Section: General Medicine

Original Research Article

A STUDY OF MICROALBUMINURIA AS A RISK INDICATOR IN RHEUMATOID ARTHRITIS

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Abstract

Background: Microalbuminuria is associated with increased risk for renal and cardiovascular mortality and morbidity in diabetes mellitus, hypertension, patients with acute myocardial infarction and elderly patients. However, the significance of microalbuminuria in rheumatoid arthritis (RA) and its correlation with disease activity is not well studied. The main aim is to study microalbuminuria as a risk factor in RA. **Materials and Methods:** A total of 50 confirmed cases of RA (2010 ACR-EULAR criteria) and 50 age and sex-matched controls were taken. Routine hemogram and biochemical tests, including fasting blood sugar, serum creatinine, urea, CRP, and ESR, were measured in all patients. A qualitative assay of rheumatoid factor was also done. Urine for albumin was measured twice in the three months, and the mean of the two positive values was taken as the result. **Results:** The maximum microalbuminuria 8(57.1%) was reported in the age group 31 to 40 years. Females were reported with higher incidences of 14(37.8%) microalbuminuria. The RA duration of >30 months showed a maximum of 5(71.4%) microalbuminuria. Of all microalbuminuria-positive patients, 16 (45.7%) patients had involvement of both upper and lower joints and 14(37.8 %) patients had morning stiffness lasting > 60 min. Microalbuminuria was significantly ($p<0.05$) associated with higher ESR, C-reactive protein (CRP) and DAS values. All the patients in the microalbuminuria-positive group were rheumatoid factor positive. However, extra-articular manifestation with microalbuminuria was found statistically insignificant ($p>0.05$). **Conclusion:** We found an increased prevalence of microalbuminuria in rheumatoid arthritis patients correlated with ESR, CRP and DAS values.

INTRODUCTION

Rheumatoid arthritis is a chronic and systemic disease of etiology which is not known. It is featured by peripheral involving symmetrical polyarthritis. It has a progressive and insidious course with remissions and exacerbations, and that is part of its natural history. Its onset could be at any age, even though it usually starts in the fourth decade of life.[1] There is a 3:1 female preponderance, which is greater in young people, and the age-related incidence is closely equal in older people. Rheumatoid arthritis is principally a joint disease but has several extra-articular manifestations. Systemic manifestations involve cardiac, pulmonary, haematological, ocular, and neurological systems.[1,2] Rheumatoid arthritis is prevalent globally and involves all ethnic groups, with a prevalence that ranges from 0.3 – 1%. Indian data establishes the prevalence to be around 0.65 – 0.75%.[3]

Microalbuminuria is a marker that contributes to vascular damage. Change in renal permeability to plasma proteins lights up increased systemic vascular permeability in inflammatory conditions. Therefore, urinary albumin excretion reflects a systemic reaction in the acute phase response.[4] Numerous studies have shown that microalbuminuria is associated with enhanced risk for renal and cardiovascular mortality and morbidity in diabetes mellitus, hypertension, acute myocardial infarction and elderly patients. Still, the significance of microalbuminuria in rheumatoid arthritis and its correlation with disease activity is not well established.[5-8] In rheumatoid arthritis, CRP and ESR are nearly always increased, which reflects the disease activity. Microalbuminuria and subclinical renal damage are frequent in rheumatoid arthritis

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patients, especially those with chronic disease and severe disease activity.[9] Urinary albumin measured by immunochemical methods is an easy, simple, and sensitive test to detect early subclinical renal dysfunction and drug-induced renal damage in rheumatoid arthritis. Therefore, the present study evaluates the association of microalbuminuria with rheumatoid arthritis and its correlation with disease activity as indicated by ESR, CRP, RA Factor and disease duration.

MATERIALS AND METHODS

The study was a case-control study done in 50 Rheumatoid arthritis patients admitted to Government Rajaji Hospital and Madurai Medical College as subjects and 50 healthy subjects as controls of the same age and sex group during the study period from March 2020 to August 2020. The written consent and ethical committee approval were taken before the start of the study.

