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# Microalbuminuria in Rheumatoid Arthritis Patients: Clinical and Biochemical Correlates

**Kamal Athar, Quaiser Saif, Khan Ruhi* and Ahmed Shadab**

*Department of Medicine, JNMC, AMU, Delhi, India*

***Corresponding author:** Ruhi Khan, Assistant Professor, Department of Medicine, AMU, Aligarh-02002 India, Tel: 0091-9267522882; E-mail: drruhi5@gmail.com

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## Abstract

**Background:** Microalbuminuria is associated with increased risk for renal and cardiovascular mortality and morbidity in diabetes mellitus, hypertension and patients with acute myocardial infarction but the significance of microalbuminuria in rheumatoid arthritis and its correlation with clinical and biochemical parameters of disease activity is not well studied. The present study is therefore aimed to determine the presence of microalbuminuria in rheumatoid arthritis patients and to correlate it with indicators of disease activity.

**Materials and methods:** Hundred confirmed cases of rheumatoid arthritis (2010 ACREULAR criteria) were taken. Those suffering from hypertension, diabetes mellitus and renal disease were excluded. Microalbumin was assessed by immunoturbidimetric method on Delta nephelometer. Disease activity was assessed by CRP and ESR.

**Results:** Out of 100 RA, 30 (30%) were males and 70 (70%) females with a mean age of patients 43(17 ± 11.16 years). 28(28%) cases had microalbuminuria. Duration of morning stiffness was significantly longer in patients with microalbuminuria. Out of 28 patients positive for microalbuminuria, 12 patients had morning stiffness lasting >60 min. Mean no. of joints involved was 18.96 ± 6.01 in microalbuminuria positive group (P<0.001).14 of the 28 patients with microalbuminuria had evidence of erosions on xray (P value of <0.001). Mean ESR in microalbuminuria positive patients was 87.93 ± 26.02 mm in 1st hour (P value of <0.001). Mean CRP in microalbuminuria positive patients was 48.78 ± 16.06 mg/l (P value of <0.001). Mean value of RA in microalbuminuria positive patients was 211.89 ± 97.39 IU/dl (P value of <0.001).An independent association was found between levels of RA Factor (β=0.540, P <0.001) and level of microalbuminuria.

**Conclusion:** RA patients having microalbuminuria have significant clinical and biochemical correlation with severe disease activity.Immunological methods for detecting microalbuminuria should routinely be used in all rheumatoid arthritis patients to detect renal involvement in an incipient stage so as to minimize disease morbidity.

**Keywords:** C reactive protein; Erythrocyte sedimentation rate; Microalbuminuria; Rheumatoid arthritis

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling and tenderness with destruction of synovial joints, leading to severe disability and premature mortality [1-3]. Prevalence of RA in the general population worldwide is estimated to be between 0.3 to 1.5% using different types of classification criteria [4-6]. Indian data suggests the prevalence of RA to be around 0.65–0.75% [7]. The peak age of onset has risen to 50 years or more and is more common in women than men with a ratio of 3:1 [6-8].

Microalbuminuria or dipstick negative albuminuria is conventionally defined as urinary albumin excretion between 30-300 mg/24 hour for timed 24 hours urine collections and between 20-200 mg/L for untimed samples [9]. Microalbuminuria is a marker of widespread vascular damage. Various studies have shown that 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 but the significance of microalbuminuria in RA and its correlation with disease activity is not well studied. It is suggested that microalbuminuria and subclinical renal damage are frequent in RA patients particularly in those with longstanding disease and with severe disease activity [10]. Urinary albumin measured by immunochemical method is a simple and sensitive test to detect early subclinical renal dysfunction and drug induced renal damage in RA [11]. Hence the present study was conducted to evaluate the association of microalbuminuria with RA and its correlation with disease activity as indicated by ESR, C reactive protein (CRP), rheumatoid factor (RAF) and duration of the disease.

## Aims and Objectives

To determine the association of microalbuminuria with RA.

To correlate microalbuminuria with other indicators of disease activity like ESR, CRP, RAF and duration of the disease.

## Material and Methods

The study was a cross sectional study done in Jawaharlal Nehru medical college, Aligarh between September 2010 to November 2012. Screening of 100 patients of rheumatoid arthritis diagnosed by NEW 2010 ACR-EULAR Criteria [12] was done after they had fulfilled the

inclusion criteria. An informed consent was taken from all the patients.

### Inclusion criteria

All patients >12yrs satisfying the NEW 2010 ACR-EULAR criteria for RA were included in the study.

