mmHg	20.6 (3.5 to 40.5)	0.010
> 140 versus < 120 mmHg	43.2 (-0.9 to 108.4)	0.06
Family history of hypertension	16.6 (1.5 to 33.0)	0.03
Urine glucose (present versus absent)	113.2 (33.9 to 222.2)	0.002
Current CD4 lymphocyte count		
200–400 versus < 200 cells/ml	-23.8 (-39.2 to -5.2)	0.009
>400 versus < 200 cells/ml	-25.7 (-40.3 to -8.3)	0.005
Current HIV RNA level (per 10-fold increase)	8.7 (0.1 to 19.0)	0.05
Current use of NNRTI	21.9 (4.5 to 41.6)	0.01

HOMA, homeostatic method of assessment; NNRTI, non-nucleoside reverse transcriptase inhibitor.