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Albuminuria in Rheumatoid Arthritis: Associations with RA Characteristics and Subclinical Atherosclerosis

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Abstract

Background—Albuminuria is a marker for subclinical cardiovascular disease (CVD) in the general population. It is uncertain whether this association is present in patients with rheumatoid arthritis (RA), a population with increased atherosclerosis and CVD events.

Methods—Urine albumin from a spot morning collection was measured and the ratio of urine albumin:creatinine (uACR) calculated for RA and a population-based sample of demographically matched non-RA controls. Associations of elevated uACR (≥ 25mg/g for women and ≥ 17mg/g for men) with CVD risk factors and measures of atherosclerosis [coronary artery calcification (CAC) and ultrasound-determined maximal intima-media thickness (IMT) of the common (CCA) and internal (ICA) carotid arteries, and presence of focal plaque in the ICA] were compared cross-sectionally according to RA status.

Results—196 RA patients were compared with 271 non-RA controls. Elevated uACR was found in 18% of the RA patients vs. 17% of the controls (p=0.89). After adjustment, RA was associated with 67% lower odds of elevated uACR (p=0.016). Higher serum creatinine levels and hypertension were both strongly and significantly associated with elevated uACR in the control group, but not in the RA group (p-value for interaction < 0.05 for both). Among RA characteristics,

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Competing Interests

None

the adjusted prevalence of elevated uACR among TNF inhibitor users was less than half that of non-users (9% vs. 20%, respectively; $p=0.047$).

Conclusion—There was no association in the RA group of elevated uACR with measures of atherosclerosis, nor with several key cardiometabolic risk factors, suggesting a lower utility for elevated uACR as an indicator of subclinical CVD in RA.

Keywords

microalbuminuria; rheumatoid arthritis; cardiovascular disease; risk factors

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory systemic autoimmune disorder, frequently resulting in significant joint deformity, disability and reduced life expectancy(1, 2). The excess mortality seen in the RA population is mainly due to cardiovascular disease (CVD)(3). As CVD is more prominent in the RA population, understanding indicators and contributors to atherosclerosis is of great importance.

Microalbuminuria, defined as increased excretion of albumin above the range for healthy individuals that is also undetectable by dipstick testing(4), has been implicated as a marker of kidney disease, subclinical cardiovascular disease(5, 6) and endothelial cell dysfunction(7). Microalbuminuria is also thought to reflect a low-grade inflammatory state(8). In non-diabetic populations, the prevalence of microalbuminuria ranges from 6.3% to 13%(9). Among adults without established CVD, higher urinary albumin excretion suggested the presence of subclinical CVD(5). Furthermore, in a study of a population of 1,568 non-diabetic and non-hypertensive individuals, even low levels of microalbuminuria were associated with a higher risk of CVD events and mortality(9). Urine albumin to creatinine ratio (uACR) is a measurement of microalbuminuria, and specifies the ratio of quantified urinary albumin to urinary creatinine.

There are few studies of elevated uACR or microalbuminuria in the RA population. Sihvonen et al. found that the most common cause of death in RA patients with microalbuminuria was CVD(10). Microalbuminuria has been reported with increased frequency in patients with RA compared with controls (27.7% vs. 7.8%)(11); however, this study included RA patients treated with gold and penicillamine. Pieringer et al. recently reported that in a large cross-sectional study of RA patients, despite an increased CV risk, urinary albumin excretion was not different in RA patients compared with non-RA controls(12). In another study, the prevalence of microalbuminuria in 342 RA patients was found to be 12%, and no association between microalbuminuria and clinical CVD, including coronary heart disease (CHD), cerebrovascular accident (CVA) and peripheral artery disease (PAD), was detected(13). However, there has not yet been a study in patients with RA exploring the association of microalbuminuria with longitudinal measures of subclinical CVD.

For this study, we explored the prevalence of elevated uACR in RA patients compared with a demographically matched group without RA. Further, we explored whether risk factors for

albuminuria differed between RA patients and controls, and whether there were RA-associated differences in the associations of elevated uACR with measures of subclinical coronary, carotid, and peripheral atherosclerosis, both at baseline and longitudinally over approximately 3 years. Finally, we explored which RA characteristics were associated with elevated uACR. We hypothesized that microalbuminuria would be more prevalent in the RA group and would be associated with a greater burden of subclinical atherosclerosis.

METHODS

Study Participants and Timing of Visits

Participants were enrolled in ESCAPE RA (Evaluation of Subclinical Cardiovascular disease And Predictors of Events in Rheumatoid Arthritis), a prospective cohort study investigating subclinical CVD in RA that has been described in detail in prior publications(14, 15).

