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ORIGINAL ARTICLE

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Urinary albumin excretion in rheumatoid arthritis is not associated with markers of vasculopathy in distal microvascular beds

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Abstract

Objective: Increased UAE is a marker of generalized vascular damage in high-cardiovascular risk patients. However, it remains unknown whether it corresponds to a state of diffuse vasculopathy in high-risk patients with RA.

Methods: UAE was estimated in 24-hour urine samples in RA and non-RA individuals. Retinal arteriolar and venular diameters were calculated from retinal images with computerized software. SEVR was estimated as an index of microvascular coronary perfusion with applanation tonometry. Dermal capillary density was measured from images obtained with nailfold capillaroscopy, using specifically designed software.

Results: In a total of 111 individuals, neither UAE (5.1 [2.8-10.8] vs 6.5 [3.0-11.7] mg/24 h) nor prevalence of microalbuminuria (11.0% vs 8.1%) significantly differed between patients (n = 74) and controls (n = 37). In the RA group, UAE was not significantly associated with inflammation, nor with any of the studied microvascular indices of the retinal microvasculature, the coronary microcirculation, and the dermal capillary network.

Conclusion: Among RA patients, UAE was not associated with markers of vasculopathy in distal microvascular beds. Increased UAE in RA might be primarily considered as a manifestation of localized, compromised function of the renal microvasculature, rather than a marker of generalized microvascular impairment.

KEYWORDS

dermal capillary density, retinal microvascular alterations, rheumatoid arthritis, subendocardial viability index, urinary albumin excretion

Abbreviations: AIx, augmentation index; AVR, retinal arteriovenous ratio; BMI, Body mass index; CRAE, central retinal arteriolar equivalent; CRP, C-reactive protein; CRVE, central retinal venular equivalent; DAS, Disease Activity Score; DBP, diastolic blood pressure; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; SEVR, subendocardial viability ratio; TNF, tumor necrosis factor; UAE, urinary albumin excretion.

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1 | INTRODUCTION

An increased rate of UAE corresponds, in general, to a derangement in glomerular filtration barrier that precedes the establishment of renal dysfunction. An arbitrary threshold for the definition of microalbuminuria has been established as 30 mg of albumin in a 24 hours urine sample.[1] Historically, microalbuminuria has been used to predict diabetic nephropathy.[2] On the other hand, microalbuminuria constitutes an early marker of microvascular damage and a potent predictor of future cardiovascular morbidity and mortality in patients with diabetes, hypertension and in the general population.[3,4] Of importance, a continuous relationship of UAE with cardiovascular risk exists, even below the threshold values usually considered.[5,6] Therefore, UAE represents a valuable index for the assessment of patients at high-cardiovascular risk.

RA is a chronic, autoimmune disease characterized by an increased cardiovascular burden by as much as 50%, compared with the general population.[7] Apart from the definite role of classical cardiovascular risk factors,[8] preclinical atherosclerosis and endothelial dysfunction triggered by systemic autoimmune inflammation contributes to excess cardiovascular risk in RA.[9] It is postulated that these proatherogenic effects mediated by RA are not only limited in large conduit arteries with the formation of atheromatous plaques, but may also manifest as a state of generalized microvascular dysfunction that involves the coronary vessels.[10] We have previously shown that RA is associated with diffuse microvascular injury, evidenced by decreased myocardial perfusion,[11] altered retinal microvascular morphology,[12] and pronounced dermal capillary rarefaction,[13] even in the absence of overt cardiovascular disease.

Altogether, these data highlight the need for novel markers of subclinical microvascular injury to be tested in RA, to enhance the accuracy of individual cardiovascular risk stratification. Considering its established value in terms of cardiovascular risk prediction in the general population, microalbuminuria appears as an elegant marker that could be utilized in RA. An increased prevalence of microalbuminuria has been described in patients with RA,[14,15] yet not all studies coincide.[16-18] Hence, an important question is whether microalbuminuria in RA patients correlates with surrogate markers of atherosclerosis and cardiovascular disease. This concept was initially met with interest as UAE has been associated with arterial stiffness[15] and recently, with carotid intima-media thickness and impaired flow-mediated dilatation[14] in RA. By contrast, more recent data seem to contradict this hypothesis, as they failed to confirm an association with carotid atherosclerosis and other measures of subclinical atherosclerosis, such as coronary artery calcification and ankle-brachial index.[17]

However, microalbuminuria, as a sensitive marker of microvascular injury in the glomerular capillaries, might be expected to correlate with indices of microvascular, rather than macrovascular, involvement in RA. Therefore, the aims of the present study were (a) to investigate whether patients with RA exhibit more pronounced UAE, compared to non-RA individuals and (b) to examine the association of UAE with subtle markers of microvascular injury in distal microvascular beds, including the coronary artery network, the retinal microvasculature, and the dermal capillary network.

