Urinary Albumin Excretion Is Increased in Patients with Rheumatoid Arthritis and Associated with Arterial Stiffness

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ABSTRACT. ***Objective.*** Rheumatoid arthritis (RA) is associated with increased risk of cardiovascular disease (CVD). High urinary albumin excretion is a risk factor for CVD in the general population, but its role in atherosclerosis in patients with RA is not well defined.

Methods. We determined the urine albumin to creatinine ratio (UACR) in 136 patients with RA and 79 controls. Individuals with diabetes or a clinical history of CVD were excluded. We measured coronary artery calcium (CAC) with electron beam computer tomography and augmentation index (AIx) using pulse wave analysis. In patients with RA, erythrocyte sedimentation rate and concentrations of vascular cell adhesion protein-1 (VCAM-1), interleukin 10 (IL-10), C-reactive protein, IL-6, tumor necrosis factor-α, and cystatin-C were measured and results correlated with UACR.

Results. Patients with RA had higher UACR [median (interquartile range): 7.6 (4.0–15.5) mg/g] than control subjects: 5.6 (3.3–9.0) mg/g; $p = 0.02$. The presence of CAC was not associated with UACR in RA or control subjects. In patients with RA, UACR was significantly correlated with AIx (rho = 0.24, $p = 0.01$), higher levels of VCAM-1 (rho = 0.2, $p = 0.01$), and lower levels of IL-10 (rho = –0.2, $p = 0.02$). The association between AIx and higher UACR remained significant in multivariate analysis [β coefficient of 1.5 (95% CI 0.1–2.8), $p = 0.03$ that adjusted for age, sex, and race].

Conclusion. Urinary albumin excretion was higher in patients with RA than controls and correlated with increased arterial stiffness, higher VCAM-1, and lower IL-10 concentrations. (First Release Feb 1 2015; J Rheumatol 2015;42:593–8; doi:10.3899/jrheum.141295)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
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Rheumatoid arthritis (RA) is a chronic inflammatory disease that is associated with an increased risk for cardiovascular disease (CVD); this increase in risk is not explained by traditional CVD risk factors[1,2]. Therefore, there is a need to identify additional markers of early CVD in this patient population. Urinary albumin excretion is a well-studied marker of CV risk in the general population. The normal rate of albumin excretion is < 30 mg/day[3], and albuminuria is defined as excretion of ≥ 30 mg/day[4]. Moderate albuminuria (previously known as microalbuminuria) is currently defined as urinary albumin excretion between 30 to 299 mg/day and appears to be a sign of renal endothelium dysfunction[5]. Macroalbuminuria is defined as urinary albumin excretion of ≥ 300 mg/day. There is a dose-response relationship between urinary albumin excretion and CV risk, with a 30% increase in CV deaths for every 2-fold increase in urinary albumin excretion. Interestingly, this increased risk was observed at concentrations far below the clinically accepted cutoff point of 300 mg/l for macroalbuminuria[6].

A report, using data from the US National Health and Nutrition Examination Survey-3, estimated that the prevalence of albuminuria in the general population was 7.8%[7]. Albuminuria appears to be frequent in RA; a study in a contemporary cohort of patients with RA who did not receive treatment with either penicillamine or gold estimated that 11.9% patients had microalbuminuria[8]. However, there is little information about the relationship between albuminuria and preclinical CVD in patients with RA. Therefore, we hypothesized that urinary albumin excretion may be higher in patients with RA and also may be a marker of inflammation and increased asymptomatic CVD.

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MATERIALS AND METHODS

Study population. In a cross-sectional study, we evaluated 136 patients with RA and 79 control subjects without inflammatory disease who were enrolled in ongoing studies of CVD and risk factors. Details of the recruitment procedures and study methods have been described[9]. In summary, eligible patients with RA met the 1987 American College of Rheumatology classification criteria for RA[10], were older than 18 years of age, and had disease duration of over 1 year. Control subjects did not meet the criteria for any autoimmune disease, and were frequency-matched to patients for age, sex, and race. Patients were recruited from local rheumatology clinics in Nashville, Tennessee, USA. For this study, patients with RA and controls with a clinical diagnosis of coronary artery disease or diabetes mellitus were excluded. All participating subjects provided written informed consent prior to enrollment. The study was approved by the Institutional Review Board at Vanderbilt University.

