Microalbuminuria associated with indicators of inflammatory activity in an HIV-positive population

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Abstract

Background. The survival of human immunodeficiency virus (HIV)-infected patients has increased significantly since the introduction of combination antiretroviral therapy, leading to the development of important long-term complications including cardiovascular disease (CVD) and renal disease. Microalbuminuria, an indicator of glomerular injury, is associated with an increased risk of progressive renal deterioration, CVD and mortality. However, the prevalence of microalbuminuria has barely been investigated in HIV-infected individuals.

Methods. Based on three prospective urine samples in an unselected nonhypertensive, nondiabetic HIV-positive cohort (n = 495), we analysed the prevalence of microalbuminuria and compared the Caucasian share with that of a nonhypertensive, nondiabetic population-based control group (n = 2091). Significant predictors for microalbuminuria were analysed within the HIV-positive cohort.

Results. The prevalence of microalbuminuria was 8.7% in the HIV-infected cohort, which is three to five times higher than that in the general population. HIV-infected patients with microalbuminuria were older, and had higher blood pressure, longer duration of HIV infection, higher serum beta 2-microglobulin, higher serum creatinine and a reduced glomerular filtration rate of ≤90 mL/min, compared with those with normal albumin excretion. In multivariate analysis, systolic blood pressure, serum beta 2-microglobulin and duration of HIV infection were found to be independent predictors of microalbuminuria.

Conclusions. Our findings indicate that in addition to haemodynamic effects, inflammatory activity may be implicated as a cause of the development of microalbuminuria. With respect to the increasing risk of developing CVD or renal diseases and mortality, the high prevalence of microalbuminuria in HIV-infected individuals warrants special attention.

Keywords: beta 2-microglobulin; blood pressure; combination antiretroviral treatment; HIV; microalbuminuria

Introduction

The introduction of combination antiretroviral therapy (cART) in the treatment of human immunodeficiency virus (HIV) infection has led to a substantial decline in HIV-related mortality and morbidity [1,2]. However, it has also resulted in important short- and long-term adverse effects [3]. Attention has mainly been focused on cardiovascular disease (CVD) and there is evidence suggesting an association between cART and coronary heart disease, especially when protease inhibitors are involved [4–7]. The adverse effect of cART on serum lipids has been suggested to at least partially explain the increased rates of myocardial infarction [8], although other metabolic disturbances caused by cART may also contribute [9,10]. In addition, endothelial dysfunction has been proposed as a putative link between HIV infection and CVD [11,12].

Kidney diseases are increasingly prevalent in the course of HIV infection [13]. Today HIV-associated nephropathy (HIVAN) is a considerable cause of end-stage renal disease in HIV-infected, African Americans [13], but other histopathological renal diseases [14,15] affecting all ethnicities have also become more discernible. Moreover, HIV-associated renal disease with overt proteinuria has been associated with increased mortality [16,17]. Besides the potential nephrotoxicity induced by cART [18], HIV itself may directly affect glomerular epithelial cells [19]. However, the pathophysiology of the various renal diseases associated with HIV infection is not yet clear.

An increased urinary albumin excretion rate, even in the microalbuminuric range, has been found to be an independent risk factor for CVD and mortality in the general population [20–22]. The pathophysiological mechanism underlying urinary albumin excretion and the increased risk of CVD is not fully understood, although systemic endothelial dysfunction and inflammation has been implicated...
Microalbuminuria has therefore gained increasing recognition as a simple marker of an atherogenic propensity [25]. Apart from a recent publication [26], there are few studies of microalbuminuria in HIV-infected patients and most of these have been undertaken in selected small cohorts limited to the pre-cART era [27–29]. Nevertheless, there is some evidence that microalbuminuria might represent an early indicator of HIVAN [30]. Thus, early detection of microalbuminuria could identify HIV-infected subjects at high risk of developing CVD and even renal diseases. To our knowledge, at the time of the initiation of our study, no large prospective population-based cohort study had investigated the prevalence of microalbuminuria in an HIV-infected population.

The aim of this study was, first, to assess the prevalence of microalbuminuria in an unselected HIV-infected cohort in comparison with a population-based control group, and second, to identify significant predictors of microalbuminuria in HIV-infected individuals.

