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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

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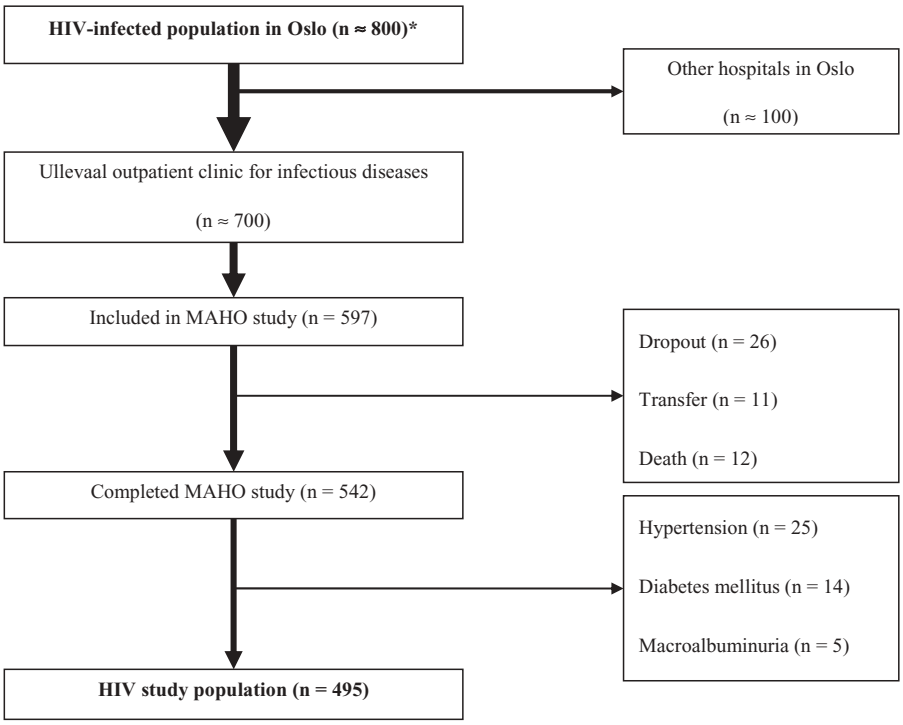

Fig. 1. Flow chart of the HIV-infected population in the study. Asterisk represents the estimated number of HIV-infected patients living in Oslo in 2004, based on the Norwegian Surveillance System for Communicable Diseases (MSIS).

[23,24]. 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 concession 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)[a]			
<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[a]			
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[a]	211 (42.6%)	163 (46%)	48 (34%)
Cholesterol (mmol/L)[b]	5.0 ± 1.1	5.0 ± 1.1	5.0 ± 1.1
BMI (kg/m^2)[b]	23.8 ± 3.4	23.8 ± 3.2	23.8 ± 3.9
HbA1c (%)[b]	5.2 ± 0.39	5.1 ± 0.35	5.2 ± 0.46
Hepatitis B positive[a]	22 (4.4%)	21 (5.9%)	1 (0.7%)
Hepatitis C positive[a]	46 (9.3%)	28 (7.9%)	18 (12.8%)
Duration since HIV test (years)[b]	7.3 ± 5.9	7.4 ± 5.9	7.2 ± 6.0
Beta 2-microglobulin (mg/L)[b]	2.1 ± 0.9	2.2 ± 0.9	2.0 ± 1.0
cART[a]			
Naïve throughout the study	141 (28.5%)	103 (29.1%)	38 (27.0%)
Naïve at study inclusion	22 (4.4%)	16 (4.5%)	6 (4.3%)
<2 years	162 (32.7%)	116 (32.8%)	46 (32.6%)
2–5 years	86 (17.4%)	56 (15.6%)	30 (21.3%)
>5 years	84 (17%)	63 (17.8%)	21 (14.9%)
HIV RNA (copies/mL)[c]	200 (0–31 000)	200 (0–35 500)	60 (0–14 000)
CD4 (10^9 cells/L)[c]	0.37 (0.24–0.55)	0.37 (0.25–0.56)	0.37 (0.22–0.53)
SBP (mmHg)[b]	129.5 ± 17.7	133.7 ± 17.0	119.1 ± 14.9
DBP (mmHg)[b]	80.2 ± 10.4	82.0 ± 10.5	75.7 ± 8.8
Creatinine (μmol/L)[b]	70.58 ± 14.5	75.3 ± 12.9	58.8 ± 11.4
GFR groups (mL/min)[a]			
>90	411 (83%)	297 (83.9%)	114 (80.9%)
<90	81 (17%)	55 (16.1%)	26 (18.4%)

BMI, body mass index; cART, combined antiretroviral therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate.
[a]Values are the number of patients and (percentage).
[b]Values are the mean ± SD.
[c]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, Matsusaka, 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^2. 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 Amplicor 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 EpiInfo database (EpiInfo™) for statistical analysis using SPSS software (SPSS Inc., version 14.0, Chicago, IL, USA). Microalbuminuric and gender groups were compared for continuous and categorical variables using Student's *t*-test, the Mann–Whitney *U* test and Pearson's χ^2 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 χ^2 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 0.2×10^9 cells/L. This rate did not differ between genders.