Participants were included in the study if they met the 1987 RA classification criteria(16), had been diagnosed with RA for ≥ 6 months, and were 45–84 years of age. Participants were excluded if they had a history of self-reported physician diagnosed cardiovascular disease at baseline.

A non-RA control group was selected from the Baltimore cohort of the Multi Ethnic Study of Atherosclerosis (MESA). MESA investigated the prevalence, correlates and progression of subclinical cardiovascular disease (CVD) in a population-based sample of 6,500 men and women aged 45–84 years old(17). Like ESCAPE, individuals with known CVD at baseline were not eligible. Controls were selected to be frequency matched to the RA group on age (within three years), gender and race/ethnicity. MESA enrollees were excluded based on the use of common RA disease modifying agents.

Among the 197 RA patients completing the baseline visit, 186 (94%) returned for the second visit (occurring an average of 21 ± 3 months post-baseline) and 158 (80%) returned for the third visit, (occurring an average of 39 ± 4 months post-baseline). Only controls with complete data were included. The study was approved by the Institutional Review Board of the Johns Hopkins Hospital and individual participants gave informed consent. Enrollment of the RA cohort occurred between October 2004 and May 2006. The final follow-up visit occurred in April 2009. MESA participants were enrolled between 2000 and 2002.

Assessment of Urinary Albumin Excretion

A spot morning-collected urine sample was obtained in all patients and stored at -70°C . Urine albumin concentration was measured by nephelometry (using a Vitros 950IRC instrument; Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY) and urine creatinine concentration was measured via the Jaffe reaction (using an Array 360 CE Protein Analyzer; Beckman Instruments, Inc., Drea, CA) at the MESA core laboratory (University of Vermont) for both the RA and control groups at the first visit only. Elevated uACR was defined as $\geq 25\text{mg/g}$ for women and $\geq 17\text{mg/g}$ for men, as previously categorized(11). In sensitivity analyses, an alternate definition of elevated uACR ($\geq 30\text{mg/g}$) was used. For urine albumin, the minimum detectable level was 0.2 mg/dl with a coefficient of variability $<3\%$.

For urine creatinine, the assay range was 0.05 – 16.50 mg/dl, with an analytical coefficient of variability range of 2.5 – 2.9%.

Other Assessments

CAC was measured using multidetector row computed tomography (MDCT), as described in detail previously(14). Scans were transmitted electronically to the MESA CT reading center where calcium scores were quantified using the method described by Agatston(18). Patients with RA had their second CAC measurement after an average of 3.2 (range: 2.2 to 4.2) years. In MESA participants, the mean follow-up time to repeat scan in controls was 2.3 (range: 0.9 to 4.6) years. Progression of CAC was restricted to those participants with any detectable CAC at baseline. Scoring of all scans was blinded to group allocation and clinical characteristics. Carotid imaging was performed as previously described (15) and involved measures in the common carotid artery (CCA), internal carotid artery (ICA) and the carotid bulb. Videotaped scans were analyzed at the Multi-Ethnic Study of Atherosclerosis (MESA) Ultrasound Reading Center. Identification of carotid plaques was limited to the ICA and bulb and was defined subjectively as a maximal focal protrusion into the lumen with reduction in the lumen diameter of 25% or more. Baseline and follow-up scans were re-analyzed concurrently by a single MESA reader aware of the temporal ordering but unaware of clinical characteristics. Ankle-brachial index (ABI) was assessed as previously described(19).

Sociodemographic and Lifestyle Covariates—Demographics and smoking history were assessed by self-report. Current use and dosage of medications were ascertained from prescription bottles. Body mass index (BMI) was calculated as body weight (kg) divided by height (meters²).

CVD Risk Factors—Insulin resistance was assessed using the HOMA-IR index from the HOMA2 model. This index is a validated estimate of glucose handling based on fasting assessments of glucose and insulin(20). Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90, or antihypertensive medication use. Diabetes was defined as a fasting serum glucose ≥ 126 mg/dL or use of anti-diabetic medications. Impaired fasting glucose was defined as a fasting glucose between 101 and 125 mg/dL.

RA Disease Characteristics—Forty-four joints were examined by a single trained assessor. RA disease duration was assessed from the self-reported date of diagnosis. RA disease activity was calculated using the Disease Activity Score for 28 joints with CRP (DAS28-CRP)(21). Current and past use of glucocorticoids and DMARDs was queried by detailed examiner-administered questionnaires. The Stanford Health Assessment Questionnaire (HAQ)(22) was used to assess disability related to common activities.