Subjects and methods

HIV patients

For the present study, all HIV-infected patients attending the outpatient clinic at the Department of Infectious Diseases, Ullevaal University Hospital, Oslo, Norway, were invited to participate. This is the main HIV clinic responsible for treatment of HIV-infected patients in the city of Oslo, which has ~500 000 inhabitants. The patients attending the clinic therefore represent an unselected group from the whole city. No exclusion criteria were used. The study included 597 HIV-positive patients enrolled between March 2004 and November 2005. Based on estimations from the Norwegian Surveillance System of Communicable Diseases (MSIS), they constitute ~75% of the entire HIV-positive population in Oslo (Figure 1). They were given written and oral information about the study and the attending physician obtained signed consent at a regular visit. The National Committee of Medical Research Ethics approved the study and consent was obtained from the National Data Inspectorate. The subjects were followed as outpatients for up to 34 months. A total of 55 patients were excluded because of dropout after the initial visit (n = 26), i.e. impossibility to establish contact, death (n = 12), moving abroad or to other clinics in Norway (n = 11) or unwillingness to continue the study after inclusion (n = 6). In addition, patients with previously diagnosed diabetes mellitus (n = 14) or hypertension (n = 25) were excluded. The database was closed in January 2007. All patients were 20 years or older, and further characteristics are presented in Table 1.

Control group

Control data from the large population-based Nord-Trøndelag Health Study (HUNT) from 1995 to 1997, in Norway (n = 2091), were used [31]. The subjects constituted a healthy, nondiabetic and nonhypertensive general population. Men and women were distributed equally (47% versus 53%), with mean ages of 49.2 ± 15.6 and 48.7 ± 15.9 years, respectively. The population was stable and ethnically homogenous with only a small percentage (3%) of non-Caucasian origin [31].
Table 1. Demographic and clinical data of HIV-infected subjects

| Characteristic or laboratory value | All (n = 495) | Male (n = 354) | Female (n = 141) |
|-----------------------------------|--------------|---------------|-----------------|
| **Age groups (years)**<sup>a</sup> |              |               |                 |
| <30                               | 58 (11.7%)   | 23 (6.5%)     | 35 (24.8%)      |
| 30–39                             | 158 (31.9%)  | 106 (29.9%)   | 52 (36.9%)      |
| 40–49                             | 164 (33.1%)  | 119 (33.6%)   | 45 (31.9%)      |
| >50                               | 115 (23.2%)  | 106 (29.9%)   | 9 (6.4%)        |
| **Ethnicity**<sup>a</sup>         |              |               |                 |
| Caucasian                         | 348 (70.3%)  | 289 (81.6%)   | 59 (41.8%)      |
| Black                             | 114 (23%)    | 50 (14.1%)    | 64 (45.4%)      |
| Asian                             | 33 (6.7%)    | 15 (4.2%)     | 18 (12.8%)      |
| Smoking<sup>a</sup>               | 211 (42.6%)  | 163 (46%)     | 48 (34%)        |
| Cholesterol (mmol/L)<sup>b</sup>  | 5.0±1.1      | 5.0±1.1       | 5.0±1.1         |
| BMI (kg/m<sup>2</sup>)<sup>b</sup> | 23.8±3.4     | 23.8±3.2      | 23.8±3.9        |
| HbA1c (%)<sup>b</sup>             | 5.2±0.39     | 5.1±0.35      | 5.2±0.46        |
| Hepatitis B positive<sup>a</sup>  | 22 (4.4%)    | 21 (5.9%)     | 1 (0.7%)        |
| Hepatitis C positive<sup>a</sup>  | 46 (9.3%)    | 28 (7.9%)     | 18 (12.8%)      |
| Duration since HIV test (years)<sup>b</sup> | 7.3±5.9   | 7.4±5.9       | 7.2±6.0         |
| Beta 2-microglobulin (mg/L)<sup>b</sup> | 2.1±0.9   | 2.2±0.9       | 2.0±1.0         |

BMI, body mass index; cART, combined antiretroviral therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate.
<sup>a</sup>Values are the number of patients and (percentage).
<sup>b</sup>Values are the mean ± SD.
<sup>c</sup>Values are the median and (interquartile range).

Clinical examination and questionnaire

Three clinical visits were undertaken days to months apart, when an HIV specialist physician investigated the patients. Blood pressure was measured using a validated semiautomatic oscillometric device (Omron M4, Omron Matsusaka Co. Ltd, Mutsuaka, Japan). Well-trained nurses performed two consecutive blood pressure measurements 2 min apart using an appropriate cuff after the patient had rested in a sitting position for 5 min in a quiet room. The average of these measurements in duplicate was used for statistical analysis of systolic blood pressure (SBP) and diastolic blood pressure (DBP). At the first clinical visit, height and weight were measured to estimate the body mass index (BMI) in kg/m<sup>2</sup>. A simple self-administered questionnaire with yes/no answers was filled out regarding smoking and intravenous drug-abuse habits, and knowledge of hypertension, diabetes, and cancer and hepatitis C status.

