A CORRELATIVE STUDY OF MICRO ALBUMINURIA IN RHEUMATOID ARTHRITIS AND ITS ASSOCIATION WITH DISEASE ACTIVITY IN THANJAVUR MEDICAL COLLEGE, SOUTHERN REGION

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ABSTRACT

BACKGROUND
This study was done to assess the subclinical renal involvement in Rheumatoid Arthritis (RA). To study (1) The prevalence of micro albuminuria in patients having rheumatoid arthritis. (2) The relationship between micro albuminuria and disease activity in rheumatoid arthritis as assessed by DAS28, ESR, CRP, RA factor, disease duration and constitutional symptoms.

MATERIALS AND METHODS
Descriptive type of cross-sectional study involving 60 patients attending Thanjavur Medical College, Thanjavur, and Rheumatology outpatient department, Thanjavur Medical College, Thanjavur diagnosed with RA by modified ACR criteria (1987). All the patients were tested for micro albuminuria by immunoassay method.

RESULTS
The mean age at diagnosis was 44.55 years (SD 13.767), females diagnosed at an earlier age than males (43.767 years (SD-14.128) vs. 46.529 years (SD-13.005)). 71.7% were females and 28.3% were males. MA was found in 19 patients (31.7%), of them, 16 patients had morning stiffness lasting for more than one hour, 18 patients had constitutional symptoms, and 10 patients were on treatment with NSAIDs or DMARDs. The mean duration of symptoms was 24.68 ± 12.06 months in MA positive group compared with MA negative group with a mean value of 14.732 ± 8.093 (p=0.0004). The mean number of swollen joints in MA positive group was 15.89 ± 5.64 as compared to MA negative Group with a mean of 11.76 ± 6.31 (p=0.018). The mean number of tender joints involved in MA positive group was 14.32 ± 6.64 as against 9.76 ± 6.25 in MA negative group (p=0.0125). In MA positive group, mean ESR was 80.16 ± 26.67, mean CRP was 25.65 ± 22.67, mean RA Factor level was 187.947 ± 141.269 and mean DAS28 was 6.73 ± 0.65 as compared to 50.12 ± 29.19, 17.22 ± 15.37, 73.627 ± 64.398 and 5.2 ± 0.63 respectively in MA negative group (p < 0.05 in all cases).

CONCLUSION
Micro albuminuria is commonly seen in Rheumatoid Arthritis. The Association between micro albuminuria and Rheumatoid Arthritis disease activity as estimated by means of DAS28, ESR, and CRP, is statistically significant. Micro albuminuria is also associated with Rheumatoid Factor, disease duration and constitutional symptoms.

KEYWORDS
Prevalence of Microalbuminuria, Rheumatoid Arthritis, Disease Activity.

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Aims and Objectives
To know
1. The prevalence of micro albuminuria in patients having rheumatoid arthritis.
2. The relationship between micro albuminuria and disease activity in rheumatoid arthritis as assessed by parameters like DAS28 score, ESR, CRP, RA Factor and presence of active symptoms.  

Materials and Methods
The study was conducted on 60 patients attending the rheumatology Outpatient Department of Thanjavur Medical College, Thanjavur. Total study duration was 6 months. This study is a cross sectional study with case control comparison, done in Thanjavur Medical College, Thanjavur, between January 2016 and August 2016. 60 patients of RA diagnosed by means of modified ACR criteria (1987) were included in the study once they had satisfied the inclusion criteria. Patients with hypertension, diabetes mellitus or renal diseases, and individuals aged below 12 years were excluded from this study. A detailed history was taken from all the patients, age, sex, duration of RA, presence and duration of morning stiffness, chest symptoms, and list of painful joints, presence of other systemic disease and presence of extra articular manifestations of RA were recorded.

Examination
All joints were systematically examined for the presence of any tenderness, swelling, or deformity as well as the possible range of movements at these joints. Examination of the cardiovascular, respiratory, gastrointestinal, and nervous system was done. Patients were carefully observed for the presence of any extra articular manifestations and the findings were documented. Calculation of Disease Activity Score (DAS28) was done for all of them by means of DAS28 calculator for ESR.

Erythrocyte Sedimentation Rate (ESR)
ESR was measured using Westergren method. Venous blood was anti coagulated by trisodium citrate dehydrate in the ratio of 4:1 and well mixed by gentle, repeated inversion and used to fill a Westergren-Katz tube up to the 0(zero) mark. Subsequently, the tube was placed vertically in a rack, which is protected from direct sunlight, draught or vibration and incubated at room temperature for 1 hour (60 minutes).
After one hour, the distance (in mm) from the bottom of the surface meniscus to the top of sedimenting red cells was noted and reported as the ESR value. This test was done within 2 hours of collecting blood samples.