2 | MATERIALS AND METHODS

The study population consisted of patients with an established diagnosis of RA according to the 1987 American College of Rheumatology criteria,[19] who attended the Rheumatology Outpatient Unit, and non-RA individuals, who were recruited from the local community and from individuals attending their regular check-up appointments in the Internal Medicine Outpatient Unit. Controls were free from health problems including cardiovascular diseases, hypertension, or diabetes and received no medical treatment. Written informed consent was obtained before the procedures. The study was conducted in accordance with the Helsinki declaration, and the protocol was approved by the Institutional Ethics Committee.

Medical history and current medication use were reported, and physical examination was performed. BMI was calculated in kg/m^2. Blood pressure was measured with a validated oscillometric device (Microlife Exact BP; Microlife AG, Widnau, Switzerland) in the sitting position according to the guidelines, and hypertension was defined as office systolic and/or DBP ≥140/90 mm Hg, and/or current antihypertensive medication use.[1] Previous cardiovascular events were defined as history of stroke, angina, and myocardial infarction based on self-report and a review of medical record and current medication. After completion of the procedures for the assessment of the microvasculature, as analyzed below, blood samples were collected to estimate fasting lipids (total cholesterol, triglycerides, LDL- and HDL-C) in RA and non-RA individuals. In addition, inflammatory markers were estimated in RA patients, specifically ESR and CRP; detection level 3.19 mg/L). Disease activity was assessed during the visit by the treating rheumatologist, with the DAS with 28 joints counted,[20] which was calculated based on the number of swollen and tender joints, the subjective intensity of pain/discomfort due to RA upon a visual analogue (0-100) scale, and ESR values. DAS28-ESR thresholds of ≤3.2, 3.2-5.1, and >5.1 are indicative of low, moderate, and high disease activity, respectively.

2.1 | Urinary albumin excretion and microalbuminuria

Twenty-four hour urine samples were collected to calculate UAE using immuno-turbidimetric method. Microalbuminuria was defined as UAE of 30-300 mg in a 24 hour urine sample. Measurement of UAE in 24 hour urine samples is considered as the gold standard

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for the diagnosis of microalbuminuria.[21] Participants were advised against any change in their usual dietary habits.

2.2 | Assessment of the coronary microvascular network

SEVR, also known as the Buckberg index, was estimated as a functional index of microvascular coronary perfusion, as it correlates with the ratio of subendocardial to subepicardial blood flow.[22] SEVR was noninvasively estimated by applanation tonometry with the SphygmoCor device (AtCorMedical, Sydney, Australia) from the average of three successive, high-quality measurements (operator quality index >90) in the supine position. SEVR corresponds to the ratio of the area under the diastolic segment of the derived aortic pressure waveform (diastolic pressure time index), which is indicative of myocardial supply, to the area under the systolic segment of the waveform (tension time index), which corresponds to cardiac workload. Lower values of SEVR, especially below 100%, indicate poorer perfusion of the subendocardium.[23]

2.3 | Assessment of the retinal microvasculature

Participants underwent bilateral, nonmydriatic digital fundus photography with a NIDEK AFC-230/210 non mydriatic digital fundus camera (NIDEK, Fremont, CA, USA). The best in quality photograph was analyzed using specifically designed, semi-automated computer software that was developed from the collaboration of our Hypertension Unit with the Institute of Computer Science, Foundation for Research and Technology-Hellas.[24] Retinal photographs were assessed according to a standard protocol, which has been tested in other populations and described in detail elsewhere.[25-27] Retinal vessel width was calculated within the measurement area, defined as the area from one half to one disk diameter from the optic disk margin. The modified Parr and Hubbard formulas according to the Atherosclerosis Risk in Communities protocol[28] were calculated to summarize indices of the average retinal arteriolar and venular diameters, referred to as the CRAE and CRVE, respectively.[28,29] The ratio CRAE/CRVE represented the retinal AVR.

