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A STUDY OF MICROALBUMINURIA IN RHEUMATOID ARTHRITIS: A CORRELATION WITH DISEASE ACTIVITY

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ABSTRACT: BACKGROUND: Rheumatoid arthritis is a systemic disease with a variety of extra-articular manifestations. Subclinical renal dysfunction and microalbuminuria are common in rheumatoid arthritis patients particularly with long standing disease and with severe disease activity. It is associated with increased risk of renal and cardiovascular mortality and morbidity in diabetes mellitus, hypertension and coronary artery disease patients. Despite the degree of interest shown in detection of microalbuminuria and its prognostic implications, the determinants of elevated urinary albumin excretion have not been studied well. The present study is therefore aimed to determine the prevalence of microalbuminuria in rheumatoid arthritis patients and to determine the relationship between microalbuminuria and disease activity. **SUBJECTS AND METHODS:** Thirty confirmed rheumatoid arthritis patients (ACR-EULAR criteria) and similar numbers of age and sex matched controls were taken. Those with other concomitant disorder potentially capable of altering urinary albumin excretion were excluded. Microalbuminuria was assessed by immunoturbidimetric method (indirect agglutination test). Disease activity was assessed with the help of modified disease activity score (DAS) and functional status was assessed with activity of daily living and visual analogue questionnaire (Callahan LF). **RESULTS:** 40 % of cases showed urinary albumin excretion in the microalbuminuria range in comparison to 6.6% in control. The mean microalbumin level was higher in cases (37.7 ± 4.75 mg/L) compared to controls (27.5 ± 1.73 mg/L). Prevalence of microalbuminuria showed a significant correlation with the age of the patients. Microalbuminuria was significantly correlated with ESR and CRP (P value <0.001). The positivity rate of microalbuminuria with disease duration was observed to be highest among the patients having more than 6 years of disease duration i.e., 55.5%. Microalbumin level correlates well with patients with high disease activity (DAS score >3.7) and with the use of combination chemotherapeutic agents. **CONCLUSION:** Microalbuminuria is a sensitive indicator of subclinical renal dysfunction and therefore its detection should be used as a routine test in rheumatoid arthritis patients specially those with high disease activity.

KEYWORDS: Microalbuminuria, Rheumatoid arthritis, Disease activity.

INTRODUCTION: Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause, with a wide variety of systemic manifestations but a persistent inflammatory synovitis as the characteristic feature. The potential of synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in joint integrity is the hallmark of the disease. The disease runs a variable course with exacerbations and remissions. The incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases. RA affects approximately 0.5-1% of the adult population worldwide.

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The prevalence of RA is approximately 0.8 percent of the population (range 0.3-2.1 percent); women have a higher prevalence of disease than man and in young man, the disease is uncommon (ranging from 0-0.5 percent).⁽¹⁾ It occurs in all races and in all parts of the world. The population in India has an increased susceptibility to RA. RA affects more than 0.5% of adult Indians, i.e more than 2.5 million adults Indian are affected with the disease.^(2,3)

RA is a systemic disease with a variety of extra-articular manifestations. No organ system has consistently escaped involvement in this disease. Although previous studies have shown a decreased frequency of involvement of renal system, recent data showed a prevalence of 1-5% involvement of renal system due to RA.

Although impairment of renal function is often mild to moderate, renal related mortality makes significant contribution to the increased mortality of RA. A variety of conditions including drugs like non-steroidal anti-inflammatory drugs (NSAIDs) and slowly acting anti-rheumatic drugs may lead to proteinuria in patients with RA, but in majority of the cases the proteinuria is non-persistent and usually reversible.⁽⁴⁾ Although remission of proteinuria is a favorable prognostic sign, the rheumatic diseases do have periodic exacerbations and remissions. Thus there is a risk for recurrence of proteinuria or proteinuria may regress into microalbuminuria range which may be persistent and may later leads to chronic renal insufficiency.