Urine samples

A urine sample was collected at each research visit for determination of the albumin/creatinine ratio (ACR), a measure for the urinary excretion rate of albumin [32]. Patients who underwent an antibiotic treatment for urinary tract infection or had ongoing symptoms, where asked to deliver a urine sample at the next visit. Urine albumin and creatinine were measured using an immunoturbimetric method (antihuman serum albumin antibody from Roche, Basel, Switzerland) and an enzymatic method (Roche), respectively. According to the ACR, based on at least two urine samples, patients were categorized as having normoalbuminuria (<2.5 mg/mmol), microalbuminuria (2.5–30 mg/mmol) or macroalbuminuria (>30 mg/mmol). A total of 460 patients delivered three urine samples each; 35 patients delivered two samples each and 3 patients delivered only one. Patients who delivered only one urine sample (n = 3) or had macroalbuminuria (n = 5) were excluded from the study. The same criterion for the definition of microalbuminuria was used for the historical control group [31]. In addition, glomerular filtration rate (GFR), a measure of kidney function, was calculated based on the Modification of Diet in Renal Diseases equations, which take into account serum creatinine, age, sex and race [33].

Demographic and laboratory data

Age, gender, race, date of the patient’s first HIV-positive test, transmission mode, CD4 cell count, HIV RNA, serum beta 2-microglobulin, serum creatinine, cholesterol,
starting date of cART, hepatitis B status and death date were obtained from the local HIV database, updated continuously from the patients’ records [34]. Data on lipids and HbA1c were obtained directly from the patient records. Duration since HIV test was calculated from the first positive HIV test. With respect to cART exposure, patients were allocated to different subgroups, while naïve (untreated) patients were divided into those who were untreated throughout the study and those who started cART between the first and last clinical visits. HIV RNA in EDTA plasma was quantified using polymerase chain reaction amplification with a COBAS Amplitaq HIV-1 Monitor Test (Roche Diagnostics, Branchburg, NJ, USA). CD4 cell count was determined by routine flow cytometry using TriTest CD4/CD8 with TruCount Tubes (Becton Dickinson Biosciences, San Jose, CA, USA). All laboratory analyses were performed at the Department of Clinical Chemistry at Ullevaal University Hospital. Data were taken from the date nearest to the inclusion in the present study.

Statistical methods

Patient data were collected in an EpilInfo database (EpiInfoTM) for statistical analysis using SPSS software (SPSS Inc., version 14.0, Chicago, IL, USA). Microalbuminuria and gender groups were compared for continuous and categorical variables using Student’s t-test, the Mann–Whitney U test and Pearson’s χ² or Fisher’s exact test as appropriate. Data are expressed either as the mean ± standard deviation (SD), as a number and percentage, or as the median with the interquartile range for skewed data. Predictors of microalbuminuria were evaluated using logistic regression analysis and a backward stepwise procedure, with P-to-enter < 0.1 and P-to-remove > 0.1, which are the default values of the SPSS statistical package. Odds ratio (OR) was determined by logistic regression analysis or a χ² test. The prevalence of microalbuminuria in the Caucasian HIV-infected subjects was compared with that in the control group defined by age and gender. All P values were two sided and significance was accepted at P < 0.05.

Results

Characteristics of an HIV-infected population

The cohort for this study included 495 HIV-infected patients (Table 1). The mean age at enrollment was 42.3 ± 10.3 years. Women were younger than men (36.8 ± 8.1 versus 44.5 ± 10.2 years, P < 0.0001) and 23% of the total population were above 50 years of age. Males had been infected mainly through homosexual activity (63.3%) and were predominantly of Caucasian ethnicity, whereas half of the females (49.6%) originated from high-endemic African areas. At the time of inclusion in the study, >60% of the patients used cART, with well-maintained immune function, as 85% had a CD4 cell count above 0.2 × 10³ cells/L. This rate did not differ between genders.