Rheumatoid Factor (IgG)
A quantitative assay was done employing a latex fixation lab kit. A value above 36 IU/ml was considered to be positive.

C - Reactive Protein
A quantitative assay was done employing ELISA technique. Values >6 mg/l were taken as positive.

Micro Albuminuria (MA)
Assessment of Urine Albumin-Creatinine Ratio (U.ACR) from spot urine sample was done by radioimmunoassay. It gives a quantitative estimation of microalbuminuria.

Disease Activity Scale Score (DAS28)
DAS28 = 0.56 x √ (28TJC) + 0.28 x √ (28SJC) +0.70 x Ln (ESR) + 0.014 x VAS

- TJC-Total tender joints
- SJC-Total swollen joints
- ESR-Erythrocyte Sedimentation Rate in mm/hr
- VAS-Visual Analogue Scale (patient puts a vertical mark on a 100 mm Scale corresponding to their general health or global disease activity Measurement is taken from the left hand side using a ruler.)

Interpretation
The DAS28 score provides a number on a scale from 0 to 10 representing the present RA disease activity.
- Remission- DAS28 ≤ 2.6
- Low Disease activity- 2.6 < DAS28 ≤ 3.2
- Moderate Disease Activity- 3.2 < DAS28 ≤ 5.1
- High Disease Activity- DAS28 >5.1

Study Design
Descriptive Cross Sectional and Analytical Study.

Inclusion Criteria
After clinical assessment and laboratory investigations, those patients aged above 12 years fulfilling the Modified ACR (American College of Rheumatology Association) criteria (1987) for Rheumatoid Arthritis were included in the study.

Exclusion Criteria
Those patients having hypertension, diabetes mellitus, previous history suggestive of renal disease and paediatric age group less than 12 years were excluded from the study.

Sample size
n=60 (n=4pq/l² p=(1-q))
prevalence in previous study, q=100-p,
l=20% of p)
An informed consent was obtained from all patients.

Statistical Methods
The significant association of clinical factors between patients with and without the presence of MA has been found out using Chi square test/Fischer Exact test. Odds ratio has been used to find the significant strength of relationship of factors in association with micro albuminuria. Student t test (two tailed, independent) has been used to find the significance of investigation parameters between the two patient groups.

Statistical Software
SPSS 20.0 was used for data analysis and Microsoft word and excel have been used to generate graphs, tables etc.
Ethical Consideration
Compilation of data required for the study was commenced only after getting clearance from the ethical committee. The privacy of the patient and the confidentiality of the clinical data were maintained during the study. A written consent was obtained from every patient before including him/her in the study. Those who did not consent were excluded from this study. No additional expenses were needed by the patients as part of this study.

OBSERVATIONS AND RESULTS
Age and Sex Distribution- The age group of the study population chosen ranged between 14 and 81 years with a mean of 44.55 yrs (SD 13.767). Among the study population, the age of males ranging from 24 to 81 years showed a mean value of 46.529 years (SD -13.005), and the age of females ranging from 14 to 72 years showed a mean of 43.767 yrs, (SD -14.128). 55% of the study population belonged to the age group of 31 to 50 years; most of them (36.7%) belonged to the age group of 41 to 50 years. (Figure 1, Figure 2) Table-1

| AGE (YEARS) | NO: OF PATIENTS (%) |
|-------------|---------------------|
| < 30        | 9 (15)              |
| 31-40       | 11 (18.3)           |
| 41-50       | 22 (36.7)           |
| 51-60       | 12 (20)             |
| > 60        | 6 (10.0)            |
| Total       | 60 (100)            |

Table 1. Age Distribution

Duration of Symptoms
The mean duration of symptoms among Rheumatoid Arthritis patients was 17.88 months, ranging from 3 to 60 months, 35% of patients had symptom duration ranging from 11 to 20 months.

Clinical Features and Investigations
A positive history of joint pains, morning stiffness and joint swelling was elicited from every patient belonging to the study group. Patients with diabetes mellitus and hypertension, as well as those who gave history of symptoms suggesting cardiac, respiratory or renal diseases like chest pain, palpitation and breathlessness on exertion, pitting pedal oedema, paroxysmal nocturnal dyspnoea (PND) or orthopnoea were excluded from the study. Those with history of constitutional symptoms such as anorexia, fever and fatigue were included in the study. 80% of patients had history of morning stiffness lasting for over 60 minutes. Constitutional symptoms were present in 70% patients. 7 patients had rheumatoid nodules. Purpura was present in 2 patients. 7 patients showed joint deformities. (Figure 4)

Joints Involved
A total of 4 to 28 joints were affected in patients with rheumatoid arthritis with the mean value for tender joints being 11.2 ± 6.671 and swollen joints being 13.067 ± 6.362. Pain involving 4-15 joints was present in 71.7% of patients and 66.4% showed oedema involving 4-15 joints. (Figure 5)
Micro Albuminuria
In this study, micro albuminuria (MA) was present in 19 patients (31.7%), which included 3 males and 16 females.