Microalbuminuria is the first manifestations of injury to the glomerular filtration barrier and predicts the development of overt nephropathy. Microalbuminuria arises from the increased passage of albumin through the glomerular filtration barrier. This requires ultrastructural changes rather than alterations in glomerular pressure or filtration rate alone.

Microalbuminuria or dipstick negative albuminuria is conventionally defined as urinary albumin excretion between 30 and 300 mg/24 hour for timed 24 hours urine collections and between 30 and 300 mg/L for untimed/random samples. It can be estimated by procedures like ELISA, radioimmunoassay, immunoturbidimetry and agglutination inhibition test using Latex etc.

Therefore early detection of microalbuminuria can be used as a routine procedure to detect renal involvement in its initial phase in order to devise the most appropriate treatment in patients with RA.

Despite the degree of interest shown in detection of microalbuminuria and its prognostic implications, the determinants of elevated urinary albumin excretion have not been studied widely till recently. Only a few studies from India had shown a good correlation between microalbuminuria and disease activity ⁽⁴⁾. A better understanding of such factors may influence the nature of therapeutics interventions in patients with or even before the development of renal complications. This intervention may reverse microalbuminuria and possibly retard the progression to vascular complication.

Considering all these facts, this study was undertaken to determine the prevalence of microalbuminuria in patients with RA and to find out the relationship between microalbuminuria and disease activity.

SUBJECTSS AND METHODS: The present study was conducted in adult Rheumatoid arthritis patients and control of same age and sex group attending medicine outpatient department of Assam Medical College and Hospital, Dibrugarh and got admitted in various medicine wards for a period of one year.

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All patients gave written informed consent before entering the study, which was approved by hospital ethics committee. A detailed history and case record containing baseline information regarding age, sex, duration of rheumatoid arthritis, presence and duration of morning stiffness, chest symptoms, cervical joint symptoms, list of painful joints, presence of other systemic disease and history of extra-articular manifestations of rheumatoid arthritis were documented. Constitutional symptoms in the form of anorexia, fever, malaise or generalized weakness were noted in every case.

All non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti rheumatic drugs (DMARDs) prescribed were noted.

All patients who fulfilled the American College of Rheumatology (ACR) Criteria for classification of RA were included in the study.^(5,6)

Disease activity was assessed according to American College of Rheumatology recommendation core set. They are:

1. American College of Rheumatology Recommendations of specific ways to assess each disease activity measure in the core set (Data from Felson et al and co-operating clinics committee of the American Rheumatism Association).⁽⁷⁾
2. Disease activity measure and methods includes-tender joint counts, swollen joint count, patients assessment of pain, patients global assessment of disease activity, physician global assessment of disease activity, patients assessment of physical of function and acute phase reactants value (ESR and CRP).
3. 28 joints to be examined for tenderness and swelling are temporomandibular joint(n=2), sternoclavicular (n=2), acromioclavicular (n=2), shoulder (n=2), elbow (n=2), wrist (n=2), MCP (N=10), interphalangeal of thumb (n=2), DIP (n=8), PIP(n=8), Hip (n=2), knee(n=2), ankle mortise (n=2), and PIP/DIP of the toes (n=2).⁽⁸⁾
4. Activities of Daily Living and Visual Analogue Questionnaire (Callahan LF et al 1987) .⁽⁹⁾ are:
 - a) Activity of daily living (ADL): version is graded as 1-4.
 - b) Visual analogue scale (VAS).
 - c) Patient's global assessment (PGA).

Disease Activity Score (DAS) and modified DAS: The DAS, a validate composite index of inflammation integrating in a continuous variable of:

- a. The erythrocyte sedimentation rate (ESR).
- b. The number of swollen joint count (total number 28).
- c. The number of tender joint count (total number 28).
- d. Patient assessment of disease activity (and patients global health) on a 0-10cm.(Patients global health)(0-100mm) horizontal Visual Analogue Scale (VAS).