Clinical variables. Patient assessment included a detailed review of medical records, a standardized interview, physical examination, and laboratory testing. We collected information about demographics, CVD risk factors, disease duration and activity for patients, medications, and smoking history. The presence of hypertension (HTN) was defined by the use of antihypertensive medications, or a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg. The average of 2 blood pressure measurements obtained 5 min apart was used. Height and weight were measured and body mass index (BMI) calculated. A fasting blood sample was obtained for laboratory testing for high-density lipoprotein and low-density lipoprotein cholesterol (LDL-C), triglycerides, glucose, insulin, and creatinine. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease formula[11]. Insulin sensitivity was determined using the homeostasis model assessment of insulin resistance index, defined as fasting glucose (mmol/l) × fasting insulin (μIU/ml/22.5). Patients were classified as having metabolic syndrome or not using the modified World Health Organization definition, which requires the presence of insulin resistance and 2 of the following 3 criteria: central obesity, dyslipidemia, and HTN[12]. We calculated the Framingham risk score[13] as an index of CV risk prediction.

Inflammatory markers and urinary albumin excretion. In patients with RA, serum concentrations of vascular cell adhesion protein-1 (VCAM-1), interleukin 10 (IL-10), IL-6, and tumor necrosis factor-α (TNF-α) were measured using a multiplex platform (Lincoplex Inc.). Serum cystatin-C concentrations were measured by ELISA. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured by the Vanderbilt University Medical Center Clinical Laboratory. Prior to 2003, this laboratory reported low concentrations as < 3 mg/dl; therefore, in patients with CRP < 3 mg/dl, CRP concentrations were re-measured by ELISA (Millipore Corp).

Early morning urine samples were also collected. Urine was stored at –80ºC. The kinetic alkaline picrate method was used to measure urine albumin concentrations and the turbidimetric immunoassay to quantify urine creatinine concentrations. Their coefficients of variation were 3.1% and 2.6%, respectively. Tests were done at the Vanderbilt University Medical Center Clinical Laboratory. To standardize the results of urine microalbumin measurements, the urine albumin to creatinine ratio (UACR) was calculated.

The primary analyses were based on results of UACR as a continuous variable, but planned secondary analyses included data categorized by presence or absence of albuminuria, defined as a UACR ratio of ≥ 30 mg/g[14].

Coronary artery calcification. As described[9], patients and control subjects underwent imaging with chest tomography using an Imatron C-150 scanner (GE/Imatron). Forty slices of 3 mm thickness and 100 ms scanning time were obtained during a single breath-holding period from the aortic arch to the level of the diaphragm. The presence of CAC was determined by a single expert investigator (PR), who was blinded to the subjects' clinical status.

Augmentation index. Augmentation index (AIx), a measure of vascular stiffness, was determined using noninvasive applanation tonometry and pulse wave analysis (AtCor Medical), as described[15]. AIx values were normalized to a heart rate of 75 bpm. Results were available in 110 patients.

Statistical analysis. For continuous variables, data are presented as mean and SD or median with interquartile range (IQR), based on the distribution. For categorical variables, data are presented as frequencies and percentages. We compared traditional risk factors, UACR, and measures of subclinical CVD between RA and controls using Fisher's exact test and Wilcoxon rank-sum for categorical and continuous variables, respectively. The association of UACR with clinical and laboratory variables was assessed using Spearman's correlation coefficient and Wilcoxon rank-sum test, as appropriate. The associations between UACR and CAC and AIx were adjusted for age, sex, and race using linear or logistic multivariate analyses, as appropriate. These covariates were selected based on their clinical significance while maintaining adequate test power. In patients with RA, we used Fisher's exact test to examine the association of moderate albuminuria (> 30 mg/g) with each of the following variables: sex, HTN, presence of metabolic syndrome, use of nonsteroidal anti-inflammatory drugs (NSAID), and presence of CAC.

All statistical analyses were conducted using STATA software version 12.1 (StataCorp). A 2-sided significance level of 5% was used.

RESULTS

Baseline characteristics. Patients with RA and control subjects had a similar mean age, race, and sex distribution (Table 1). There was no significant difference between the 2 groups regarding other traditional risk factors for CVD including HTN, BMI, family history of coronary artery disease, Framingham score, or renal function. Fifty-four percent of patients with RA were taking low doses of prednisone, 74% were taking low doses of weekly methotrexate (MTX), 18% were taking leflunomide, and 21% were receiving an anti-TNF agent.

As reported in patients from this cohort[9,15], patients with RA had higher prevalence of CAC (p = 0.03) and higher AIx (p = 0.01) than control subjects (Table 1).