Disease Activity (DAS28)
In this study, the disease activity as defined by DAS28 was moderate in 19 patients (31.7%) and severe in 41 (68.3%). None had mild disease activity. (Table 2)

| DAS28   | NUMBER OF PATIENTS (%) |
|---------|------------------------|
| Mild    | 0                      |
| Moderate| 19 (31.7)              |
| Severe  | 41 (68.3)              |
| Total   | 60 (100)               |

Table 2. Disease Activity (DAS 28)

Out of 19 patients with micro albuminuria in this study, 16 (84.2%) had morning stiffness, 18 (94.7%) had constitutional symptoms, and 10 patients (52.6%) were on treatment with DMARDs or NSAIDs. The duration of symptoms was significantly greater in patients with micro albuminuria with a mean value of 24.68 ± 12.06 months when compared with 14.732 ± 8.09 in patients with negative MA (p=0.0004). The mean value for swollen joints was 15.89 ± 5.64 in micro albuminuria positive group when compared with 11.76 ± 6.31 in micro albuminuria negative group (P=0.018). The mean value for tender joints was 14.32 ± 6.64 in micro albuminuria positive group when compared with 9.76 ± 6.25 in micro albuminuria negative group. The mean value for ESR was also found to be significantly greater in patients with micro albuminuria (80.16 ± 26.67 v/s 50.12 ± 29.19), with p value 0.0003. The mean value for CRP was 27.23 ± 21.26 in micro albuminuria positive group when compared with 14.63 ± 14.85 in micro albuminuria negative group (P=0.0103). Only 3 out of 19 MA positive patients (15.79%) had negative RF. The mean value for RF was 187.95 ± 141.27 in micro albuminuria positive group when compared with 73.63 ± 64.39 in micro albuminuria negative group (P=0.0001). The mean DAS28 score was 6.73 ± 0.65 in micro albuminuria positive group when compared with 5.2 ± 0.63 in micro albuminuria negative group (P < 0.0001) (Table 3).

Study Parameters
Out of the 60 patients who participated in this study, 19 were having moderate disease activity and 41 patients with severe disease activity according to the DAS28 score. The mean value for age in patients with moderate disease activity was 45.26 ± 12.44 years while in patients with severe disease activity, it was found to be 44.22 ± 14.48 years. Of the 48 patients with morning stiffness lasting more than an hour, 15 belonged to the moderate disease activity group and 33 had severe disease activity. Of the 42 patients with constitutional symptoms, 13 had moderate disease activity and 29 had severe disease activity. Of the 21 patients receiving treatment for RA, 6 patients belonged to the moderate disease activity group and 15 patients belonged to severe disease activity group. 5 patients with moderate disease activity and 2 patients with severe disease activity showed deformity of joints. 3 patients with moderate disease activity and 4 patients with severe disease activity had rheumatoid nodules. Only 2 patients in the moderate disease activity group and none in the severe disease activity group showed presence of purpura. The duration of symptoms was higher in patients with severe disease activity with a mean value of 20.02 ± 10.96 months when compared with 13.26 ± 7.91 in patients with moderate disease activity. The mean value for swollen joints was 13.66 ± 6.16 in severe disease activity group when compared with 11.79 ± 6.76 in moderate disease activity group. The mean value for tender joints was 11.9 ± 6.4 in severe disease activity group when compared with 9.86 ± 7.16 in moderate disease activity group.

The mean value for ESR was found to be 55.89 ± 25.83 in patients with moderate disease activity when compared with 61.37 ± 33.99 in patients with severe disease activity. The mean value for CRP was 19.64 ± 16.65 in moderate disease activity group when compared with 20.01 ± 19.12 in severe disease activity group. The mean value for RF was found to be 111.21 ± 85.99 in the moderate disease activity group and 109.19 ± 188.49 in the severe disease activity group. The mean value for MA was found to be 34.47 ± 45.35 in the moderate disease activity group and 94.39 ± 91.48 in the severe disease activity group. (Table 4)
### Table 3. Mean Levels of Study Parameters (1)