2.4 | Assessment of the dermal capillary network

Dermal capillary density, defined as the number of capillaries per visual field, was calculated using previously described methodology.[27,30] Images depicting the capillaries n transverse section were obtained with nailfold capillaroscopy (DS Medica, Milan Italy, ×200 magnification), which was applied in the distant phalanx, after mineral oil placement to improve image quality, with the hand supported in the sitting position. The number of capillaries was estimated in a couple of images with a semi-automated software that was developed in collaboration with the Foundation for Research and Technology-Hellas,[31] and the mean number was used for the analysis.

2.5 | Statistical analysis

Analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 22. Results were expressed as frequencies for qualitative variables and as mean (m) ± SD or median (1st-3rd interquartile range) for continuous variables, according to whether they were normally distributed or not. Frequencies for qualitative variables were compared with the Pearson chi-square test, while mean values for continuous variables were compared with Student t or Mann-Whitney test. Correlation coefficients were calculated with the parametric Pearson or the nonparametric Spearman rank tests, according to the normality of their distribution. A probability value of $P \leq 0.05$ was considered statistically significant.

3 | RESULTS

A total of 111 participants were included in the study, 74 of whom were RA and 37 non-RA individuals. In the RA group, median disease duration was 9 (4-16.5) years and mean DAS score was representative of moderate disease activity (3.58 ± 1.35). Median ESR was 16 (10-28) mm/h, and median CRP was 3.19 (3.19-4.63) mg/L, both indicative of low levels of inflammation. As expected, the majority of patients were treated with DMARDs in their majority (73%), biologics (40.5%) and glucocorticoids (36.5%). A large portion of RA patients received antihypertensive medication (53.4%) and statins (20.3%).

Baseline characteristics of the study population are depicted in Table 1. Microvascular involvement among RA patients was evident in the retinal microvasculature, in the coronary microvascular network and in the dermal capillary bed. In particular, RA patients exhibited decreased CRAE and AVR ($P < 0.001$), decreased SEVR ($P = 0.038$), and a lower number of dermal capillaries ($P = 0.007$), compared to non-RA individuals. By contrast, UAE was similar between patients and controls, and the same was observed when it was studied as a categorical variable for the assessment of microalbuminuria (Table 1).

In the RA group, UAE did not differ between patients with diabetes, compared to nondiabetic patients (4.7 [1.1-15.0] vs 5.0 [2.9-9.9] mg/24 h, $P = 0.514$). UAE was comparable between hypertensive and normotensive patients with RA (5.2 [2.9-12.6] vs 4.7 [2.8-7.3] mg/24 h, $P = 0.318$) and was only associated with DBP ($r = 0.247$, $P = 0.034$) among classical cardiovascular risk factors. Of note, systolic/DBP was relatively well controlled in the subgroup of patients with RA and concomitant hypertension (131.6 ± 15.3/75.4 ± 8.0 mm Hg). UAE was not significantly associated with inflammatory markers, disease duration and did not differ according to medical treatment with DMARDs, biologics, or glucocorticoids.

3.1 | Association of UAE and microalbuminuria with markers of diffuse microvascular involvement in RA

Regarding the relationship between UAE and markers of microvascular damage, an association was not observed with retinal

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TABLE 1 Baseline characteristics of study population

Variable	RA group (n = 74)	Control group (n = 37)	*P* value
Age (y)	61.3 ± 11.7	57.9 ± 7.3	0.064
Male sex (%)	18.9	21.6	0.736
Office SBP (mm Hg)	124.6 ± 16.2	125.2 ± 10.4	0.795
Office DBP (mm Hg)	73.9 ± 7.9	79.4 ± 9.7	0.002
Heart rate (beats/min)	69.9 ± 11.4	68.6 ± 7.6	0.858
BMI (kg/m^2)	26.7 ± 4.9	26.8 ± 4.1	0.892
Hypertension (%)	58.9	0.0	<0.001
Diabetes mellitus (%)	8.1	0.0	0.073
Cardiovascular events (%)	9.5	0.0	0.052
Smoking (%)	21.6	24.3	0.756
Total cholesterol (mg/dL)	205.0 ± 34.3	217.2 ± 32.4	0.085
Triglycerides (mg/dL)	113 (82-142)	95 (66-124)	0.077
HDL-C (mg/dL)	54.9 ± 14.1	51.7 ± 9.7	0.178
LDL-C (mg/dL)	125.0 ± 32.2	144.9 ± 26.9	0.002
UAE (mg/24 h)	5.1 (2.8-10.8)	6.5 (3.0-11.7)	0.661
Microalbuminuria (%)	11.0	8.1	0.638
CRAE (μm)	78.0 ± 8.9	87.4 ± 10.0	<0.001
CRVE (μm)	114.5 ± 14.9	112.2 ± 11.6	0.440
AVR	0.69 ± 0.10	0.78 ± 0.10	<0.001
SEVR (%)	140.6 ± 22.3	150.7 ± 21.6	0.038
Capillaries/visual field	132.5 ± 28.2	151.2 ± 25.6	0.007