Microalbuminuria in HIV-infected patients

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 χ^2 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[a]

Age groups	HIV-infected patients			Control group			OR (95% CI)	*P*
	Total	MA	Percentage	Total	MA	Percentage		
	n	*n*		*n*	*n*			
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 χ^2 test.
Women aged > 50 years were not analysed because of the low number in the HIV-infected group ($n = 7$).
[a]From the HUNT study population.

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)[c]
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)[c]	1.89 (0.56–6.34)[c]
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)[c]
GFR groups (mL/min)		
>90	Reference	Reference
<90	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.
[a]$P < 0.0001$; [b]$P < 0.01$; [c]$P < 0.05$; [d]$P > 0.05$.
[e]DBP excluded because of the high Pearson correlation (>0.7) between SBP and DBP.

total population ($P = 0.019$) and men ($P = 0.003$), but not in women ($P = 0.51$), and for beta 2-microglobulin quartiles in the total population ($P = 0.035$) and women ($P = 0.027$), but not for men ($P = 0.3$). The prevalence of microalbuminuria in relation to duration of HIV infection and beta 2-microglobulin is presented for the total population and for men and women separately in Figure 2a and b.

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

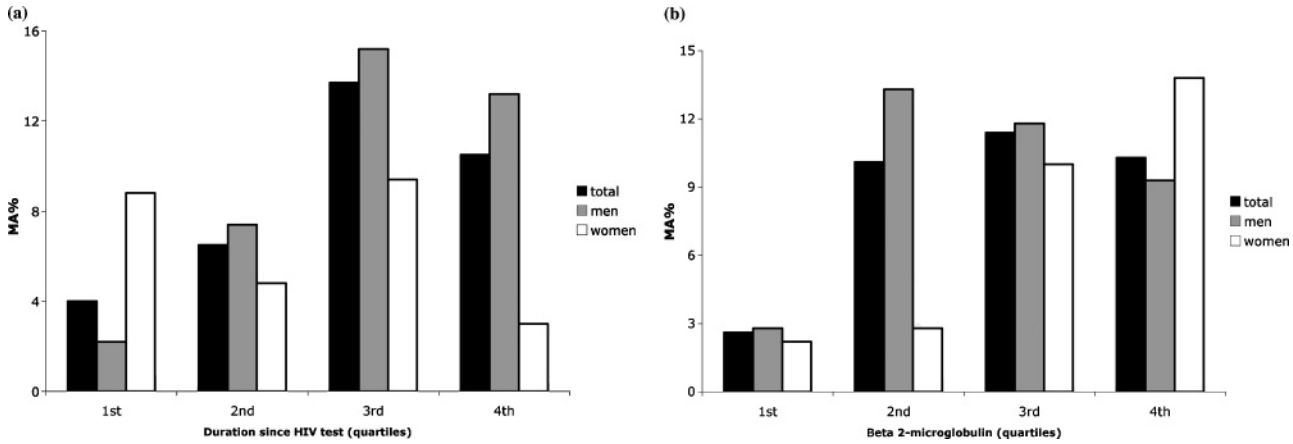

Fig. 2. (**a**) Distributions of the prevalence of microalbuminuria (MA) related to the quartile durations since HIV test in the total population ($n = 495$), men ($n = 354$) and women ($n = 141$). (**b**) Distributions of the prevalence of MA related to the quartile levels of serum beta 2-microglobulin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

state. This is further supported by the observation that subjects with microalbuminuria had longer durations of HIV infection than those without microalbuminuria. Inflammatory activity as a cause of microalbuminuria has been observed in nondiabetic subjects with cancer, inflammatory bowel disease and rheumatoid arthritis as well as in subjects with type 2 diabetes mellitus [39]. Moreover, endothelial dysfunction maintained by various inflammatory processes has been proposed as a possible cause of microalbuminuria [40]. Therefore, we hypothesize that microalbuminuria could depend on some chronic inflammatory process induced by HIV infection itself, not excluding the possibility that surrogate parameters of the immune function may play a role, even though we did not find any association between CD4 cell count or HIV RNA and microalbuminuria in the present study.