### Exclusion criteria

Diagnosed patients of hypertension, diabetes mellitus and renal disease were excluded from the study. Investigations included erythrocyte sedimentation rate (ESR), rheumatoid factor (IgG), C-reactive protein (CRP), X-ray hands. Urinary microalbumin was quantitatively determined by fully automated immunoturbidometric assay which is based on the measurement of immunoprecipitation in liquid phase. Antibodies against human albumin are added to an aliquot of patient urine and reaction buffer. The antibodies undergo an agglutination reaction with albumin in urine, resulting in an increase in turbidity of the mixture. Turbidity is measured using a clinical chemistry analysis at a wavelength of Ca 405 nm.

### Statistical methods

All statistical data were analysed by using SPSS software version 15.0. Statistical significance was set at two-sided p-value ≤ 0.05. In comparison of patients and controls data, one-way ANOVA and t-test was used for quantitative variables and chi-squared test for qualitative variables. The relationship for continuous variables was examined by Pearson's correlation coefficients and categorical variables by Spearman correlation analysis. Multivariate modeling was done by linear regression analysis.

## Results

A total of 100 patients were diagnosed as Rheumatoid Arthritis by NEW 2010 ACR-EULAR criteria, out of which 70 were females and 30 were males. Age of patients ranged between 21-70 years with a mean age of 43.17 years. The mean duration of symptoms among RA patients was 13.03 ± 9.46 months with a range of 2-46 months.

### Clinical features

In our study, morning stiffness was present in 74% of patients while 70% patients had constitutional symptoms. Other less common symptoms were rheumatoid nodules, purpura and joint deformity as shown in Table 1. Only 24(24%) of our patients were already on treatment with DMARDs (methotrexate, leflunomide, sulphasalazine and hydroxychloroquine) and NSAIDs. None of the patients included in the study group had a history of gold salts or penicillamine in the past or at present.

| Presenting complaint | Number | % |
|---|---|---|
| Morning stiffness | 74 | 74 |
| Constitutional symptoms | 70 | 70 |
| Rheumatoid nodule | 13 | 13 |
| Purpura | 4 | 4 |
| Joint deformity | 10 | 10 |

**Table 1:** Clinical features of RA patients in study group.

Complete evaluation of patients by detailed clinical examination, plain radiography, blood tests and electrocardiogram was done. Total no. of joints involved in patients with RA ranged from 4-30 with a mean of 12.51, as shown in Table 2.

| Number of joints involved | Patient no. | % |
|---|---|---|
| ≤10 | 38 | 38 |
| 11-15 | 33 | 33 |
| 16-20 | 16 | 16 |
| >20 | 13 | 13 |
| Total | 100 | 100 |
| Mean ± SD | 12.51 ± 6.30 | |

**Table 2:** Clinical and biochemical parameters in RA patients.

### Microalbuminuria in RA patients

In our study, microalbuminuria was found in 28 patients (28%), 8 being males and 20 being females as shown in Figure 1.

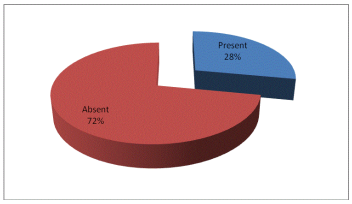


**Figure 1:** No. of RA patients with microalbuminuria.

| Study parameter | Microalbuinuria (mg/dl) | | P value |
|---|---|---|---|
| | Present | Absent | |
| Age in years(Mean ± SD) | 43.28 ± 9.25 | 39.84 ± 11.93 | 0.173 |
| Sex (Male:Female) | 8:20 | 22:50 | 0.84 |
| Morning stiffness, n(%) | 24(85.7%) | 50(71.4%) | 0.096 |
| Constitutional symptoms | 28(100%) | 42(58.33%) | <0.001 |
| Duration of symptoms | 23.6 ± 10.72 | 8.91 ± 4.46 | <.001 |
| No. of joints involved | 18.96 ± 6.01 | 10.0 ± 4.34 | <.001 |
| ESR, Mean ± SD (mm in 1st Hr) | 87.93 ± 26.02 | 50.44 ± 22.76 | <.001 |
| CRP, Mean ± SD (mg/l) | 48.78 ± 16.06 | 18.43 ± 18.83 | <.001 |
| RAF ± SD (IU/dl) | 211.89 ± 97.39 | 76.85 ± 44.53 | <.001 |
| Patients on treatment | 10(35.7%) | 18(25%) | 0.284 |
| Joint deformity | 1(3.5%) | 9(12.5%) | 0.181 |

| | | | |
|---|---|---|---|
| Rheumatoid nodule | 5(17.85%) | 8(11.11%) | 0.368 |