Laboratory Covariates—High sensitivity C-reactive protein (CRP) and IL-6 were measured as previously described(23). No participants fell below the detectable threshold for IL-6. Plasma lipids and glucose were measured by standard assays; LDL-cholesterol was estimated using the Friedewald equation, individuals were ineligible if triglycerides were greater than 400mg/dL. Rheumatoid factor (RF) was assessed by ELISA, with

seropositivity 40 units. Anti-CCP antibody was assessed by ELISA, with seropositivity 60 units. HLA alleles bearing the “shared epitope” were identified by DRB1 gene sequencing as previously described (19).

Statistical Analysis

Differences in participant characteristics between the RA and control groups were cross-sectionally compared using t-tests for normally distributed continuous variables, the Kruskal-Wallis test for non-normally distributed continuous variables, and the chi-square goodness-of-fit test or Fisher’s exact test, as appropriate, for categorical variables. Ordinary multivariable logistic regression was used to model the association of RA status with elevated uACR, with characteristics unbalanced by RA status at $p < 0.20$ from univariate comparisons (to account for potential residual confounding) included as covariates in the model. Non-contributory confounders were excluded from the model using the Likelihood Ratio Test for nested models.

Next, differences in the associations of clinical characteristics with elevated uACR according to RA status were explored in logistic regression adjusting for relevant confounders. Further, differences in the associations of elevated uACR with measures of atherosclerosis were modeled using linear or logistic regression, depending on the atherosclerosis outcome, with [RA x elevated uACR] interaction terms modeled as the primary exposure. Finally, within the RA group only, ordinary multivariable logistic regression was used to model the associations of RA characteristics with elevated uACR, with similar model building and covariate exclusion as described above. Finally, we explored the association of abnormal uACR with baseline and longitudinal measures of coronary, carotid, and peripheral arterial atherosclerosis, using multivariable linear and logistic regression, as appropriate to the outcome, using the same methods as described above. For all multivariable models, variance inflation factors (VIFs) were calculated to ensure that covariates with excessive collinearity were not co-modeled. All statistical calculations were performed using Intercooled Stata 12 (StataCorp, College Station, TX). A two-tailed α of 0.05 was used throughout.

RESULTS

A total of 196 RA patients were compared with 271 non-RA controls (Table 1). As expected based on matching, the groups did not significantly differ on age, gender, or race. Compared with the control group, the RA group was less likely to receive postmenopausal hormone replacement, but did not differ on anthropometrics, smoking, or the presence of reported kidney or thyroid disease. Although the presence of diabetes was similar in the two groups, the RA group was less likely to have impaired fasting glucose. In spite of this, HOMA-IR levels were significantly higher in the RA group, as was the prevalence of hypertension. As expected, CRP and IL-6 levels were significantly higher, on average, for the RA group compared with controls. Among medications with the potential to affect albuminuria, RA patients were more likely than controls to be treated with angiotensin receptor blockers (ARBs), diuretics and non-steroidal anti-inflammatory agents (NSAIDs). None of the RA patients were being treated with gold or penicillamine. As previously reported, the prevalence of severe CAC (i.e. 100 units) was higher in the RA group compared with

controls, and the RA group had higher mean ICA-IMT, more prevalent carotid plaque, and higher mean ABI than the control group.

Comparison of Elevated uACR According to RA Status

Although the average serum creatinine level was higher in the control group, the two groups had the same urinary albumin concentration and did not differ significantly on creatinine clearance, or elevated uACR in univariate analyses (Table 1). Without adjustment, RA was not associated with a higher odds of elevated uACR (Table 2, Crude Model). However, after considering potential confounders of the association of RA status with elevated uACR (Table 2, MV Models), RA was associated with a 67% lower adjusted odds of elevated uACR compared with controls (OR=0.43; $p=0.016$). This corresponded to an adjusted prevalence of uACR of 11% vs. 23% for the RA vs. control groups, respectively (Figure 1). This was largely driven by the effects of the unbalanced characteristics of hormone replacement therapy, HOMA-IR, hypertension, and IL-6 level. Using an alternate definition of elevated uACR (≥ 30 mg/g) in a sensitivity analysis, elevated uACR was observed in 7% of the RA group compared with 8% of controls ($p=0.53$). After similar adjustment as above, the adjusted prevalence of elevated uACR was 4% in the RA group compared with 7% in controls ($p=0.052$) (data not shown).