Categorization of patients at baseline according to disease activity score (DAS) are:

DAS < 1.6- indicates remission.

DAS ≤ 2.4- low disease activity.

DAS >2.4 and ≤ 3.7-moderate disease activity.

DAS >3.7- indicates high disease activity.

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The activity of disease is reevaluated at each visit and so also the disease activity score. Modified DAS -28 with three variables was calculated according to the variables and scoring system described above. The range of DAS varies from 0 to 10.

Laboratory Assessment: Random urine samples were collected in the morning. Urinary micro-albumin was measured by immunoturbidimetric method (Microtex slide agglutination test) using antihuman albumin reagents and the concentration of antibodies to human albumin is adjusted to provide sensitivity of about 25 mg/L and above of microalbuminuria.

Routine hemogram and biochemical tests including fasting blood sugar, acute phase reactants like CRP (immunoturbidimetric method) 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 period and mean of the two positive values was taken as the result. Subjects were classified as having microalbuminuria if they had a mean value between 30 and 300 mg/L.

Rheumatoid arthritis patients with other concomitant disorder that are capable of altering urinary albumin excretion were excluded from the study. These are diabetes mellitus, congestive cardiac failure, urinary tract infections, other preexisting renal disease, uncontrolled hypertension, acute illness, pregnancy and heavy physical exercise prior to test for microalbuminuria.

STATISTICAL ANALYSIS: History, clinical features and biochemical features were collected from all patients. The prevalence of Rheumatoid arthritis was analyzed by Fishers test. Differences between continuous variables were assessed using student t test and those between categorical variables using the Chi square test.

RESULTS AND OBSERVATIONS: By strictly following the inclusion and exclusion criteria of our study finally we have enrolled 30 cases of adult RA patients from various medicine wards for the present study, with similar number of age and sex matched control.

Out 30 patients 8 patients were male and 22 were female. Majority of the patients were in the age group of 31-45 years (10 patients) and 46 -60 years (14 patients). All patients presented with polyarthritis (100%).

Fig. 1: Age incidence of Rheumatoid arthritis patients

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Maximum number of patients presented with morning stiffness (66.66%), difficulty in walking (53.33%) and generalized weakness (50%). Fever, anemia and wasting of muscles were present in maximum number of patients while subcutaneous nodules and hepatomegaly were seen only in 16 % of cases. The minimum duration of the disease was 6 months and the maximum duration was 8.5 years. Maximum patients presented with duration of disease between 2-6 years.

Duration of disease (in years)	Male (Numbers)	Female (Numbers)	Total	
			No	%
½-1	0	1	1	3.34
1-2	2	3	5	16.67
2-4	2	3	5	16.67
4-6	2	8	10	33.40
>6	2	7	9	30.0

Table 1: Showing the Duration of Disease

The mean value of swollen joint count was 893 ± 5.19 . The mean tender joint count in our cases was 10.06 ± 4.87 . About 80% of our cases were sero-positive while only 20% were sero-negative. The mean CRP in cases was 8.03 mg/l ($SD \pm 7.08$) and in control was 3.0 mg/l ($SD \pm 2.0$).

MICROALBUMINURIA IN CASES AND CONTROLS: 40% of cases showed urinary albumin excretion in the microalbuminuria range, in comparison to 6.6% in controls. The mean microalbuminuria level in the cases were 37.7 ± 4.75 mg/l and for those in the control were 27.5 ± 1.73 mg/l.

Fig. 2: Microalbuminuria (MAU) in cases and Control

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The difference in the proportion of positivity of microalbuminuria in RA cases and age and sex matched controls is found to be statistically significant (p value <0.001). The percentage of patients with microalbuminuria increases with age i.e 0%, 70%, 28.5% and 33.3 % from 16-61 years and above. The difference in proportion between the age group is found to be statistically significant (P <0.001). There was no statistical difference in the prevalence of microalbuminuria between males and females.