| Study parameters                      | Microalbuminuria | P value |
|---------------------------------------|------------------|---------|
|                                       | Absent(n=41)     | Present(n=19) |
| Age in years, mean ± SD               | 42.81±13.39      | 48.32±14.18 | 0.151 # |
| Sex – male:female                     | 10:31            | 7:12     | 0.492 # |
| Morning stiffness 60 min, n(%)        | 32(78.05%)       | 16(84.21%) | 0.835 ## |
| Constitutional symptoms, n(%)        | 24(58.54%)       | 18(94.74%) | 0.005** |
| Patients on treatment, n (%)          | 11 (26.83%)      | 10 (52.63%) | 0.031** |
| Deformed joints                       | 7(17.07)         | 0        | >0.05** |
| Rheumatoid nodules                    | 4(9.76)          | 3(15.79) | >0.05** |
| Purpura                                | 2(4.88)          | 0        | >0.05** |
| Duration of symptoms, mean ± SD       | 14.73±8.09       | 24.68±12.06 | 0.0004* |
| Number of swollen joints, mean ± SD   | 11.76±6.31       | 15.89±5.64 | 0.018* |
| Number of tender joints, mean ± SD    | 9.76±6.25        | 14.32±6.64 | 0.0125* |
| ESR, mean ± SD                        | 50.12±29.19      | 80.16±26.67 | 0.0003* |
| CRP, mean ± SD                        | 14.63±14.85      | 27.23±21.26 | 0.0103* |
| RAF, mean ± SD                        | 73.63±64.39      | 187.95±141.27 | <0.0001* |
| DAS28, mean ± SD                      | 5.2±0.63         | 6.73±0.65 | <0.0001* |

Independent sample t test  

### Table 4. Mean Levels of Study Parameters (2)

| Study parameters                      | DAS28 |
|---------------------------------------|-------|
|                                       | Moderate(n=19) | Severe(n=41) |
| Age in years, mean ± SD               | 45.26±12.44 | 44.22±14.48 |
| Sex – male:female                     | 4:15    | 13:28       |
| Morning stiffness, n(%)               | 15(78.95%) | 33(80.49%) |
| Constitutional symptoms, n(%)        | 13(68.42%) | 29(70.73%) |
| Patients on treatment, n (%)          | 6(31.58%) | 15(36.59%) |
| Deformed joints, n(%)                 | 5(26.32%) | 2(4.88%)    |
| Rheumatoid nodules, n(%)              | 3(15.79%) | 4(9.76%)    |
| Petechiae, n(%)                       | 2(10.53%) | 0           |
| Duration of symptoms, mean ± SD       | 13.26±7.91 | 20.02±10.96 |
| Number of swollen joints, mean ± SD   | 11.79±6.76 | 13.66±6.16 |
| Number of tender joints, mean ± SD    | 9.86±7.16  | 11.9±6.4   |
| ESR, mean ± SD                        | 55.89±25.83 | 61.37±33.99 |
| CRP, mean ± SD                        | 19.64±16.65 | 20.01±19.12 |
| RAF, mean ± SD                        | 111.21±85.99 | 109.19±188.49 |
| MA, mean ± SD                         | 34.47±45.35 | 94.39±91.48 |
Age and Micro Albuminuria
Micro albuminuria was observed to be more frequent in the study population aged above 50 years. P value was not significant (0.628). (Figure-7)

Sex and Micro Albuminuria
Among the 19 patients in whom micro albuminuria was found to be present, there were 7 males and 12 females. There was no significant association between micro albuminuria and gender of the patient (p value=0.492) Figure 8.

Duration of Symptoms and Microalbuminuria
Out of the 19 patients who tested positive for the presence of microalbuminuria, 8 patients (42.1%) had symptoms lasting for 21-30 months and 6 patients (31.6%) had symptom duration of more than 30 months. (31-60 months). 73.7% of patients were seen to have symptoms lasting for more than 20 months. (Figure 9).

Limbs Involvement and Micro Albuminuria
Out of the 19 patients who had micro albuminuria, 2 patients had involvement of the upper limbs alone, none showed involvement of lower limbs alone, and 17 patients had involvement of both upper limb and lower limb joints. There was no statistically significant association found between any of the groups (p value >0.05). Figure 10.

Morning Stiffness and Microalbuminuria
Duration of morning stiffness was found to be lasting for a significantly longer period in those patients having microalbuminuria.

Out of the 19 patients with microalbuminuria, 16 patients had morning stiffness for more than 60 minutes, 2 patients had between 30 minutes and 60 minutes, 1 patient had morning stiffness lasting less than 30 minutes. But there was no significant association statistically. (The Chi-square value for trend is 0.043 at degree of freedom 1 with p-value of 0.8351). Table 5

ESR and Micro Albuminuria
In microalbuminuria positive group, the mean value of ESR was 80.158 ± 26.671, while in microalbuminuria negative group it was 50.122 ± 29.194; this was seen to be statistically significant. Significantly higher values of ESR were observed in patients with positive microalbuminuria. 17 out of the 19 patients with microalbuminuria had ESR values above 50; and 7 had values above 100. Table 6.
The Chi-square value for trend is 10.488, degree of freedom is 1 and p value 0.0012.