Results are demonstrated as mean ± SD/median (IQ range).
SBP, systolic blood pressure.

microvascular alterations, evidenced by CRAE (r = −0.136, P = 0.227), CRVE (r = −0.102, P = 0.417), or AVR (r = 0.001, P = 0.998). UAE was not associated with the index of coronary microvascular perfusion SEVR (r = 0.046, P = 0.706), nor with dermal capillary density (r = −0.212, P = 0.082).

When patients were classified into two groups according to the presence of microalbuminuria, patients with microalbuminuria exhibited non-significantly lower CRAE (72.9 ± 4.9 vs 78.1 ± 8.5 μm, P = 0.153) and CRVE (104.6 ± 13.7 vs 115.4 ± 14.8 μm, P = 0.092), with similar AVR (0.70 ± 0.08 vs 0.68 ± 0.09, P = 0.573), compared to patients without microalbuminuria. SEVR was non-significantly lower among patients with microalbuminuria (133.2 ± 26.0 vs 141.1 vs 22.0, P = 0.378). Likewise, the number of capillaries per visual field was non-significantly lower among patients with microalbuminuria (111.5 [99.0-183.5] vs 133.5 [110.5-150.0], P = 0.645).

4 | DISCUSSION

In the present study, we studied for the first time the association of UAE with markers of microvascular injury in distal microvascular beds, in a population of RA patients. We included subtle markers indicative of microvascular injury in the coronary artery network, in the retinal microvasculature, and the dermal capillary network, which have been previously shown to be impaired in patients with RA, even in the absence of overt cardiovascular disease.[11-13] By contrast, neither UAE nor the prevalence of microalbuminuria differed in the present cohort of RA patients, compared to the control group (Table 1). Moreover, no significant associations were observed between UAE and any of the included microvascular indices denoting morphological alterations in the retinal microvasculature, impaired myocardial perfusion, and dermal capillary rarefaction.

Interest on the prevalence and significance of microalbuminuria in RA origins more than two decades ago, when a profoundly increased rate was observed among patients with RA.[32] However, at that time penicillamine and gold were common treatment modalities with nephrotoxic effects, clearly associated with microalbuminuria. In the era of modern rheumatology, interest on the role of microalbuminuria in RA has been renewed. Considering its established role as an early marker of microvascular damage and a potent predictor of cardiovascular outcomes in high-cardiovascular risk patients and the general population,[3,4] microalbuminuria has been examined in RA under this perspective. A small but statistically significant increase in UAE was shown in a study of 136 RA patients free from diabetes and cardiovascular disease compared to non-RA individuals (7.6 vs 5.6 mg/g),[15] but larger studies failed to confirm this finding. According to data from the US National Health and Nutrition Examination Survey, no evidence for a difference in microalbuminuria was found in patients with or without RA (10.46% vs 13.39%), despite the fact that RA was more often associated with diabetes and previous cardiovascular events.[16] Likewise, prevalence of microalbuminuria was similar between RA and non-RA individuals in a large population-based study (5.63% vs 5.91%).[18] In a recent study of 342 RA patients, microalbuminuria affected 11.9% of patients, which was similar to our estimated prevalence of 11.0%, and was likewise not associated with therapy or inflammation.[33] When RA patients with metabolic syndrome and hypertension were excluded, prevalence of microalbuminuria fell from 11.9% to 3.1%,[33] considerably less than expected among non-RA individuals without hypertension and diabetes (6.6%).[34] Even though increased rates of microalbuminuria were recently described in a small cohort of patients, compared to controls (33.3% vs 6.66%),[14] careful adjustment for potential confounders in a larger study by Sammut et al[17] showed that RA was actually associated with 67% lower odds of elevated UAE (P = 0.016). Our study appears in accordance with previous results showing similar levels of both microalbuminuria and UAE between RA and non-RA individuals. It needs to be highlighted that in our cohort of RA patients, blood pressure was well controlled and only six subjects with diabetes were included, which might account for the nonsignificant differences in UAE according to the presence of diabetes or hypertension in our RA population.