Microalbuminuria and HIV

Microalbuminuria was present in 8.7% of the HIV-infected population. Less than 1% of subjects had a GFR < 60 mL/min and 83% had a GFR ≥ 90 mL/min. In comparison with subjects without microalbuminuria, subjects with microalbuminuria were older (47.6 ± 12.5 versus 41.8 ± 9.9 years, P < 0.0001), had higher blood pressure (SBP 141.9 ± 27.8 versus 128.4 ± 15.9 mmHg, P < 0.0001; DBP 84.5 ± 12.9 versus 79.8 ± 10.1 mmHg, P = 0.005), longer duration of HIV infection (9.0 ± 5.5 versus 7.2 ± 5.9 years, P = 0.05), higher levels of serum beta 2-microglobulin (2.6 ± 1.3 versus 2.1 ± 0.9 mg/L, P = 0.002) and higher serum creatinine (76.5 ± 23.1 versus 70 ± 13.3 μmol/L, P = 0.005). In those individuals with GFR ≤ 90 mL/min, microalbuminuria occurred more frequently (28.0 versus 15.2%, P = 0.021). In contrast, gender, race, smoking, BMI, high-density lipoprotein or cholesterol level, presence of previous or current hepatitis B and C infection, CD4 cell count and HIV RNA level did not differ between those with and without microalbuminuria. Even when excluding patients treated with cART, CD4 cell count and HIV RNA level did not differ between those with or without microalbuminuria. No statistically significant difference was found in the prevalence of microalbuminuria between cART groups based on the duration of therapy (< 2 years, 8.6%; 2–5 years 10.5%; > 5 years 9.5%). When analysing gender separately, women with microalbuminuria showed no difference in age, SBP, DBP, HIV duration, creatinine and GFR groups compared with those without microalbuminuria, whereas men with microalbuminuria had higher cholesterol (5.4 ± 1.6 versus 5.0 ± 1.1 mmol/L, P = 0.038), but no difference in the beta 2-microglobulin level (2.4 ± 1.1 versus 2.2 ± 0.8 mg/L, P = 0.76), compared with those without microalbuminuria.

Microalbuminuria in HIV-infected Caucasian subjects compared with the general population

The prevalence of microalbuminuria was significantly higher in the HIV-infected, Caucasian, male subjects than in the population-based controls [31] in groups defined by age and gender (Table 2). No statistically significant difference was found in the prevalence of microalbuminuria between Caucasian, HIV-infected women, <50 years of age compared to the population-based controls.

Predictors of microalbuminuria among HIV-infected patients

Including the HIV-infected cohort in a multivariate analysis (adjusted OR), with microalbuminuria as the dependent variable and SBP, age, quartiles of HIV duration, serum beta 2-microglobulin, serum creatinine and GFR groups as independent variables, only SBP (P < 0.0001) and beta 2-microglobulin (P = 0.001) were found to be predictive of microalbuminuria (Table 3). Furthermore, the prevalence of microalbuminuria was significantly higher in subjects in the third quartile compared with the first quartile for duration of HIV infection (P = 0.018). These results were confirmed in a linear-by-linear association using an χ² test as a trend analysis for HIV duration quartiles in both the
Table 2. Prevalence of microalbuminuria among 348 HIV-infected Caucasian men and women compared with 2091 subjects from the control group

| Age groups | HIV-infected patients | Control group | OR (95% CI) | P      |
|------------|-----------------------|---------------|-------------|--------|
|            | Total | MA | Percentage | Total | MA | Percentage |             |        |
| Men < 50 years | 189   | 13  | 6.9       | 520   | 8   | 1.5       | 4.73 (1.8–12.70) | 0.0002 |
| Men 50–59 years | 81    | 11  | 13.6      | 200   | 8   | 4.0       | 3.77 (1.34–10.78) | 0.0038 |
| Men 60–79 years | 18    | 5   | 27.8      | 232   | 26  | 11.2      | 3.05 (0.87–10.22) | 0.04   |
| Women < 50 years | 52    | 3   | 5.8       | 614   | 16  | 2.4       | 2.29 (0.51–8.75)  | 0.18   |

MA, microalbuminuria. P-values were determined by the χ² test.
Women aged > 50 years were not analysed because of the low number in the HIV-infected group (n = 7).

Table 3. Predictors for microalbuminuria in HIV-infected subjects presented as unadjusted and adjusted odds ratios (n = 495)

| Characteristic or laboratory value | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------|------------------------|----------------------|
| Age (years)                       | 1.05 (1.02–1.08)ᵃ       | 1.007 (0.97–1.05)ᵃ   |
| SBP (mmHg)                        | 1.04 (1.02–1.05)ᵃ       | 1.03 (1.02–1.05)ᵃ    |
| DBP (mmHg)                        | 1.04 (1.01–1.07)ᵇ       | e                    |
| Duration since HIV test, quartiles (years) |  |                  |
| 1st                               | Reference               | Reference            |
| 2nd                               | 1.66 (0.53–5.2)ᵇ        | 1.89 (0.56–6.34)ᵇ    |
| 3rd                               | 3.78 (1.35–10.6)ᵈ       | 3.76 (1.26–11.2)ᵈ    |
| 4th                               | 2.79 (0.96–8.1)ᶜ        | 2.67 (0.88–8.14)ᶜ    |
| Beta 2-microglobulin (mg/L)       | 1.57 (1.17–2.1)ᵇ        | 1.69 (1.23–2.33)ᵇ    |
| Creatinine (µmol/L)               | 1.03 (1.01–1.05)ᵇ       | 1.0 (0.97–1.02)ᵇ     |
| GFR groups (mL/min)               |  |                  |
| <90                               | Reference               | Reference            |
| 2.75 (1.38–5.48)ᵈ                  | 1.91 (0.91–3.99)ᶜ       |

SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate.
Values were determined by logistic regression analysis. The candidate variables were defined with P-to-enter < 0.1.
ᵃP < 0.0001; ᵇP < 0.01; ᶜP < 0.05; ᵈP > 0.05.
DBP excluded because of the high Pearson correlation (>0.7) between SBP and DBP.

Discussion

The prevalence of microalbuminuria was 8.7% in this unselected cohort of HIV-infected patients and 9.2% in the Caucasian patients only, which is 2–4.7 times higher than in the general population. The association between HIV infection and microalbuminuria based on a single urine sample has previously been observed in selected study populations in the pre-cART era, with a prevalence ranging from 19 to 34% [27–29]. A recently published multicenter study, with selection bias of significant lipodystrophy as an entry criterion and not primarily aimed at the investigation of microalbuminuria, found a fivefold higher rate of microalbuminuria in HIV-infected patients than in a matched, but not population-based, control group [26], a result similar to ours despite disparities in study design and urine sampling procedures. In our study, the presence of microalbuminuria was based on three consecutive urine analyses collected prospectively. The importance of taking repeated measurements has been emphasized by Romundstad et al. [35], as albumin excretion may vary substantially and single-sample measurements lead to an overestimation of the true prevalence of microalbuminuria. To further minimize such overestimation, patients with known diabetes, hypertension or macroalbuminuria were not included in the HIV cohort or in the control group. Other strengths of our study are the unselected, single-center population, and standardized investigation with robust and repetitive measurements of urinary albumin excretion, using the same laboratory for all analyses.

Blood pressure was a major determinant of albumin excretion in our study, as has previously been demonstrated for other populations [36,37] and in an HIV-infected cohort [26]. Furthermore, serum beta 2-microglobulin, an inflammatory marker of HIV Immunoactivity [38], emerged as an independent predictor for urinary albumin excretion. This novel finding may suggest that other pathophysiological mechanisms beyond the haemodynamic effect may be linked to microalbuminuria in the HIV-infected
Microalbuminuria and HIV

Fig. 2. (a) Distributions of the prevalence of microalbuminuria (MA) related to the quartile durations since HIV test in the total population (n = 495), men (n = 354) and women (n = 141). (b) Distributions of the prevalence of MA related to the quartile levels of serum beta 2-microglobulin in the total HIV-infected population (n = 493), men (n = 353) and women (n = 140).

In this study, we could not show any association between the use of cART and microalbuminuria, which is in harmony with the results by Szczech et al. [26]. Nor did we observe significant differences between the duration of cART and microalbuminuria. Several studies have demonstrated increased CVD in HIV-infected patients receiving cART [5–7,41]. Consequently, metabolic side effects induced by cART have been implicated in the pathophysiological mechanism leading to CVD, but endothelial dysfunction may also be an important contributor [42]. Endothelial dysfunction has been proposed as a link between the presence of microalbuminuria and the increased risk of CVD in selected populations as well as in the general population [23,31,43], but remains to be evaluated in the HIV-infected population. However, be that as it may, microalbuminuria could serve as an early marker of enhanced cardiovascular risk and even of renal complications in the HIV-infected population as has been reported for other populations [30].

In conclusion, the prevalence of microalbuminuria in Caucasian, nondiabetic, nonhypertensive HIV-infected subjects was found to be 2–4.7 times higher than in a healthy, nondiabetic and nonhypertensive control population. The duration of HIV infection, serum beta 2-microglobulin level and SBP were independent predictors of microalbuminuria in our HIV cohort. Thus, we suggest that the mechanisms causing microalbuminuria in HIV-infected subjects are linked not only to haemodynamic factors, but also to some yet unknown factor related to the HIV infection, possibly endothelial dysfunction. This might associate microalbuminuria to the increased risk of CVD seen in...
HIV-infected subjects. However, the prognostic and clinical significance of microalbuminuria in HIV-infected patients is not yet known and prospective studies addressing this issue are clearly needed.

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Conflict of interest statement. None declared.

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