**CRP and Microalbuminuria**

In microalbuminuria positive group, the mean value of CRP was 25.647 ± 22.67 mg/l, while in microalbuminuria negative group it was 17.219 ± 15.366 mg/l. (p=0.0103). Significantly higher values of CRP were observed in patients with positive microalbuminuria. Out of the 19 patients with MA, 16 had positive CRP values. Out of the 19 patients who had microalbuminuria positive, CRP value was ≤ 30 mg/l in 10 patients, between 30 and 60 mg/l in 8 patients, and > 60 mg/l in one patient. Figure 12

**Rheumatoid Factor and Microalbuminuria**

Out of the 19 patients who have microalbuminuria, only 3 were negative for rheumatoid factor. In microalbuminuria positive group, the mean value of RF was 187.947 ± 141.269 IU/l, while in microalbuminuria negative group it was 73.627 ± 64.398 IU/l, with a p value of <0.0001. Figure 12

**Extra-articular Manifestations and Microalbuminuria**

9 out of the 60 patients who participated in this study showed extra articular manifestations- 7 had rheumatoid nodules and 2 had purpura. Only 3 patients with rheumatoid nodules had microalbuminuria. Patients with purpura did not test positive for microalbuminuria. There was no statistically significant association between microalbuminuria and extra-articular manifestations. Of the 9 patients with extra articular manifestations, 8 patients had positive RF. Table 7

**Table 7. Correlation between extra-articular Manifestations with Microalbuminuria**

**Drugs and Microalbuminuria**

21 out of the 60 (35%) patients who participated in this study were on treatment- 7 patients were on NSAIDs alone, 4 patients on NSAIDs + HCQS, one patient was on NSAIDs + HCQS + STEROID, 6 patients were on NSAIDs + HCQS + METHOTREXATE, and 3 patients were on NSAIDs + HCQS + STEROID + METHOTREXATE. Out of the 21 patients receiving treatment, 10 showed positive microalbuminuria. Table 13

**Table 13. Correlation between Drugs used and Microalbuminuria**

**DAS 28 and Micro Albuminuria**

In microalbuminuria positive group, the mean value of DAS28 was 6.73 ± 0.65, while in microalbuminuria negative group it was 5.2 ± 0.63, with a significant p value of 0.003. Of the 19 patients with microalbuminuria, 18 (94.74%) had severe disease activity according to DAS28 score. Table 14

**Table 14. Correlation between DAS28 and Micro Albuminuria**

DISCUSSION

This study was done to investigate, The prevalence of microalbuminuria in patients with Rheumatoid Arthritis and the relationship between microalbuminuria and disease activity in Rheumatoid Arthritis as assessed by DAS28. Our study was conducted in Thanjavur Medical College, Thanjavur. Being a tertiary care centre, the patients
attending the outpatient department include all those referred from other centres. The average number of patients attending our Rheumatology OPD, on Tuesdays and Thursdays every week is around 100 in number. These include nearly all connective tissue disorders like Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjogren’s syndrome, mixed connective tissue disorders, etc. About 30 patients with Rheumatoid Arthritis attend the OPD daily, out of which 10-20% were new patients attending the clinic for the first time. These patients are either undiagnosed previously or diagnosed and referred from other centres. 20-30% patients were our own patients on regular follow up. 30-40% patients were those on irregular follow up. The irregular follow up in majority of them was due to financial difficulties. The Rheumatoid Arthritis patients in our study were seen to have either moderate or severe disease activity as defined by DAS28 score. This may possibly be due to the reason that this institution being a tertiary health care level will have only referred cases. The duration of symptoms in every one of them was less than five years.

In the present study, the mean age of the population was 44.5 years. Maximum number of patients was in the 41-50 age groups. The mean value for age in both micro albuminuria positive and negative group was similar, 48.32 ± 14.18 and 42.81 ± 13.39 respectively. The mean value for age in females was 43.77 yrs. (SD-14.128) whereas in males it was 46.53 yrs. (SD-13.005). This is according to the observation by Akil M et al that occurrence of Rheumatoid Arthritis is highest in the forties.11

In the present study, age was not a significant factor for MA (P- 0.151).Pederson L M et al also got similar results.12 Among the participants in this study, there were 43 females (71.7%) and 17 males (28.3%), with a female to male ratio of 2.53. This is a bit lower than the usually observed ratio of 3:1. The mean duration of symptoms among Rheumatoid Arthritis patients in this study was 17.88 months. Most of the patients (35%) had symptom duration ranging between 11-20 months. 80% of the patients gave a definite history of morning stiffness of more than 1 hour duration. 70% patients had constitutional symptoms. Rheumatoid nodules were present in 11.67% of patients. Joint deformity and purpura were observed in 11.7% and 3.3% of patients respectively.

A total of 4 to 28 joints were involved in patients with rheumatoid arthritis with the mean value for tender joints being 11.2 ± 6.671 and swollen joints being 13.067 ± 6.362. 71.7% of patients had 4 -15 painful joints and 66.4% patients had oedema of 4 -15 joints.