Urinary albumin excretion in RA and control subjects. Patients with RA had higher urinary excretion of albumin [median (IQR) UACR 7.6 (4.0–15.5) mg/g] than control subjects [5.6 (3.3–9.0) mg/g, p = 0.02; Figure 1].

None of the study participants had severe chronic kidney disease. Their mean creatinine was 0.8 ± 0.2 mg/dl and their mean GFR was 89 ± 23 (range: 28–161) ml/min per 1.73 m^2. Four study participants (3 patients with RA and 1 control subject) had an estimated GFR < 45 ml/min per 1.73 m^2. Excluding them from the analysis did not change our results (p = 0.02).

The prevalence of albuminuria (UACR > 30 mg/g) was also higher in patients with RA (11.8%) than in control subjects (3.8%, p = 0.04).

Traditional CVD risk factors and urinary albumin excretion in patients with RA. The association between UACR and traditional CVD risk factors was assessed in patients with RA. No association was observed between UACR and multiple other CVD risk factors including age, sex, BMI, LDL-C, insulin resistance, or Framingham score (Table 2).

Table 1. Baseline characteristics of patients with rheumatoid arthritis and matched controls. Data presented as n (%), mean ± SD, or median (interquartile range).

Characteristics	RA	Controls	p
Age	52.9 ± 12.1	51.6 ± 10.5	0.52
Sex, female	100 (73.5)	54 (68.4)	0.44
Race, white	120 (88.2)	67 (84.8)	0.24
Smoking			
Current	36 (26.5)	7 (8.9)	0.002
Past	60 (44.1)	28 (35.4)	0.25
Family history of early CAD	38 (27.9)	21 (26.6)	0.88
Weight, kg	81.8 ± 19.2	79.2 ± 17.4	0.35
Height, m	1.7 ± 0.1	1.7 ± 0.1	0.75
BMI, kg/m^2	29.0 ± 6.3	28.1 ± 5.5	0.37
Waist circumference, cm	93.9 ± 15.5	87.7 ± 12.5	0.003
Hypertension	66 (48.5)	27 (34.2)	0.07
Systolic BP, mmHg	131.1 ± 19.8	127.1 ± 16.1	0.15
Diastolic BP, mmHg	74.2 ± 10.6	72.2 ± 9.1	0.24
Use of antihypertensives	42 (30.9)	17 (21.5)	0.11
Use of ACE inhibitors	18 (13.6)	9 (11.5)	0.42
Use of ARB	7 (5.1)	3 (3.9)	0.46
HDL cholesterol, mg/dl	47.4 ± 14.1	47.2 ± 12.4	0.88
LDL cholesterol, mg/dl	113.2 ± 32.6	123.4 ± 31.8	0.02
Triglycerides, mg/dl	125.0 ± 68.8	111.3 ± 51.5	0.20
Total cholesterol, mg/dl	185.7 ± 35.4	192.9 ± 34.4	0.13
Statin use	11 (8.1)	7 (8.9)	0.82
Serum creatinine, mg/dl	0.8 ± 0.2	0.8 ± 0.2	0.66
GFR, ml/min per 1.73 m^2	89.6 ± 25.5	88.0 ±17.7	0.66
Insulin resistance – HOMA-IR index	1.9 ± 1.9	0.8 ± 0.7	< 0.001
Metabolic syndrome	39 (28.7)	13 (16.5)	0.05
Framingham risk score, units	11.5 ± 6.1	10.4 ± 5.4	0.21
Coronary artery calcium score (Agatston units)	0 (0–68.0)	0 (0–4.8)	0.03
Augmentation index*, %	29.9 ± 9.8	25.6 ± 10.2	0.01
DAS28	3.6 ± 1.6	N/A	

* Augmentation index is normalized to a heart rate of 75 bpm. ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; GFR: glomerular filtration rate; BP: blood pressure; CAD: coronary artery disease; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; DAS28: 28-joint Disease Activity Score; N/A: not applicable.

The association of the presence of albuminuria (UACR > 30 mg/g) and CVD risk factors was also assessed in patients with RA. We found a significant association between albuminuria and HTN (p = 0.01), but not with the metabolic syndrome.

Urinary albumin excretion and inflammatory markers in RA. In patients with RA, we found a significant association between UACR and VCAM-1 with a rho of 0.2 and p value of 0.01 (Table 2). There was also a significant association between UACR and IL-10, with a rho of –0.2 and p value of 0.02. No association was observed with other studied inflammatory markers including ESR, CRP, IL-6, TNF-α, and cystatin-C.