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 a univariate analysis, microalbuminuria was linked to renal function, even if this was not maintained in a multivariate analysis. In contrast, Szczech *et al*. found no difference in serum creatinine or GFR in microalbuminuric compared to normoalbuminuric HIV-infected individuals [26]. On the other hand, in a selected South African HIV cohort where persistent microalbuminuric patients underwent renal biopsy, microalbuminuria was found to be an early indicator of renal disease [30]. A variety of renal diseases may occur and constitute an increasingly frequent complication during the course of HIV infection [13], hence the presence of microalbuminuria cannot be neglected.

We used a historical but population-based and nondiabetic control group [31]. During the 10-year time span, there has most likely been a change in awareness and treatment of microalbuminuria in diabetic subjects in Norway. However, little change in healthcare has occurred in the nondiabetic population. The age distribution of subjects younger than 50 years was slightly different compared with our cohort. This resulted in higher proportions of younger men and older women in the control group than in our study population. Furthermore, the ethnicity differed between the HIV-infected group and the control group, as the proportion of immigrants was higher in the HIV-infected group. Therefore, comparison to the population-based control group was limited to Caucasian HIV-infected patients. To establish a separate control group, including groups of different ethnicity, for this study would most likely not be possible or require an immense effort and would seem rather futile given that a very meticulous investigation had already been undertaken in Norway [21,31,35,44]. Nevertheless, ethnicity did not affect the results in this study.

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.

References

1. Palella FJ, Jr, Delaney KM, Moorman AC *et al*. (HIV Outpatient Study Investigators). Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; 338: 853–860
2. d'Arminio Monforte A, Sabin CA, Phillips A *et al*. The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy. *Arch Intern Med* 2005; 165: 416–423
3. Hicks C, Currier J, Sax P *et al*. Current management challenges in HIV: tolerability of antiretrovirals and metabolic complications. *Aids Patient Care STDS* 2003; 17: 221–233
4. Mary-Krause M, Cotte L, Simon A *et al*. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS* 2003; 17: 2479–2486
5. Friis-Moller N, Sabin CA, Weber R *et al*. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; 349: 1993–2003
6. Iloeje UH, Yuan Y, L'Italien G *et al*. Protease inhibitor exposure and increased risk of cardiovascular disease in HIV-infected patients. *HIV Med* 2005; 6: 37–44
7. Bozzette SA, Ake CF, Tam HK *et al*. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med* 2003; 348: 702–710
8. Law MG, Friis-Moller N, El-Sadr WM *et al*. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med* 2006; 7: 218–230
9. Valcour VG, Shikuma CM, Shiramizu BT *et al*. Diabetes, insulin resistance, and dementia among HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2005; 38: 31–36
10. Samaras K, Wand H, Law M *et al*. Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and hypoadiponectinemia. *Diabetes Care* 2007; 30: 113–119
11. Baliga RS, Chaves AA, Jing L *et al*. AIDS-related vasculopathy: evidence for oxidative and inflammatory pathways in murine and human AIDS. *Am J Physiol Heart Circ Physiol* 2005; 289: H1373–H1380
12. Stein JH, Klein MA, Bellehumeur JL *et al*. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. *Circulation* 2001; 104: 257–262
13. Schwartz EJ, Szczech LA, Ross MJ *et al*. Highly active antiretroviral therapy and the epidemic of HIV+ end-stage renal disease. *J Am Soc Nephrol* 2005; 16: 2412–2420
14. Szczech LA, Gupta SK, Habash R *et al*. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int* 2004; 66: 1145–1152
15. Franceschini N, Napravnik S, Eron JJ, Jr *et al*. Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. *Kidney Int* 2005; 67: 1526–1531
16. Gardner LI, Holmberg SD, Williamson JM *et al*. Development of proteinuria or elevated serum creatinine and mortality in HIV-infected women. *J Acquir Immune Defic Syndr* 2003; 32: 203–209
17. Szczech LA, Hoover DR, Feldman JG *et al*. Association between renal disease and outcomes among HIV-infected women receiving or not receiving antiretroviral therapy. *Clin Infect Dis* 2004; 39: 1199–1206
18. Valle R, Haragsim L. Nephrotoxicity as a complication of antiretroviral therapy. *Advances in Chronic Kidney Disease* 2006; 13: 314–319
19. Bruggeman LA, Ross MD, Tanji N *et al*. Renal epithelium is a previously unrecognized site of HIV-1 infection. *J Am Soc Nephrol* 2000; 11: 2079–2087
20. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B *et al*. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 2004; 110: 32–35
21. Romundstad S, Holmen J, Kvenild K *et al*. Microalbuminuria and all-cause mortality in 2,089 apparently healthy individuals: a 4.4-year follow-up study. The Nord-Trondelag Health study (HUNT), Norway. *Am J Kidney Dis* 2003; 42: 466–473
22. Stuveling EM, Hillege HL, Bakker SJL *et al*. C-reactive protein and microalbuminuria differ in their associations with various domains of vascular disease. *Atherosclerosis* 2004; 172: 107–114
23. Stehouwer CD, Nauta JJ, Zeldenrust GC *et al*. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. *Lancet* 1992; 340: 319–323
24. Russo LM, Comper WD, Osicka TM. Mechanism of albuminuria associated with cardiovascular disease and kidney disease. *Kidney Int–Suppl* 2004: S67–S68
25. Weir MR. Microalbuminuria and cardiovascular disease. *Clin J Am Soc Nephrol* 2007; 2: 581–590
26. Szczech LA, Grunfeld C, Scherzer R *et al*. Microalbuminuria in HIV infection. *AIDS* 2007; 21: 1003–1009
27. Kabanda A, Vandercam B, Bernard A *et al*. Low molecular weight proteinuria in human immunodeficiency virus-infected patients. *Am J Kidney Dis* 1996; 27: 803–808
28. Luke DR, Sarnoski TP, Dennis S. Incidence of microalbuminuria in ambulatory patients with acquired immunodeficiency syndrome. *Clin Nephrol* 1992; 38: 69–74
29. Kimmel PL, Umana WO, Bosch JP. Abnormal urinary protein excretion in HIV-infected patients. *Clin Nephrol* 1993; 39: 17–21
30. Han TM, Naicker S, Ramdial PK *et al*. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. *Kidney Int* 2006; 69: 2243–2250
31. Romundstad S, Holmen J, Hallan H *et al*. Microalbuminuria, cardiovascular disease and risk factors in a nondiabetic/nonhypertensive population. The Nord-Trondelag Health study (HUNT, 1995–97), Norway. *J Intern Med* 2002; 252: 164–172
32. Pontremoli R, Sofia A, Ravera M *et al*. Prevalence and clinical correlates of microalbuminuria in essential hypertension: the MAGIC Study. Microalbuminuria: a Genoa investigation on complications. *Hypertension* 1997; 30: 1135–1143
33. Levey AS, Bosch JP, Lewis JB *et al*. (Modification of Diet in Renal Disease Study Group). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; 130: 461–470
34. Ormaasen V, Bruun JN, Sandvik L *et al*. Prognostic value of changes in CD4 count and HIV RNA during the first six months on highly active antiretroviral therapy in chronic human immunodeficiency virus infection. *Scand J Infect Dis* 2003; 35: 383–388
35. Romundstad S, Holmen J, Hallan H *et al*. Microalbuminuria and all-cause mortality in treated hypertensive individuals: does sex matter? The Nord-Trondelag Health study (HUNT), Norway. *Circulation* 2003; 108: 2783–2789