In this study, 19 patients (31.67%) had micro albuminuria out of which 12 were females and 7 were males. There was no significant difference in sex distribution between micro albuminuria positive and negative groups (p- 0.365).In the study by Pederson L M et al, they observed that there is no difference in the median ratio of albumin excretion between males and females in Rheumatoid Arthritis patients (p-0.1).12 Similar observation was made by Monica Verma et al also. We observed that out of the 19 patients with positive microalbuminuria, 18 patients showed presence of constitutional symptoms like anorexia, fever and tiredness (p-0.0054). In our study, out of the 19 patients having microalbuminuria, 16 (84.2%) patients had morning stiffness lasting more than one hour; but there was no significant statistical association between morning stiffness and microalbuminuria. From the currently obtained data, it suggests that microalbuminuria is an indicator of severe disease activity. 9 patients in our study had extra articular manifestations in the form of purpura (2) and rheumatoid nodules.7 Rheumatoid nodules was found to be the most common extra articular manifestation in this study, similar to the observations made in the studies by Turesson et al13 Tests for detecting microalbuminuria was positive only in 3 patients with rheumatoid nodules and none with purpura. No significant statistical association was found between MA and EAM. In view of the fact that the majority of the patients were having shorter disease duration, it is difficult to comment about the relationship between microalbuminuria and EAM. 8 out of the 9 patients with EAM had positive RF. This is also according to the studies by Turesson et al13 The prevalence of microalbuminuria in Rheumatoid Arthritis was found to be 31.7% in our study. This was similar to the findings obtained in other studies including Pederson L M et al and Bhatt G et al. According to Pederson L M et al12, the prevalence of microalbuminuria in Rheumatoid Arthritis was 27.7%. Bhatt G et al 101 observed the prevalence of microalbuminuria to be 30%. In the studies by Monica Verma et al, the relative occurrence of microalbuminuria in Rheumatoid Arthritis patients was 26%. In our study, there were no age and sex matched controls since this was not a case control study. However in the study conducted by Pederson L M et al and Bhatt G et al14, the prevalence of microalbuminuria was significantly more in Rheumatoid Arthritis cases 27.7% v/s 7.8% in age and sex matched controls and 30% as compared to 5% in age and sex matched controls, respectively. According to Monica Verma et al, the relative incidence of microalbuminuria in rheumatoid arthritis patients was 26% as against 4% in controls.

Saito M et al compared the urinary albumin indices in patients having Rheumatoid Arthritis, osteoarthritis and normal control subjects and observed that the urinary albumin indices were 25.7 ± 38.2, 11.4 ± 11.5 and 7.7 ± 3.5 respectively, significantly greater in patients with Rheumatoid Arthritis.11 Siivonen et al in 2004 saw that microalbuminuria was present in 34 out of 600 Rheumatoid Arthritis patients and 27 out of 470 controls. Rheumatoid Arthritis patients with micro albuminuria were seen to have higher mortality rate when compared with those patients without MA, with a hazard ratio of 2.77 in MA positive patients.15 These observations suggests that microalbuminuria is comparatively common in patients with Rheumatoid Arthritis.

In inflammatory diseases, there seems to be increased systemic vascular permeability to plasma proteins. Hence, excretion of microalbumin urine is indicative of a systemic response in cases of an acute phase reaction.14 The
increased rate of albumin excretion in RA can either be due to its inflammatory effect on vascular permeability or due to the side effects caused by the nephrotoxic drugs used for the disease therapy. Renal complications are more in Rheumatoid Arthritis patients,\textsuperscript{16} and higher mortality is observed in the presence of proteinuria.\textsuperscript{17} So, it is essential to have a sensitive method for reliable clinical measurement of dysfunction of the kidneys. The present study confirms the occurrence of pathological albuminuria in several RA patients without any history suggestive of renal dysfunction, diabetes or hypertension. This is consistent with the earlier reports regarding subclinical renal dysfunction in RA.\textsuperscript{18}