The observation that RA individuals in our study did not exhibit increased rates of UAE merits further consideration. Albuminuria has been linked to both endothelial dysfunction and atherosclerosis, which are considered inherent to the RA-triggered systemic inflammatory

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process. It appears that specific factors might be implicated in the prevalence of microalbuminuria in RA. Chronic anti-inflammatory treatment in patients with RA, specifically anti-TNF treatment, might be accompanied by significant renoprotective effects by altering the mechanism thought to underlie albuminuria.[17,35] Of note, our patients were characterized by low inflammatory burden and well-controlled disease. It might be possible that under such circumstances, renal endothelial cells are not susceptible to renal damage and albuminuria. Further studies are needed to draw safe conclusions regarding prevalence and mechanisms of microalbuminuria in RA, and the conditions under which the inflammatory process in RA might skip the renal vascular bed.

Few studies have assessed the relationship between UAE and markers of vasculopathy in patients with RA. This emerges as an interesting approach, as firm data from the general population and high-cardiovascular risk patients with diabetes and hypertension indicate that microalbuminuria is associated with generalized vascular damage and predicts cardiovascular outcomes.[3,4] Still, few studies have investigated the association between UAE and the herein included measures of microvascular impairment. Among participants of the Multi-Ethnic Study of Atherosclerosis without baseline clinical cardiovascular disease, albuminuria was associated with both narrower and wider retinal arteriolar caliber.[36] In type 1 diabetes, lower SEVR was also independently related to the presence of microalbuminuria and degree of albuminuria within normo- and microalbuminuric participants.[37] Relevant studies in RA have focused on the association of UAE with markers of macrovascular dysfunction, rather than markers of microangiopathy. In this concept, Becetti et al found that UAE in RA patients was associated with macrovascular involvement, specifically, arterial stiffness, evaluated by measurement of AIx. However, they failed to reveal an association with coronary artery calcification in the same population.[15] On the contrary, UAE was not associated with AIx in the study by Pieringer et al[38] in RA patients with and without diabetes. It needs to be considered that AIx is an indirect index of arterial stiffness, compared to the gold standard pulse wave velocity.[39] Firm measures of subclinical atherosclerosis were studied in relation to microalbuminuria in RA by Sammut et al, including carotid intima-media thickness, detection of focal plaques in the carotid arteries, and ankle-brachial index. None of these measures correlated with UAE in RA. In addition, no association was shown with coronary artery calcification, calculated from chest tomography.[17] The presently observed nonsignificant association of UAE with SEVR, which represents a functional index of myocardial perfusion, appears in line with the previously described lack of association with coronary artery calcification scoring, which evaluates morphological features of the coronary vessels.[15,17] Altogether, the results of the present study, as well as others, do not support the hypothesis that UAE can be considered as an index of diffuse microvascular impairment in patients with RA.

The strengths of this study include the reliable evaluation of UAE with the gold standard 24-hour urine collection, and the meticulous assessment of distinct microvascular beds, which are important either in terms of functionality (coronary microcirculation) or accessibility (retina, dermal capillary network), using methodology that has been previously applied in RA patients[11-13] and other populations.[25-27,30] An important limitation of our study concerns the relatively small sample size. However, it is unlikely that it might have obscured potential associations between UAE and different forms of microvascular damage. Our study is limited by the different composition of the RA and the control groups regarding the presence of cardiovascular comorbidities. We included a real-life cohort of patients with RA and hence, a significant portion presented with comorbidities, especially hypertension. The impact of hypertension and diabetes on microalbuminuria was not confirmed in our population, probably because of the relatively well-controlled hypertension and the small number of diabetic patients. Finally, even though no association was found between UAE and the studied markers of vasculopathy, it cannot be excluded that an association might exist with alterations in other microvascular beds. Likewise, it cannot be excluded that an association might exist between UAE and macrovascular alterations, but this cannot be deduced from the present study.

In conclusion, our data suggest that UAE is not associated with markers of vasculopathy in distal microvascular beds (coronary microvascular perfusion, retinal microvasculature, and dermal capillary network). Hence, microalbuminuria in patients with RA needs to be primarily considered as a manifestation of compromised function of the renal microvasculature, rather than a marker of generalized microvascular impairment.

5 | PERSPECTIVE

The present study showed that UAE was not associated with functional and morphological alterations of the retinal microvasculature, the coronary microcirculation and the dermal capillary network in patients with RA. Considering the prognostic value of UAE in the general population in terms of cardiovascular outcomes, future studies are needed to determine whether microalbuminuria may be used as an indicator of cardiovascular risk in patients with RA.

CONFLICT OF INTEREST

None.

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