Heterogeneity in the Association of Clinical Characteristics with Elevated uACR According to RA Status

We next explored whether selected clinical characteristics differed in their associations with elevated uACR differently in RA compared with controls (Table 3). After adjustment, the associations of age, education, and hormone replacement therapy with elevated uACR did not significantly differ according to RA status (p -values for interaction all >0.05). While higher serum creatinine levels were associated with elevated uACR in the control group, this was not the case in the RA group, in which higher serum creatinine level was not associated with a higher prevalence of uACR (p -value for interaction=0.013). While diabetes was similarly associated with uACR in the two groups, higher HOMA-IR levels were associated with elevated uACR only in the control group (OR=1.21 in controls vs. 2.36 in the RA groups). However, the p -value for this interaction was only of borderline statistical significance ($p=0.10$). Hypertension was strongly and significantly associated with elevated uACR in the control group (OR=3.06), but only weakly and not significantly associated in the RA group (OR=1.34), a difference that was statistically significant ($p=0.013$ for interaction). IL-6 levels were similarly associated with elevated uACR in both groups. After adjustment, the use of ARBs, diuretics, and NSAIDs were not associated with elevated uACR in either group.

Association of Elevated uACR with Measures of Atherosclerosis According to RA Status

Crude and adjusted associations of elevated uACR with measures of coronary/carotid atherosclerosis and peripheral arterial disease are summarized in Table 4. In unadjusted analyses, elevated uACR was associated with higher CAC scores for the combined RA +Control groups, and these associations did not differ according to group status (p -value for interaction >0.05). However, associations of elevated uACR with CAC, in the combined as well as the individual groups, were not significant after adjustment for age, educational

attainment, HRT, HOMA-IR, hypertension, and IL-6 levels. Elevated uACR was not associated with change in CAC in either the RA or control groups. Before adjustment, elevated uACR was associated with a significantly higher average CCA-IMT in the control, but not the RA, group (p-value for interaction=0.007). However, the magnitude of the association was diminished and lost significance in the control group upon adjustment. There were no significant associations of uACR with ICA-IMT, carotid plaque, or ABI in either group. Similar findings were observed using the alternate definition of elevated uACR (≥ 30 mg/g) (data not shown).

Associations of RA Characteristics with Elevated uACR

In univariate models of the RA group only, longer RA duration, higher SHS scores, and higher IL-6 levels were positively and significantly associated with an elevated uACR, and TNF inhibitor use (but not use of other biologics) was inversely associated (Supplemental Table). Serologies, articular disease activity characteristics, and prednisone use were not associated with uACR; however, a trend of a significant inverse association for HCQ use was noted. When RA characteristics were co-modeled and adjusted for age, education, HRT, HOMA-IR, and hypertension, only TNF inhibitor use and IL-6 remained significantly associated with elevated uACR. Specifically, the adjusted prevalence of elevated uACR among TNF inhibitor users was less than half that of RA patients not prescribed TNF inhibitors (9% vs. 20%, respectively; $p=0.047$, Figure 2.a). For IL-6, on average, each log unit was associated with a 78% higher odds of uACR ($p=0.015$; Figure 2.b). There was no evidence of interaction between TNF inhibitor use and IL-6 level on uACR, as the ORs for elevated uACR were 1.97 vs. 1.66, respectively, for RA patients receiving vs. not receiving TNF inhibitors (p-value for interaction=0.73, data not shown).

DISCUSSION

To our knowledge, ours is the largest study of the indicators of elevated uACR in RA, and the only one to explore the associations of uACR with measures of atherosclerosis in multiple vascular beds of RA patients. We found that after adjusting for unbalanced correlates of elevated uACR, RA patients had a lower prevalence of elevated uACR. This was partially due to the finding that several clinical characteristics, such as serum creatinine level, hypertension, insulin resistance, and hyperhomocysteinemia, were markedly associated with elevated uACR in the non-RA control group, but not in the RA group. Although we detected some differences in the associations of elevated uACR with measures of coronary and carotid atherosclerosis between the RA and control groups, elevated uACR was not independently associated with any of the atherosclerosis measures in either group after adjusting for traditional CVD risk factors. Among RA characteristics, TNF inhibitor treated patients had a $> 50\%$ lower prevalence of elevated uACR, and those with higher levels of IL-6 had a higher prevalence.

In the non-RA population, microalbuminuria has been associated with diabetes, hypertension(24), greater age, non-Caucasian race/ethnicity and male sex(25, 26). There is a well-established association of higher uACR with the presence of subclinical CVD among adults without established CVD. This was supported by Kramer et al. in a report that

examined the association between urine albumin excretion and common and internal carotid artery intima-media thickness (IMT), left ventricular end-diastolic mass, and coronary calcification (CAC) scores using data from MESA(5). Furthermore, in the Framingham Heart Study, 1568 non-hypertensive and non-diabetic patients with microalbuminuria had a higher risk of CVD events and mortality(27).