The reversible subclinical stage of renal disease may stay unnoticed for a long duration, and it's necessary to detect it at the earliest. The usual measures used for measuring kidney function like urine total protein assays, urine dipstick testing, urine cytology and serum creatinine may not identify mild to moderate damages to the kidneys. Every patient having microalbuminuria in this study showed normal levels of serum creatinine, macro albuminuria was absent and also showed normal 24 hour urine protein. Estimation of urine albumin levels by immunochemistry or other immunochemical methods is a simple and sensitive method for identifying early subclinical damage to the kidneys.\textsuperscript{19} RA patients in this study belonged either to the moderate or severe disease activity group categorised according to the DAS28 score. This may be due to the reason that being a tertiary care centre, more of referred cases are seen here. In this study, it was found that there is significant association between ESR and MA. In microalbuminuria positive group, the mean value of ESR was 80.158 ± 26.671, while in microalbuminuria negative group it was 50.122 ± 29.194 (p=0.0003). 17 out of the 19 patients (89.47\%) with microalbuminuria had ESR values above 50; and 7 (36.84\%) had values above 100. Results in our study showed that MA increases with increasing ESR levels. According to Monica Verma et al, there is significant relationship between MA and ESR (p <0.001). Pederson L M et al observed no statistically significant association between ESR and MA in patients with Rheumatoid Arthritis, even though elevated ESR levels were observed in patients having microalbuminuria. This could be partly due to the reason that some patients with normal urine albumin levels showed elevated ESR levels for causes other than rheumatoid arthritis. Another explanation given by them was that majority of the patients in the study were already on treatment with DMARDs.\textsuperscript{12}

In our study, the mean value for CRP was 25.65 ± 22.67 in MA positive patients when compared to 17.22 ± 15.37 in MA negative patients (p=0.0301). Significantly elevated levels of CRP were observed in patients having MA. Out of the 19 patients with MA, 16 (84.2\%) showed positive CRP results. Of the 19 patients with microalbuminuria, CRP value was ≤30 mg/l in 10 patients, between 30 and 60 mg/l in 8 patients, and > 60 mg/l in one patient. In our study, it was found that levels of microalbuminuria increases as the CRP levels increase suggesting a direct association between the two. As elevated ESR and CRP are markers of severe disease, microalbuminuria also suggests a severe disease. In the study by Nakamura et al,\textsuperscript{20} CRP levels representing low grade inflammation was found to be significantly associated with microalbuminuria. Pederson L M et al\textsuperscript{21} also got similar results and observed that the median values (ranges between) were 112 (16-1615) nmol/l for CRP and also that CRP was significantly associated with UACR. Significant relationship between MA and CRP was also noted by Bhatt G et al\textsuperscript{14}, and Monica Verma et al. In this study, only 3 (15.79\%) patients in MA positive group had RA factor negative, while 16 (84.21\%) had positive RF. In microalbuminuria positive group, the mean value of RF was 187.947 ± 141.269 IU/l, while in microalbuminuria negative group it was 73.627 ± 64.398 IU/l, with a p value of <0.0001. A significant association was observed between RA factor and microalbuminuria in our study. Similar results were also obtained by Gordon et al, Turesson et al and Young et al, and found that RA factor was generally absent in patients with milder disease. This indicates that microalbuminuria is related with severe disease activity. According to this study, the mean value for swollen joints was 15.89 ± 5.64 in microalbuminuria positive group when compared with 11.76 ± 6.31 in microalbuminuria negative group (P=0.018), and the mean value for tender joints was 14.32 ± 6.64 in microalbuminuria positive group when compared with 9.76 ± 6.25 in microalbuminuria negative group (p=0.0125). These results suggest that microalbuminuria is significantly associated with disease activity in RA. Similar number of joints was involved in the study by Monica Verma et al (p <0.05). However in this study, no significant relationship was found between occurrence of microalbuminuria and the limb involved (upper or lower limb or both). In this study, it was observed that the mean duration of symptoms was significantly more in MA positive group (24.68 ± 12.06) than MA negative group with a p value of 0.0004. Same results are obtained by statistical analysis suggesting that microalbuminuria increases with increase in disease duration. Hence, patients having symptoms for a longer period are more prone to have microalbuminuria. In the study by Pederson L M et al,\textsuperscript{12} results indicate that patients having microalbuminuria had significantly longer median disease duration than the group with normal UACR. Similar results were also in the studies by Bhatt G et al and Monica Verma et al. The relationship between MA and disease duration may be either due to severe and chronic disease affecting the kidneys increasing the permeability of systemic vessels, or due to the additional nephrotoxic therapy given to the patients having severe chronic disease. Our study showed significant association between MA and DAS28 score. The mean DAS28 score was 6.73 ± 0.65 in microalbuminuria positive group when compared with 5.2 ± 0.63 in microalbuminuria negative group (p=0.0001). Out of the 19 patients having microalbuminuria, 18 (94.74\%) had severe disease activity. There was statistically significant association between MA and DAS28 score with a p value of 0.007. The mean value for MA was found to be 34.47 ± 45.35 in the moderate disease activity group and 94.39 ± 91.48 in the severe disease activity group. This difference was also observed to
be statistically significant with a p value 0.009. Observations made by Harikrishan Aggarwal et al and V Raveendran et al were also similar. In our study, we got statistically significant association between drug therapy and the presence of MA. Out of the 19 patients with MA, 10 were on treatment with DMARDs or NSAIDs or both. In the study by Pedersen L M, MA was found to be significantly more in patients treated with gold and penicillamine. Also in the study by Bhatt G et al, treatment with NSAIDs, methotrexate, salazopyrene, chloroquine and steroids was found to be significant. However, these patients have severe disease activity and longer duration of disease. The mean values for DAS28 score, CRP, ESR and RF were higher in the patients having microalbuminuria than those who do not have. Moreover, the number of swollen/tender joints, and duration of symptoms were found to be more in patients with MA. MA was noted to be significantly associated with these parameters. Since ESR, CRP, and DAS28 are considered as indicators of disease activity, presence of MA indicates a severe disease. Microalbuminuria and subclinical damage to the kidneys are more common in RA especially in those having greater disease duration. Routine investigations like serum creatinine may not be helpful in identifying subclinical damage to kidneys. Since microalbuminuria is a good predictor of kidney dysfunction, our study shows that subclinical renal disease is frequently observed in Rheumatoid Arthritis patients. Still, the long term prognosis for renal involvement in rheumatoid arthritis patients needs to be clarified by means of longitudinal studies. We think that in most of the patients having microalbuminuria in RA, renal involvement is irreversible and the chances of developing end stage renal disease is scarce if timely intervention done.