Inclusion Criteria

Rheumatoid Arthritis patients both naïve and on treatment of age greater than 16 years fulfilling NEW 2010 ACR-EULAR Criteria.1

Exclusion Criteria

Patients with diabetes mellitus, congestive cardiac failure, urinary tract infections, pre-existing renal disease, hypertension, acute illness, pregnancy and Usage of nephrotoxic drugs for the last three months. In addition, patients under heavy physical exercise before the test for microalbuminuria were excluded.

Methodology

After confirmation of diagnosis and explaining the purpose & procedure of the study, written informed consent in Tamil was obtained. Random urine samples were collected in the morning. Urinary microalbumin was measured by an immunoturbidimetric method using antihuman albumin reagents. The antibody concentration to human albumin is adjusted to provide a sensitivity of about 25 mg/L and above of microalbuminuria. Routine hemogram and biochemical tests, including fasting blood sugar, serum creatinine, urea, acute phase reactants like CRP (immunoturbidimetric method), and ESR, were measured in all patients. A qualitative assay of rheumatoid factor was done by latex agglutination method. Urine for albumin was measured twice in the three months, and the mean of the two positive values was taken as the result. Subjects were classified as having microalbuminuria if a mean value was between 30 and 300 mg/L.

Statistical Analysis

The data collected during the study was formulated into a master chart in Microsoft office excel, and statistical analysis was done with computer help using the statistical software package SPSS-17 for Windows. Using this software, frequencies, range, mean, standard deviation and p were calculated through the student t-test, one-way ANOVA, Pearson correlation and chi-square test. A p-value of < 0.05 was taken as significant.

RESULTS

The mean age in the control group was 45.38 ± 11.43 years; in the case group, it was 43.66 ± 11.16 years. The maximum number of patients was reported in the age group of 41 to 50 years in both control and case groups (Control: 34%; Case: 30%). A female majority, 38 (76%), was found in case group patients. The mean duration of symptoms among RA patients was 23.6 months. History of morning stiffness was present in 37 (74%) patients, and 35 (70%) patients had constitutional symptoms. The majority of RA patients were recorded with ≤ 10 joints. Microalbuminuria RA patients were found in 18 (36%) cases, whereas, in the control group, it was reported as 2 (4%). Microalbuminuria was found in 18 (36%) cases in RA patients, whereas only 2 (4%) control patients were observed with microalbuminuria (Table 1).

Table 1: Observation of Microalbuminuria to different demographic parameters

Parameters	Number of patients	Microalbuminuria		
Age in years		Absent	Present	P value
20-30	7	5 (71.4%)	2 (28.6%)	0.335
31-40	14	6(42.9%)	8(57.1%)	
41-50	15	12(80%)	3(20%)	
51-60	11	7(63.6%)	4(36.4%)	
61-70	3	2(66.7%)	1 (33.3%)	
Gender				
Male	12	8 (66.7%)	4(33.3%)	0.901
Female	38	24(63.2%)	14(37.8%)	
Duration of symptoms				
< 10	13	10 (76.9%)	3(23.1%)	0.029
11 - 20	17	14(82.4%)	3(17.6%)	
21 - 30	13	6(46.2%)	7(53.8%)	
>30	7	2(28.6%)	5(71.4%)	
Number of joints involved				
Upper limb	12	10 (83.3%)	2(16.7%)	0.079
Lower limb	3	3 (100%)	0	
Both	35	19 (54.3%)	16 (45.7%)	
Morning stiffness				

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<30 min	5	4 (80%)	1 (20%)	0.904
31-60 min	8	5 (62.5%)	3 (37.5%)	
>60 min	37	23 (62.16%)	14(37.8%)	

The maximum microalbuminuria 8 (57.1%) was reported in the age group of 31 to 40. Females were reported with higher incidences of 14 (37.8%) microalbuminuria. The RA duration of >30 months showed a maximum of 5 (71.4%) microalbuminuria. Of all microalbuminuria-positive patients, 2 (16.7%) patients had involvement of only upper limb joints, 16 (45.7%) patients had involvement of both upper and lower joints and 14 (37.8%) patients had morning stiffness lasting > 60 min (Table 2).