In terms of prevalence of microalbuminuria in RA vs. non-RA patients, a study of non-diabetic, non-hypertensive RA patients had significantly higher prevalence of microalbuminuria (27.7% vs. 7.8%); however, the patients with RA were treated with gold or penicillamine, both of which have been associated with increased kidney damage and microalbuminuria(11, 13). None of the RA patients in our study were receiving these treatments. In 1995, another study showed a similar prevalence of microalbuminuria amongst 605 RA patients and 457 controls (5.63% vs. 5.91%). In 2004, the prevalence of microalbuminuria in a small study of 39 RA patients was found to be 7.7%, comparable to the general population(28). In a more recent study from 2011, the prevalence of uACR was 11.9% in the RA group, which is similar to our study's finding of 11%. However, the prevalence was only 3.1% in the RA patients who were non-diabetic and non-hypertensive(13).

Several studies have examined the association of microalbuminuria with CVD risk factors and incident CVD in patients with RA. In the majority of these studies, there are no control groups for comparison. In a study of 39 RA patients, no association was found between microalbuminuria and CVD; however, the small sample size was a limitation(28). In a cross-sectional study of 136 RA patients and 79 non-RA patients with no diabetes or clinical history of CVD, no association of microalbuminuria with CAC score was detected(29). The investigators reported a higher prevalence of microalbuminuria in RA relative to non-RA controls and an association between urinary microalbuminuria and increased arterial stiffness, measured by the augmentation index.

Our study did not find an association of elevated uACR with subclinical CVD, unlike previous studies, including the report by Kramer et al. in the MESA cohort as a whole(5). A possible explanation for this difference may be that our study has smaller numbers of patients with elevated uACR in both the RA and the control groups.

Hypertension has a well-established link with microalbuminuria. In our study, as expected in the non-RA control group, hypertension was associated with a higher prevalence of elevated uACR in the non-RA control group. Surprisingly, this was not observed in the RA group. However, in the study by Daoussis et al.(13), a significant association of hypertension with microalbuminuria in RA patients was reported. Their study, however, only studied RA patients and did not compare results with a suitable control group.

These differences raise the possibility that specific factors in RA patients may influence the prevalence of microalbuminuria. One possibility is that patients with RA are on anti-inflammatory medications, which overtime may be reno-protective. Another possibility is that endothelial cells in RA patients may not be as susceptible to damage by hypertension. Further data are needed to draw conclusions.

Of interest in our study, RA patients who were treated with TNF inhibitors had a 50% lower prevalence of elevated uACR compared with non-treated patients. This is a new finding that calls for further exploration. Could anti-TNF agents be reno-protective? Could anti-TNF agents alter the mechanism thought to underlie albuminuria? Or are the anti-TNF agents leading to lower levels of systemic and/or renal inflammation and thus leading to a lower prevalence of microalbuminuria? We identified no published studies on anti-TNF agents and their association with albuminuria in RA patients. Endothelial dysfunction has been linked to both albuminuria and atherosclerosis, and TNF inhibitors have been shown to decrease circulating markers of endothelial activation and functional tests of endothelial dysfunction(30, 31). TNF-alpha also plays a role in the pathogenesis of salt-sensitive hypertension and its associated renal damage. In a rat model of salt-sensitive angiotensin II induced hypertension, rats treated with etanercept had significant reductions in blood pressure, albuminuria and proteinuria(32). Furthermore, blocking TNF-alpha reduced urinary MCP-1 excretion and renal macrophage infiltration in rats. In a single study of a mouse model of lupus, treatment with anti-TNF agents were associated with decreased blood pressure, glomerulosclerosis and albuminuria(33), suggesting a reno-protective effect of anti-TNF alpha agents. More studies are needed to draw conclusions on the association of TNF inhibitors and albuminuria.

Strengths of our study include the relatively large number of patients with RA. Also, there were multiple measures of subclinical CVD for each individual. Additionally, unlike most previous studies there is a non-RA comparison group drawn from a population-based sample. There are also some limitations to our study. Only one urine specimen was studied per individual, introducing the possibility of misclassification of abnormal uACR. In addition, despite the large overall sample size, the prevalence of abnormal uACR was low, limiting the ability to robustly co-model all possible covariates simultaneously. However, none of the final parsimonious models were limited by the standard of 7–10 individuals per modeled covariate.