Urinary albumin excretion and preclinical atherosclerosis in RA. In patients with RA, there was a significant association between log-transformed UACR and AIx with a β coefficient of 1.9 (95% CI, 0.4–3.4) and a p value of 0.01 (Table 3). This association remained significant after adjusting for age, sex, and race (p value 0.03). Additional multivariate analyses confirmed that our primary finding was significant. The first analysis was done with a model including age, sex, race, HTN, and current use of hydroxychloroquine (HCQ; β coef. 1.55, p = 0.026). Second, a model in which age, sex, race, other traditional CVD risk factors including smoking, HTN, ESR, and disease duration were also adjusted for (β coef. 1.62, p = 0.024) showed that the significant association between UACR and AIx in this group remained significant. The association between UACR and AIx also remained significant after adjustment for smoking status and abdominal circumference (p = 0.038). This association was not observed in controls.

There was also no significant association between UACR and CAC in either group of subjects (Table 3).

Medications and urinary albumin excretion in RA. In patients with RA, UACR was not associated with the use of angiotensin-converting enzyme inhibitors, angiotensin II

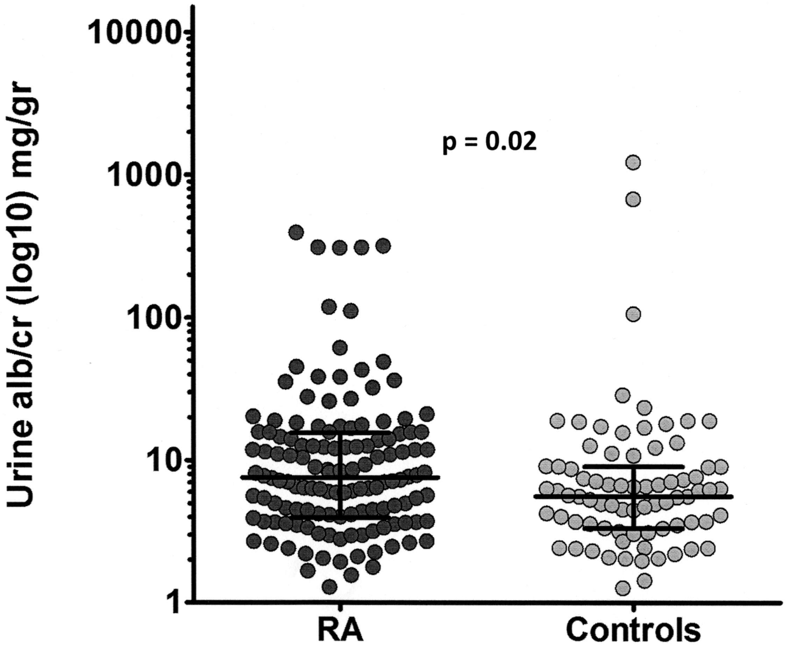

Figure 1. Patients with rheumatoid arthritis (RA) had higher urinary excretion of albumin than control subjects.

Table 2. The association between CVD risk factors and markers of inflammation with UACR in patients with rheumatoid arthritis.

	Spearman rho	p
Cardiovascular risk factors		
Age	0.16	0.07
Cumulative smoking	–0.11	0.19
BMI	–0.11	0.21
Waist circumference	–0.08	0.38
Systolic BP	0.07	0.44
Diastolic BP	–0.09	0.28
LDL	0.02	0.80
Total cholesterol	0.04	0.63
Creatinine	–0.13	0.13
Insulin resistance – HOMA-IR	0.0	0.80
Framingham Risk Score	0.07	0.40
Inflammatory markers		
ESR	0.13	0.13
CRP	0.07	0.31
IL-6	–0.02	0.87
TNF-α	–0.01	0.88
VCAM-1*	0.22	0.01
IL-10*	–0.20	0.02
Cystatin-C	–0.03	0.72

*p < 0.05. CVD: cardiovascular disease; UACR: urine albumin to creatinine ratio; BMI: body mass index; BP: blood pressure; LDL: low-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL: interleukin; TNF-α: tumor necrosis factor-α; VCAM-1: vascular cell adhesion protein-1.

receptor blockers, steroids, NSAID, MTX, or anti-TNF. However, there was a trend toward a lower UACR in patients with RA who were taking HCQ [median 5.7 (3.0–8.6)] compared to those who were not [9.0 (4.2–15.8) mg/g; p = 0.05].