36. Damsgaard EM, Froland A, Jorgensen OD *et al*. Microalbuminuria as predictor of increased mortality in elderly people. *BMJ* 1990; 300: 297–300
37. Yudkin JS, Forrest RD, Jackson CA. Microalbuminuria as predictor of vascular disease in non-diabetic subjects. Islington diabetes survey. *Lancet* 1988; 2: 530–533
38. Lacey JN, Forbes MA, Waugh MA *et al*. Serum beta 2-microglobulin and human immunodeficiency virus infection. *AIDS* 1987; 1: 123–127
39. Festa A, D'Agostino R, Howard G *et al*. Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: the insulin resistance atherosclerosis study. *Kidney Int* 2000; 58: 1703–1710
40. Gosling P. Microalbuminuria: a marker of systemic disease. *Hosp Med* 1995; 54: 285–290
41. Saves M, Chene G, Ducimetiere P *et al*. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin Infect Dis* 2003; 37: 292–298
42. Triant VAa, Grinspoon SKb. Vascular dysfunction and cardiovascular complications. *Curr Opin in HIV & AIDS* 2007; 2: 299–304
43. Pedrinelli R, Giampietro O, Carmassi F *et al*. Microalbuminuria and endothelial dysfunction in essential hypertension. *Lancet* 1994; 344: 14–18
44. Hallan H, Romundstad S, Kvenild K *et al*. Microalbuminuria in diabetic and hypertensive patients and the general population—consequences of various diagnostic criteria—the Nord-Trondelag Health study (HUNT). *Scand J Urol Nephrol* 2003; 37: 151–158

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