Table 2: Observation of different evaluation parameters of patients

Parameters	Microalbuminuria			
	Absent	Present	Total	P value
ESR				
< 30	6 (85.7%)	1 (14.3%)	7	<0.001
31-50	11 (100%)	0	11	
51-100	14 (58.3%)	10 (41.7%)	24	
>100	1 (3.9%)	7 (77.8%)	8	
CRP levels (mg/l)				
< 5.0	10 (90.9%)	1 (9.1%)	11	<0.001
5.0-10.0	10 (100%)	0	10	
10.0-20.0	4 (80%)	1 (20%)	5	
20.0-40.0	3 (27.3%)	8 (72.7%)	11	
40.0-60.0	4 (50%)	4 (50%)	8	
>60.0	1 (20%)	4 (80%)	5	
DAS score				
< 1.6	4 (100%)	0	4	<0.001
1.6 - 2.4	11(91.66%)	1 (8.33%)	12	
2.4 - 3.7	9 (64.2%)	5 (35.71%)	14	
> 3.7	8 (40%)	12 (60%)	20	
Extra articular manifestations				
Rheumatoid nodules	3	4	7	0.28
Purpura	2	0	2	
Normal	27	14	41	

Microalbuminuria was significantly ($p<0.05$) associated with higher ESR, CRP and DAS values. All the patients in microalbuminuria-positive group were rheumatoid factor positive. Mean values were significantly higher in microalbuminuria-positive patients (206.75 IU/dl vs 82.24 IU/dl). However, extra-articular manifestation with the presence of microalbuminuria was found statistically insignificant ($p>0.05$) (Table 2, Figure 1).

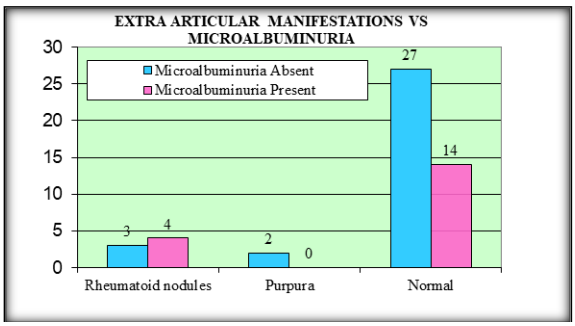

Figure 1: Observation of Microalbuminuria to extra-articular manifestation

DISCUSSION

Our study showed that the relative frequency of microalbuminuria in patients with Rheumatoid arthritis was 36%. Studies conducted by Nordin et al. showed similar results to our study.[10] The frequency of positivity of microalbuminuria in patients with rheumatoid arthritis was higher in cases when compared to controls (36% vs 4%). Studies conducted by Saito et al. and Bhatt et al. showed results similarly.[11-12] The relative frequency of microalbuminuria in Rheumatoid arthritis was 27.7% in cases and 7.8% in controls. Pederson et al., in their investigation, also showed a relative frequency of microalbuminuria of 30%.[13]

The Mean microalbuminuria level among positive cases in our study was about 38.8±4.82, and in controls was about 26.8±1.84 mg/L. Other studies showed the results alike. A study conducted by Pedersen et al. showed 37.1± 5.26 mg/L in cases vs 12.8±4.68mg/L, and Bhatt et al. showed 39.5±5.48 in cases vs 12.0±8.72mg/L in controls.[13,12]

The mean age of patients was similar in both microalbuminuria positive and negative groups, about 43.66±11.16 and 45.38 ± 11.43, respectively. Age was not a significant factor for microalbuminuria. Pederson et al. also obtained similar results. Out of 18 patients positive for microalbuminuria, 4 were males, and 14 were females in our study.[13] This difference in sex distribution was insignificant (p-0.999) in microalbuminuria positive and negative groups. According to Pederson et al., the median ratio of albumin excretion did not differ between men and women in RA patients.[13]

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All patients who were microalbuminuria positive had constitutional symptoms in our study in the form of anorexia, malaise, fever or generalized weakness. Out of 18 patients who had positive microalbuminuria test, 14 (77.78%) had morning stiffness, and the duration of morning stiffness was also significantly longer than lasted > 60 minutes. The present data imply that microalbuminuria is a marker of severe disease activity.