An exploratory analysis suggests that patients with microalbuminuria (n = 16) were older and had higher ESR than those without microalbuminuria (n = 120).

DISCUSSION

There are 3 main findings of our study. First, patients with RA have higher urinary albumin excretion and a higher prevalence of albuminuria than control subjects. Second, high urinary albumin excretion was associated with arterial stiffness in patients with RA. Third, in patients with RA, urinary albumin excretion correlated positively with VCAM and negatively with IL-10 concentrations.

There are several reasons why patients with RA can develop albuminuria. Initial studies attributed the presence of albuminuria to either side effects of medications (primarily gold and penicillamine)[16] or to glomerular or tubular nephropathies. However, Niederstadt, *et al* found that albuminuria in patients with RA was secondary to either drug therapy or to vasculitis in only 25% of patients[17]. And later, a study in a more contemporary cohort of patients with RA found that in the absence of treatment with gold or penicillamine, microalbuminuria was associated with

Table 3. The association between UACR and subclinical cardiovascular disease.

		UACR			
		Unadjusted		Adjusted for Age, Sex, and Race	
		β coef. (95% CI)	p	β coef. (95% CI)	p
AIx	RA	1.9 (0.4–3.4)	0.01	1.5 (0.1–2.8)	0.03
	Controls	–1.3 (–3.6 to 1.0)	0.26	–0.9 (–2.8 to 1.0)	0.34
		OR (95% CI)	p	OR (95% CI)	p
CAC	RA	0.9 (0.7–1.2)	0.64	0.7 (0.5–1.1)	0.13
	Controls	0.6 (0.4–1.1)	0.11	0.7 (0.4–1.3)	0.31

UACR: urine albumin to creatinine ratio; AIx: augmentation index; RA: rheumatoid arthritis; CAC: coronary artery calcium.

cardiovascular risk factors, including HTN and insulin resistance[8]. Thus, rather than just being a manifestation of primary renal diseases, albuminuria also emerged as a potential marker of diffuse vascular injury.

Consistent with the notion that albuminuria is a marker of diffuse vascular injury, our results indicate that higher urinary albumin excretion correlates with AIx, a marker of arterial stiffness. These results are also consistent with findings in other populations, showing that hypertensive patients with increased urinary albumin excretion had significantly increased AIx independent of other risk factors[18]. In patients with type I diabetes mellitus, there was also a significant association between increased albumin excretion rate and higher augmentation pressure, another measure of arterial stiffness[19]. Increased arterial stiffness can occur as a result of functional changes, for example endothelial dysfunction, or because of structural changes, such as atherosclerosis.

Further supporting the connection between albuminuria and endothelial dysfunction, our data showed a significant association between UACR and VCAM-1. These findings are consistent with previous reports indicating that VCAM-1 levels are associated with atherosclerosis, as determined by carotid media thickness and carotid plaque[20] and with endothelial dysfunction and inflammation in patients with RA[21,22,23].

VCAM-1 is expressed on the endothelium and serves as a marker of endothelial cell activation and vascular inflammation. It mediates the adhesion of inflammatory cells to the endothelium and their penetration into areas of inflammation and has been implicated in numerous conditions, including atherosclerosis and heart failure[24]. A similar association between microalbuminuria and VCAM-1 was previously observed in patients with type I and type II diabetes[25,26]. On the other hand, we found a significant inverse association between UACR and IL-10, a molecule with antiinflammatory properties[27]. Additional studies are needed to further investigate the role of IL-10 and the other inflammatory cytokines in atherosclerosis in patients with RA.

In contrast to our findings with AIx, no significant association was observed between UACR or albuminuria with CAC in patients with RA. Sammut, *et al*[28] showed an association between albuminuria and CAC; however, this association lost statistical significance after adjusting for other cardiovascular risk factors.

Our study has a few limitations. Because it is cross-sectional, we cannot establish a temporal sequence. Also, only 1 measure of UACR was obtained. Because urine albumin excretion is highly dependent on multiple factors including exercise within 24 h, fever, pyuria, and hyperglycemia, the prevalence of microalbuminuria might have been overestimated. However, we excluded patients with diabetes and no patient reported fever or urinary symptoms.

Urinary albumin concentrations were higher in patients with RA than controls. Urine albumin correlated with increased arterial stiffness, higher VCAM-1, and lower IL-10 concentrations, providing further evidence for the hypothesis that albuminuria is a marker of atherosclerotic risk.

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