The positivity rate of microalbuminuria with disease duration is observed to be highest among the patients having more than 6 years of disease duration i.e 55.5%. The corresponding rates for ½-1 years, 1-2 years, 2-4 years, and 4-6 years of disease duration are 0%, 20%, 80% and 50% respectively. The difference in the proportion of positivity with disease duration is found to be statistically significant between patients with more than 6 years and less than 6 years of disease duration (P<0.001).

Duration in Years	MAU +ve group		MAU -ve group		Total
	No	%	No	%	
½	0	0	1	100	1
1-2	1	20	4	80	5
2-4	1	20	4	80	5
4-6	5	50	5	50	10
>6	5	55.5	4	44.5	9
Total	12		18		30

Table 2: Microalbuminuria and disease duration

There was no statistical difference in the prevalence of microalbuminuria between males and females.

RELATIONSHIP OF MICROALBUMINURIA AND DISEASE ACTIVITY SCORES (DAS): The positivity rate of microalbuminuria shows a statistically very highly significant increase, with increase in the disease activity score (DAS), P value<0.001.

DAS (Score)	MAU +ve group		MAU -ve group		Total
	No	%	No	%	
<1.6	0	0	0	0	0
<2.4	1	14.3	6	85.6	7
>2.4<3.7	5	31.25	11	68.7	16
>3.7	6	85.7	1	14.2	7
Total	12		18		30

Table 3: Relationship of Microalbuminuria with Disease Activity Score (DAS)

RELATIONSHIP BETWEEN MICROALBUMINURIA AND CRP: The prevalence of microalbuminuria correlates well with the elevation of the CRP value, which was seen to be statistically very highly significant in our cases.

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CRP Value (mg/L)	Cases		Controls	
	No	%	No	%
≤5	16	53.3	25	83.4
6-10	2	6.7	3	10.0
11-15	2	6.7	1	3.3
16-20	4	13.3	1	3.3
21-25	3	10.0	0	0
>25	3	10.0	0	0

Table 4: Relationship between microalbuminuria and CRP Level (mg/L)

Similarly the positivity rate of microalbuminuria correlates well with increase in the ESR value with a P value of <0.001, which is statistically significant.

All of our patients who were microalbuminuria positive had constitutional symptoms in the form of anorexia, fever, malaise or generalized weakness. Duration of morning stiffness was also significantly longer in microalbuminuria positive group. 10 (83.3%) out of 12 microalbuminuria positive patients had morning stiffness lasting more than and mean microalbuminuria level was also higher in this group.

DISCUSSION: The frequency of positivity of microalbuminuria in patients with Rheumatoid arthritis was higher as compared to controls (40 % vs 6.6%). Similar studies conducted by H. Nordin et al in Kobenhavn (1995), Saito M et al in Japan (1997), G. Bhatt et al in India (2000), L.M Pedersen et al in Denmark (1995) showed similar results..^(10,11,12,13)

The mean microalbuminuria level in our study among positive cases was 37.7 ± 4.75 mg/L in comparison to 27.5 ± 1.73 mg/L in control. Different studies conducted by different author showed similar result (L.M Pedersen 37.1 ± 5.26 mg/L in cases vs 12.8 ± 4.68 mg/L and G. Bhatt et al 39.5 ± 5.48 in cases vs 12.0 ± 8.72 mg/L in controls).^(12,13)

The present study showed an increase in the prevalence of microalbuminuria as the age increases. There was no case of microalbuminuria in the age of less than 31 years of age group. The mean age of microalbuminuria group was 48.2 ± 8.72 years in comparison to 47.6 ± 11.86 years in the non microalbuminuria group which was statistically significant ($P < 0.01$). Previous studies did not showed any statistical correlation between age of the patient and microalbuminuria positivity among patients with RA. There was no significant difference in the prevalence of microalbuminuria between male and females.