ESR levels were significantly higher in microalbuminuria patients. The mean ESR in the microalbuminuria-positive group was 87.61±30.87 compared to 52.18±25.39 in the microalbuminuria-negative group ($p<0.001$). A total of 8 out of 18 patients had ESR >100 ($P=0.002$). However, although ESR was higher in patients with microalbuminuria, Pederson et al. did not show a statistically significant relation between ESR levels and microalbuminuria. This was explained because some patients with normoalbuminuria had increased values of ESR for reasons other than RA.[13]

The mean CRP value was 40.857 in positive microalbuminuria patients and 26.43 in negatives ($P=0.001$). All microalbuminuria-positive patients were CRP-positive. Out of 18, 8 patients in the microalbuminuria-positive group had CRP between 20-40 mg/l, four between 40-60 mg/l ($P=0.065$), and four patients had CRP > 60 mg/l. With the data collected in our study, the presence of microalbuminuria also indicates the severity of the disease since both ESR and CRP are indicators of the severity of the disease. A study by Nakamura et al. showed that low-grade inflammation, as represented by CRP levels, was significantly related to microalbuminuria.14 Median values were 112 (16-1615) nmol/l for CRP, and CRP was significantly correlated with urinary albumin: creatinine ratio according to Pederson et al. 13 In the study by Bhatt et al. there was a conclusion that microalbuminuria was associated with significantly higher CRP values.[12]

All the patients in microalbuminuria-positive group were Rheumatoid factor positive. RA factor had a significant correlation with microalbuminuria. Mean values were significantly higher in microalbuminuria-positive patients (206.75 vs 82.24) with a P value of $p<0.001$. In our study mean no. of joints involved was 15.66 in the microalbuminuria-positive group as against 12.406 in the microalbuminuria-absent group ($P<0.08$), which showed that microalbuminuria significantly correlates with disease activity. These findings in the present study follow earlier reported studies.[15]

In our study, the mean duration of symptoms was significantly longer in patients with microalbuminuria (23.61 months) than those with negative microalbuminuria (15.03 ±7.528 months). The p-value was significant, about 0.007. Patients with longer duration of symptoms are more likely to have microalbuminuria. Pederson et al. also concluded that patients with microalbuminuria had a significantly greater median duration of RA than the group with normal albumin: creatinine ratio (1 1-2 v 7-8 years; p< 0001).[13] Bhatt et al. showed similar results that microalbuminuria was associated with disease duration. The possible correlation between urinary excretion of albumin, disease activity, and duration of RA is explained in two mechanisms: severe and long-standing RA tends to affect the kidneys and the systemic vascular permeability more, or patients with more severe and long-standing disease receive more nephrotoxic treatment.[12]

Our study showed that microalbuminuria's positivity rate increases with a disease activity score (DAS) increase. The patients with moderate (DAS >2.4≤3.7) and severe (DAS≥3.7) disease activity were statistically significant with microalbuminuria. The mean microalbuminuria concentration also significantly correlates with moderate and severe disease activity with a p-value of < 0.001. These findings in the present study follow earlier reported studies.[16]

In our study, extra-articular manifestations were present in 9 patients only. They were in the form of rheumatoid nodules (7) and purpura (2). Only two patients with rheumatoid nodules and none with purpura had positive microalbuminuria tests. The correlation was not statistically significant in our study. We screened only 50 patients with rheumatoid arthritis; most were newly diagnosed, so it is difficult to conclude the association between microalbuminuria and extra-articular manifestations. Verma et al., an investigation showed consistent results with our study.[17]

CONCLUSION

Microalbuminuria is a sensitive indicator of increased renal vascular permeability in RA patients. Microalbuminuria correlates significantly with ESR, RA, CRP, DAS and disease duration. Urine albumin measured by an immunological method is a simple and sensitive test to detect subclinical renal function. Therefore, microalbuminuria is used as a routine test to detect renal involvement in its initial phase in patients with Rheumatoid Arthritis to choose the most appropriate and relevant treatment.

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