CONCLUSIONS
About one third of the patients having rheumatoid arthritis were seen to have microalbuminuria. In this study microalbuminuria was found to be significantly associated with disease activity in rheumatoid arthritis as assessed by DAS28, ESR, CRP and RA Factor. Microalbuminuria were also found to be associated with duration of disease and presence of active symptoms. There was no significant association between gender, age and drugs with microalbuminuria.

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REFERENCES
[1] Longo D, Fauci A, Kasper D, et al. Harrison’s principles of internal medicine. 18th edn. McGraw-Hills 2012:2378-2752.
[2] Copeman WSC. A short history of gout. Berkeley and Los Angeles: University of California Press 1964.
[3] Garrod AE. A treatise on rheumatism and rheumatoid arthritis. London: Charles Griffin and Company 1890.
[4] Caughhey DE. The arthritis of Constantine IX. Ann Rheum Dis 1974;33(1):77-80.
[5] Aurelianus C, Drabkin IE, Ephesus S. On acute diseases and on chronic diseases. Chicago: University of Chicago Press 1950.
[6] Fraser KJ. Anglo-French contributions to the recognition of rheumatoid arthritis. Ann Rheum Dis 1982;41(4):335-343.
[7] Snorrason E. Landré-Beauvais and his "goutte asthénique primitive". Acta Med Scand Suppl 1952;266:115-118.
[8] Short CL. The antiquity of rheumatoid arthritis. Arthritis Rheum 1974;17(3):193-205.
[9] van Riel PL, van Gestel AM. Area under the curve for the American College of Rheumatology improvement criteria: a valid addition to existing criteria in rheumatoid arthritis? Arthritis Rheum 2001;44(7):1719-1721.
[10] van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41(10):1845-1850.
[11] Saito M, Uuchi Y, Nakabayashi K, et al. Clinical significance of microalbuminuria in patients with rheumatoid arthritis. Nihon Jinzo Gakkai Shi 1993;35(7):815-821.
[12] Pedersen LM, Nordin H, Svensson B, et al. Microalbuminuria in patients with rheumatoid arthritis. Ann Rheum Dis 1995;54(3):189-192.
[13] Allawi J, Jarrett RJ. Microalbuminuria and cardiovascular risk factors in type 2 diabetes mellitus. Diabet Med 1990;7(2):115-118.
[14] Bhatt G, Mathur DS, Saxena GN, et al. Microalbuminuria in rheumatoid arthritis: a correlation with disease activity. J Assoc Physicians India 2002;50(82).
[15] Sihvonen S, Korpela M, Mustonen J, et al. Renal disease as a predictor of increased mortality among patients with rheumatoid arthritis. Nephron Clin Pract 2004;96(4):c107-114.
[16] Duthie JJ, Brown PE, Truelove LH, et al. Course and prognosis in rheumatoid arthritis. A further report. Ann Rheum Dis 1964;23:193-204.
[17] Jacobsson LT, Knowler WC, Pillemer S, et al. Rheumatoid arthritis and mortality. A longitudinal study in Pima Indians. Arthritis Rheum 1993;36(8):1045-1053.
[18] Dieppe PA, Doyle DV, Burry HC, et al. Renal disease in rheumatoid arthritis. Br Med J 1976;1(6010):611-612.
[19] Watts GF, Bennett JE, Rowe DJ, et al. Assessment of immunochemical methods for determining low concentrations of albumin in urine. Clin Chem 1986;32(8):1544-1548.
[20] Nordin H, Pedersen LM, Svensson BH, et al. Microalbuminuria in rheumatoid arthritis. Ugeskr Laeger 1996;158(22):3141-3143.