In conclusion, we found that prevalence of elevated uACR in both the RA and non-RA groups and their associations with subclinical markers of cardiovascular disease were similar. Although the association of uACR with measures of subclinical coronary atherosclerosis was similar between RA and non-RA groups, we observed no association in the RA group of uACR with measures of carotid atherosclerosis, nor with several key cardiometabolic risk factors. This could suggest differing mechanisms linking urinary albumin excretion with cardiometabolic risk factors and atherosclerosis in RA compared with non-RA controls, and a lower utility for uACR as an indicator of subclinical CVD in RA. We also found 50% lower prevalence of microalbuminuria in TNF-alpha inhibitor treated RA patients compared with those not so treated. This is a novel observation and merits further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATION

- This is the largest study of the indicators of elevated uACR in RA and the only one to explore the associations of uACR with measures of atherosclerosis in multiple vascular beds of RA patients.
- RA patients had a lower prevalence of elevated uACR after adjusting for unbalanced characteristics
- TNF inhibitor treated RA patients had a >50% lower prevalence of elevated uACR

Figure 1. Crude and Adjusted Differences in the Frequency of Elevated Urinary Albumin/Creatinine Ratio (uACR): RA vs. Control Groups

The unadjusted frequency of any abnormal urinary albumin:creatinine did not differ between the two groups. However, there was a significant difference in the frequency of abnormal urinary albumin:creatinine after adjustment for unbalanced characteristics (age, education, hormone replacement use, HOMA-IR, presence of hypertension, and IL-6 level), with the control group demonstrating a more than doubling of the adjusted frequency of the outcome compared with the RA group.

Figure 2. Adjusted Associations of TNF inhibitor Use and IL-6 Level with the Presence of an Abnormal Urinary Albumin to Creatinine Ratio

After adjustment for age, education, hormone replacement, hypertension, HOMA-IR and IL-6 level, RA patients prescribe TNF inhibitors had a lower adjusted prevalence of elevated uACR (OR=0.41; $p=0.047$) as depicted in Panel A. After adjusting for age, education, hormone replacement, hypertension, HOMA-IR and TNF inhibitor use, each log unit higher IL-6 level was associated with a 78% higher frequency of elevated uACR, as depicted in Panel B.

uACR=urinary albumin to creatinine ratio; TNFi=tumor necrosis factor inhibitor;
IL=interleukin; OR=odds ratio

Table 1

Characteristics According to Rheumatoid Arthritis Status

	RA (n=196)	Control (n=271)	p
Age, years	59 ± 9	58 ± 8	0.13
Male, n (%)	78 (40)	115 (42)	0.57
Caucasian, n (%)	168 (86)	230 (85)	0.80
Any college, n (%)	147 (75)	217 (81)	0.17
Post-menopausal, n (%)	92 (47)	111 (41)	0.20
Hormone replacement, n (%)	16 (8)	60 (22)	<0.001
Body mass index, kg/m ²	28.4 ± 5.3	28.8 ± 5.7	0.37
Waist circumference, cm	96 ± 16	97 ± 15	0.22
Ever smoker, n (%)	114 (58)	141 (52)	0.20
Current smoker, n (%)	23 (12)	38 (14)	0.49
Reported kidney disease, n (%)	5 (3)	1 (1)	0.13
Thyroid disease, n (%)	24 (12)	26 (10)	0.37
Diabetes, n (%)	12 (6)	23 (8)	0.38
Impaired fasting glucose, n (%)	34 (17)	72 (27)	0.019
HOMA-IR	0.8 (0.5–1.4)	0.6 (0.4–1.0)	0.004
Hypertension, n (%)	104 (53)	109 (40)	0.005
SBP	128 ± 19	122 ± 19	0.001
DBP	76 ± 9	71 ± 10	<0.001
LDL	116 ± 30	118 ± 29	0.47
HDL	55 ± 18	51 ± 13	0.005
Triglycerides	104 (68–150)	107 (80–159)	0.22
Lipid lowering medication, n (%)	35 (18)	50 (18)	0.87
CRP	2.5 (1.1–7.4)	2.0 (0.8–4.7)	0.004
IL-6	3.9 (1.8–8.1)	1.1 (0.7–1.8)	<0.001
Homocysteine	9.0 (7.5–10.6)	8.0 (6.8–9.9)	0.001
ACE inhibitor use, n (%)	18 (9)	22 (8)	0.69
ARB use, n (%)	21 (11)	14 (5)	0.025
Any ACEi or ARB, n (%)	39 (20)	36 (13)	0.055
Any diuretic, n (%)	35 (18)	31 (11)	0.049
Any NSAID, n (%)	127 (65)	66 (24)	<0.001
COX non-selective, n (%)	83 (42)	48 (18)	<0.001
COX-2 selective, n (%)	47 (24)	22 (8)	<0.001
Aspirin, n (%)	34 (17)	59 (22)	0.24
CAC	4 (0–168)	0 (0–71)	0.066
CAC>0, n (%)	106 (55)	132 (49)	0.21
CAC 100, n (%)	68 (35)	58 (21)	0.001
CCA-IMT, mm	0.82 (0.74–0.92)	0.80 (0.73–0.90)	0.28
ICA-IMT, mm	1.09 (0.84–1.54)	0.87 (0.79–1.10)	<0.001
Plaque, n (%)	42 (22)	19 (7)	0.001