**Table 3:** Various parameters in relation to microalbuminuria.

Out of 28 patients who had positive microalbuminuria test, 24(87.5%) had morning stiffness lasting for >60 minutes and all 28 patients had constitutional symptoms. Only 10 patients (35.7%) were on treatment with DMARDs or NSAIDs. One of the patients had joint deformities and 5(17.85%) had rheumatoid nodules. Duration of symptoms was significantly longer in patients positive for microalbuminuria with mean duration being 23.6 ± 10.72 as compared to 8.91 ± 4.46 (P<0.001). Mean no. of joints involved was 18.96 ± 6.01 in microalbuminuria positive group as against 8.91 ± 4.46 in microalbuminuria negative group (P<0.001). Mean ESR was also significantly higher in microalbuminuria positive patients (87.93 vs 50.44), with P<0.001. Mean CRP was 48.78 in microalbuminuria positive patients as compared to 18.43 in microalbuminuria negative patients (P<0.001). Meanvalues of rheumatoid factor were significantly higher in microalbuminuria positive patients (211.89 vs 76.85) with a P value of <0.001 as shown in Table 3.

## Association of morning stiffness with presence of microalbuminuria

Duration of morning stiffness was significantly longer in patients with microalbuminuria. Out of 28 patients positive for microalbuminuria, 24 patients had morning stiffness lasting >60 min, 2 patients had between 31- 60 min and 2 patient had morning stiffness <30 min as shown in Table 4 and Figure 2.

| Morning stiffness | No. of patient | Microalbuminuria | |
|---|---|---|---|
| | | Present | Absent |
| ≤ 30 minute | 10 | 2(20%) | 8(80%) |
| 31-60 minute | 16 | 2(12.5%) | 14(87.5%) |
| >60 minute | 74 | 24(32.4%) | 50(67.6%) |

**Table 4:** Association of morning stiffness involved with microalbuminuria.

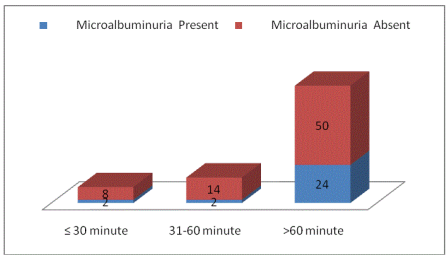


**Figure 2:** Association of morning stiffness involved with microalbuminuria.

## Association of ESR with microalbuminuria

Microalbuminuria was significantly associated with higher ESR values. Out of 28 patients positive for microalbuminuria, 15 patients had ESR>50.7 mm in 1st hour and 11 patients had ESR>100 mm in 1st hour. Mean ESR was also significantly higher in microalbuminuria positive patients (87.93 vs 50.44), with P<0.001 as shown in Table 5 and Figure 3.

| ESR( mm in 1st hour) | No. of patients | Microalbuminuria (mg/l) | | P value |
|---|---|---|---|---|
| | | Present | Absent | |
| <30 mm | 15 | 2(13.3%) | 13(86.7%) | |
| 31-50 mm | 20 | 0 | 20(100%) | |
| 51-100 mm | 50 | 15(30%) | 35(70%) | |
| ≥ 101 mm | 15 | 11(73.3%) | 4(26.7%) | |
| Mean ESR | | 87.93 | 50.44 | <0.001 |

**Table 5:** Association of ESR with microalbuminuria.

There was a positive correlation between microalbuminuria and ESR (r=0.6, P<0.001).

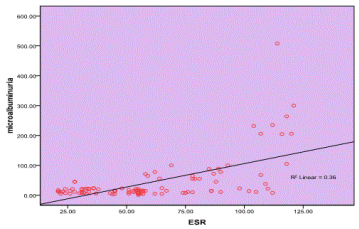


**Figure 3:** Correlation of microalbuminuria with ESR.

## Association of CRP with microalbuminuria

Microalbuminuria was significantly associated with higher CRP values. Out of 28 patients with microalbuminuria, 19 patients had CRP>40. Mean CRP was 48.78 in microalbuminuria positive patients as compared to 18.43 in microalbuminuria negative patients (P<0.001) as shown in Table 6 and Figure 4.

| CRP (mg/l) | No. of patient | Microalbuminuria (mg/dl) | | P value |
|---|---|---|---|---|
| | | Present | Absent | |
| <10 | 40 | 0 | 40(100%) | |
| 11-20 | 11 | 0 | 11(100%) | |
| 21- 40 | 18 | 9(50%) | 9(50%) | |
| ≥ 41 | 31 | 19(61.3%) | 12(38.7%) | |
| Mean CRP | | 48.78 | 18.43 | <0.001 |

**Table 6:** Association of CRP levels with presence of microalbuminuria.

There was a positive correlation between microalbuminuria and CRP (r=0.524, P<0.001).