	RA (n=196)	Control (n=271)	p
ABI	1.15 (1.06–1.23)	1.11 (1.04–1.18)	<0.001
low ABI, n (%)	8 (4)	7 (3)	0.43
high ABI, n (%)	27 (14)	9 (3)	<0.001
Serum creatinine, mg/dL	0.88 ± 0.20	0.92 ± 0.20	0.020
Creatinine clearance, mL/min/1.73m ²	89 (72–109)	86 (70–105)	0.30
Urinary albumin, mg/dL	0.5 (0.3–0.9)	0.5 (0.2–1.1)	0.66
Urinary albumin/creatinine ratio	4.5 (3.3–9.0)	4.5 (2.9–8.0)	0.40
Elevated uACR, n (%)	35 (18)	47 (17)	0.89

RA = Rheumatoid Arthritis; HOMA-IR=Homeostatic Model Assessment Insulin Resistance Index; SBP= systolic blood pressure; DBP = diastolic blood pressure; LDL = low density lipoprotein; HDL = high density lipoprotein; CRP = c-reactive protein; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; NSAID = non-steroidal anti-inflammatory drug; CAC = coronary calcium score; ICA = internal carotid artery; CCA = common carotid artery; IMT = intimal medial thickness; ABI = ankle brachial index; uACR = urine albumin to creatinine ratio

Crude and Adjusted Associations of RA Status with Elevated Urinary Albumin/Creatinine Ratio

Table 2

	Crude Model		Extended MV Model		Reduced MV Model	
	OR	P	OR	P	OR	P
RA	1.04	0.89	0.44	0.027	0.43	0.016
Age, per year			1.04	0.031	1.04	0.017
Any college vs. none			0.44	0.006	0.47	0.008
Hormone replacement			0.50	0.13	0.49	0.091
Ever smoking vs. never			1.04	0.88		
Reported kidney disease			0.45	0.51		
Serum creatinine, per mg/dL			1.99	0.35		
log HOMA-IR, per log unit			1.62	0.035	1.64	0.017
Hypertension			1.85	0.056	2.13	0.009
HDL-C, per mg/dL			1.00	0.97		
log IL-6, per log unit			1.56	0.012	1.57	0.008
log Homocysteine			1.07	0.90		
Any angiotensin receptor blocker use			1.01	0.98		
Any diuretic use			1.38	0.38		
Any NSAID use			1.27	0.44		

RA=rheumatoid arthritis; OR=odds ratio; MV=multivariable; HOMA-IR=Homeostatic Model Assessment Insulin Resistance Index; HDL-C=high density lipoprotein cholesterol concentration; IL=interleukin; NSAID=non-steroidal anti-inflammatory drug use

Table 3
Associations of Characteristics Shared by RA and Control Groups with Abnormal Urinary Albumin to Creatinine Ratio

	Adjusted*				
	RA		Control		
	OR	p	OR	p	p-interaction
Age, per year	1.03	0.21	1.05	0.031	0.54
Any college vs. none	0.50	0.11	0.44	0.034	0.81
Hormone replacement	0.65	0.60	0.45	0.10	0.70
Serum creatinine, per mg/dL	0.63	0.64	4.50	0.088	0.013
Diabetes	1.05	0.95	3.13	0.026	0.29
log HOMA-IR, per log unit	1.21	0.48	2.36	0.006	0.10
Hypertension	1.34	0.45	3.06	0.004	0.013
log IL-6, per log unit	1.90	0.007	1.24	0.42	0.23
log Homocysteine	0.32	0.14	3.14	0.057	0.017
Any ARB use	0.72	0.60	1.52	0.52	0.39
Any diuretic use	1.23	0.67	1.65	0.29	0.66
Any NSAID use	1.85	0.16	1.19	0.67	0.46

* Adjusted for age, education, hormone replacement use, HOMA-IR, presence of hypertension, and IL-6 level (as appropriate)

RA=Rheumatoid Arthritis; HOMA-IR=Homeostatic Model Assessment Insulin Resistance Index; ARB=angiotensin receptor blocker; NSAID=non-steroidal anti-inflammatory drug

Table 4
Atherosclerosis Measures According to RA Status and Presence of Abnormal Urinary Albumin to Creatinine Ratio