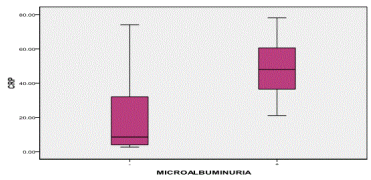


**Figure 4:** Correlation of CRP levels with presence of microalbuminuria.

## Association of Rheumatoid factor levels with microalbuminuria

Microalbuminuria was significantly associated with higher values of RAF. Out of 28 patients positive for microalbuminuria, 21 patients had RAF>150 and 7 patients had RAF<150. Mean values of RAF were significantly higher in microalbuminuria positive patients (211.89 vs 76.85) with a P value of <0.001 as shown in Table 7 and Figure 5.

| RA factor( IU/dl) | No. of patients | Microalbuminuria (mg/dl) | | P value |
|---|---|---|---|---|
| | | Present | Absent | |
| <50 | 22 | 1(4.5%) | 21(95.5%) | |
| 51-100 | 37 | 2(5.4%) | 35(94.6%) | |
| 101-150 | 15 | 4(26.7%) | 11(73.3%) | |
| ≥ 151 | 26 | 21(80.8%) | 5(19.2%) | |
| Mean RA Factor | | 211.89 | 76.85 | <0.001 |

**Table 7:** Association of RAF levels with microalbuminuria.

There was a positive correlation between microalbuminuria and RAF (r=0.676, P<0.001).

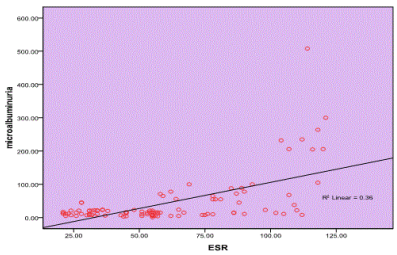


**Figure 5:** Association of RAF levels with microalbuminuria.

## Multiple regression

Multiple linear regression analysis was done using levels of microalbumin in urine as dependent variable, and duration of disease, number of joints involved, ESR, CRP and level of RAF as independent variables. An independent association was found between levels of RAF (β=0.540, P<0.001) and level of microalbuminuria as shown in Table 8.

| S.No | Variable | β(Standardized Coefficients) | P value | $R^2$ and P of overall module |
|---|---|---|---|---|
| 1. | Duration of disease | 0.084 | 0.36 | $R^2$=0.485 |
| 2. | No. of joints involved | 0.166 | 0.168 | P<0.001 |
| 3. | ESR | 0.182 | 0.322 | |
| 4. | CRP | 0.227 | 0.156 | |
| 5. | RAF | 0.540 | <0.001 | |

**Table 8:** Multiple linear regression analysis.

## Discussion

The present study was undertaken to evaluate the association of microalbuminuria with rheumatoid arthritis and to determine the correlation of microalbuminuria with ESR, CRP, RAF and duration of disease. Our study revealed that the relative frequency of microalbuminuria in patients with Rheumatoid Arthritis was 28%, which was similar to other studies like Pederson LM et al. and Bhatt G et al. According to Pederson LM et al., the relative frequency of microalbuminuria in Rheumatoid Arthritis was 27.7% [11]. Bhatt G et al. also reported a relative frequency of microalbuminuria of 30% [10].

It is suggested that changes in renal permeability to plasma protein reflect increased systemic vascular permeability in inflammatory conditions. Thus urinary albumin excretion reflects a systemic reaction in acute phase response [10]. The increased albumin excretion can be accounted for by either effect of systemic inflammatory rheumatoid disorders on vascular permeability or nephrotoxic side effects of treatment. Patients with RA are at risk of developing renal complications [13,14] and proteinuria increases the mortality rate [15].

Our study confirms the presence of pathological albuminuria in many RA patients without a history of renal dysfunction, hypertension, or diabetes mellitus. Our findings are consistent with earlier reports concerning subclinical renal dysfunction in RA [16,17].