	Combined RA+Control			RA			Control		
	Normal uACR (n=385)	Abnormal uACR (n=82)	p	Normal uACR (n=161)	Abnormal uACR (n=35)	p	Normal uACR (n=224)	Abnormal uACR (n=47)	p-interaction
Baseline CAC									
<i>Crude</i>									
Agatston CAC Score, units	8 (7, 11)	22 (12, 38)	0.002	11 (7, 17)	25 (11, 57)	0.11	7 (5, 9)	20 (10, 41)	0.009
CAC in CAC>0 only, units	81 (63, 103)	128 (80, 204)	0.090	107 (74, 154)	131 (65, 263)	0.61	65 (46, 90)	125 (67, 233)	0.066
CAC>0, (%)	49 (54, 44)	63 (73, 53)	0.016	52 (44, 60)	66 (49-79)	0.15	46 (40-53)	62 (47-74)	0.052
CAC>100, (%)	25 (21, 29)	38 (28, 49)	0.017	33 (26, 40)	46 (30, 62)	0.15	19 (15, 25)	32 (20-46)	0.056
<i>Adjusted*</i>									
Agatston CAC Score, units	10 (8, 12)	11 (6, 18)	0.71	10 (7, 14)	12 (6, 28)	0.59	10 (7, 14)	10 (5, 20)	0.96
CAC in CAC>0 only, units	88 (69, 112)	97 (60, 157)	0.73	113 (76, 167)	101 (47, 218)	0.79	70 (48, 102)	103 (53, 199)	0.31
CAC>0, (%)	52 (46, 57)	52 (39, 65)	0.97	48 (39, 58)	55 (34, 75)	0.53	54 (46, 62)	49 (32, 65)	0.56
CAC>100, (%)	22 (18, 27)	23 (14-34)	0.90	28 (20, 37)	32 (16, 53)	0.64	18 (13, 25)	19 (10, 33)	0.92
Change in CAC									
<i>Crude</i>									
Change in CAC, units/year	2.1 (1.5, 2.7)	1.6 (0.3, 2.8)	0.46	2.4 (1.4, 3.3)	1.9 (-0.1, 3.9)	0.68	1.9 (1.2, 2.7)	1.3 (-0.3, 3.0)	0.50
Change in CAC>0 units, (%)	56 (51, 62)	57 (45, 68)	0.93	61 (52, 69)	48 (30, 66)	0.21	52 (45, 60)	62 (47, 76)	0.25
Significant in CAC ^{**} , (%)	13 (10, 17)	12 (6, 22)	0.83	15 (10, 22)	7 (2, 25)	0.31	11 (8, 17)	15 (7, 30)	0.54
Baseline Carotid U/S Measures									
<i>Crude</i>									
CCA-IMT, mm	0.82 (0.80, 0.84)	0.83 (0.80, 0.87)	0.51	0.83 (0.81, 0.85)	0.81 (0.77, 0.85)	0.35	0.80 (0.78, 0.82)	0.91 (0.83, 1.00)	0.010
ICA-IMT, mm	1.06 (1.01, 1.11)	1.13 (1.10, 1.26)	0.30	1.16 (1.09, 1.22)	1.14 (1.01, 1.29)	0.85	0.93 (0.87, 1.00)	1.10 (0.88, 1.36)	0.16
Carotid plaque, (%)	16 (12, 20)	20 (34, 11)	0.50	21 (16, 28)	23 (12, 39)	0.85	7 (3, 13)	9 (1, 44)	0.77
<i>Adjusted*</i>									
CCA-IMT, mm	0.83 (0.81, 0.84)	0.80 (0.77, 0.84)	0.26	0.82 (0.80, 0.84)	0.77 (0.73, 0.82)	0.029	0.82 (0.80, 0.86)	0.89 (0.81, 0.97)	0.015
Baseline Peripheral Arterial Measures									
<i>Crude</i>									
ABI	1.13 (1.11, 1.14)	1.13 (1.10, 1.16)	0.70	1.15 (1.13, 1.17)	1.17 (1.13, 1.21)	0.34	1.11 (1.09, 1.12)	1.10 (1.07, 1.14)	0.74

Means and 95% CIs depicted. Where required, adjusted log means were back-transformed to un-exponentiated means for ease of interpretation

* Adjusted for age, education, hormone replacement, HOMA-IR, hypertension, IL-6

** Significant change in CAC is 0 units/year among those with no baseline CAC and 100 units/year among those with baseline CAC (ref Budoff et al. JACC 2013 2013;61(12):1231-9).

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RA = Rheumatoid Arthritis; uACR = urine albumin to creatinine ratio; CAC = coronary calcium; CCA = common carotid artery; IMT = intimal medial thickness; ICA = internal carotid artery; ABI = ankle brachial index; U/S = ultrasound