Renal involvement may remain unnoticed for a long period in a reversible subclinical stage and should be detected as early as possible [14]. Routine measures for renal function such as assays for urine total protein, urine dipstick testing, urine cytology, and serum creatinine may not reflect the renal changes until severe renal damage has occurred. In our study, all patients with microalbuminuria had a normal serum creatinine concentration and only one patient had

macroalbuminuria. Urinary albumin measured by immunoturbidimetry or other immunochemical methods is a simple and sensitive test of early subclinical renal damage [18]. According to our study, out of 28 patients who had positive microalbuminuria test, 24 (85.7%) had morning stiffness lasting >60 minutes. 14 of the 28 patients with microalbuminuria had evidence of erosions on X-ray association of which was statistically significant with a P value of <0.001. From the present data, it implies that microalbuminuria is a marker of severe disease activity.

In our study the presence of microalbuminuria correlated significantly with ESR. Mean ESR in microalbuminuria positive group was 87.93 ± 26.02 mm in 1st hour as compared to 50.44 ± 22.76 mm in 1st hour in microalbuminuria negative group (p-0.001). Out of 28 patients positive for microalbuminuria, 26 patients (92.85%) had ESR>50. 11mm in 1st hour patients (39.28 %) had ESR>100 mm in 1st hour. However Pederson L M et al. found no statistically significant relation between ESR levels and microalbuminuria in Rheumatoid Arthritis patients, although ESR was higher in patients with microalbuminuria. The latter is partially explained by the fact that some patients with normoalbuminuria had increased values of ESR for reasons other than RA [11]. Other reason could be that most of the patients in the study were already on DMARDs.

According to our study, mean CRP was 48.78 ± 16 mg/l in microalbuminuria positive patients as compared to 18.43 ± 18 mg/l in microalbuminuria negatives (P<0.001). None of the microalbuminuria positive patients were CRP negative. 9 patients in microalbuminuria positive group had CRP between 21-40 mg/l, 19 patients >40-60 mg/l.

Since both ESR and CRP are indicators of severity of the disease, presence of microalbuminuria also indicates a severe disease. According to Nakamura et al., low grade inflammation as represented by CRP levels was significantly related to the presence of microalbuminuria [19]. Similar results were obtained by Pederson LM et al., who found that Median values (ranges) were 112 (16-1615 nmol/l) for CRP and CRP was significantly correlated with urinary albumin:creatinine ratio. Bhatt G et al. also found that microalbuminuria was associated with significantly higher CRP values [11].

According to our study, mean RAF was 211.89 ± 97IU/dl in microalbuminuria positive patients as compared to 76.85 ± 44 IU/dl in microalbuminuria negatives (P<0.001). RAF statistically correlated with microalbuminuria in our study.

None of the microalbuminuria positive patients were RAF negative. 3 patients in microalbuminuria positive group had RAF<00IU/dl, 15 patients>100IU/dl.

An independent association was found between levels of RAF (β=0.540, P<0.001) and level of microalbuminuria. Microalbuminuria can be independently used for assessing the severity of disease.

Microalbuminuria and subclinical renal damage are frequent in RA, particularly in those with long standing disease. A subclinical renal involvement may not berevealed by routine laboratory tests such as serum creatinine.

Treatment with gold and penicillamine seems to increase the risk of developing microalbuminuria [20,21]. In a study conducted by L M Pedersen et al. [22] 58% percent of patients with microalbuminuria were treated with either gold or penicillamine versus 21% of patients treated with other DMARDs. There was no difference in treatment with NSAIDs between patients with normal urinary albumin and those with microalbuminuria. In our study also only 24 patients were receiving DMARDS and NSAIDS but none received gold or penicillamine.

Our results suggest that microalbuminuria is a more sensitive predictor of renal dysfunction in patients at risk. Its measurement may serve as a useful tool for the diagnosis of RA without overt clinical nephropathy. However, the long term renal prognosis in patients with microalbuminuria requires clarification in longitudinal studies.

## Conclusion

The study concludes that presence of microalbuminuria indicates severe disease activity and longstanding rheumatoid arthritis. Also microalbuminuria is a sensitive indicator of increased renal vascular permeability in Rheumatoid Arthritis patients. Thus immunological methods for detecting microalbuminuria should routinely be used in all rheumatoid arthritis patients to detect renal involvement in its initial phase in order to devise the most appropriate treatment.

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