The duration of the disease from diagnosis showed no statistically significant difference of MAU in those with less than 4 years of disease duration. But in those with four or more year duration the MAU was significantly higher than those with 4 years of disease. Previous studies conducted by L.M Pedersen et al (1995) and Saito M et al (1997) showed that prevalence of microalbuminuria was significantly higher in those having disease duration of more than 4 and 4.5 years respectively.

The present study showed a significant correlation between tender and swollen joint count and positivity of microalbuminuria. Patients presented with 16-20 tender and swollen joint count was associated with a prevalence of MAU of about 100% (P value <0.001) for both tender and

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swollen joint count which were very highly significant. But in other studies no correlation was observed between the joint count (tender and swollen joint) and the prevalence of microalbuminuria.

This was an exception in our study.

The ESR was significantly elevated in patients with microalbuminuria. The mean ESR level in MAU positive group was 86.25 ± 34.3 mm AEFH, which was statistically significant compared to non-microalbuminuria group 52.5 ± 24.05 . Similar study done by H. Nordin et al showed a mean ESR value of 81.5 ± 23.7 mm AEFH in the MAU group compared to 46.8 ± 22.8 mm AEFH in non-MAU group. As ESR value correlated well with the incidence of microalbuminuria, hence can be used as an index to measure the disease activity of RA.

The CRP level statistically correlates with MAU positivity in our study. The maximum numbers of MAU positive (100%) were found to have a CRP value between 16-20 mg/L. The mean CRP value in the microalbuminuria positive patients was 16.25 ± 6.28 mg/l compared to 3.0 ± 2.17 mg/l in non microalbuminuria group. The patient having maximum CRP value (mg/L) also had a higher disease activity score and higher prevalence of microalbuminuria. Therefore like ESR, CRP which is an acute phase reactant can also be used to measure the disease activity in RA patients.

In our study the positivity rate of MAU increases with the increase in the disease activity scores (DAS). The positivity of MAU between patients with mild ($DAS \leq 2.4$) and moderate disease ($DAS > 2.4 \leq 3.7$) was not statistically significant whereas the difference between patients with mild ($DAS < 2.4$) and severe ($DAS > 3.7$) and between those with moderate ($DAS > 2.4 \leq 3.7$) and severe disease activity was statistically significant ($P < 0.001$).

The mean microalbuminuria concentration between patients with mild and moderate disease activity was also not statistically significant but the difference between patients with mild and severe and between those with moderate and severe disease activity was statistically significant ($P < 0.001$).

88.8% of patient having microalbuminuria were on combination chemotherapy where 33% patients were only on NSAIDs. The positivity rate of microalbuminuria for those taking Methotrexate (MTX) and Hydroxy Chloroquine (HCQS) was low i.e 14.8% and 12.5 % respectively. Similar study by Nordin et al found a different result with high prevalence of microalbuminuria with the use of gold and penicillamine. G.Bhatt et al had found a good correlation between of microalbuminuria and use of combination chemotherapeutic agents.

CONCLUSION: Microalbuminuria and subclinical renal dysfunction are frequent in rheumatoid arthritis patients, particularly in those with a longer standing disease and with severe disease activity. Treatment with combination chemotherapy and NSAIDs seems to increase the risk. Urinary albumin excretion was found to be significantly correlated with ESR and CRP and therefore, they can both be used as an index to measure disease activity in patients with rheumatoid arthritis.

Our results suggest that microalbuminuria is a sensitive indicator of increased renal vascular permeability in RA patient. Urinary albumin measured by immunological method is a simple and sensitive test to detect subclinical renal dysfunction. Hence it should be used as routine test to detect renal involvement in its most initial phase in order to devise the most appropriate treatment.

LIMITATIONS OF THE STUDY: The chief limitation of our study was the small sample size. Therefore various result yielded by the present study would have been more significant if a large sample had been included.

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Secondly, although the prevalence of microalbuminuria was significantly higher in those patients who were receiving combination of drugs, this group of patients also had higher mean duration of disease and higher disease activity and hence we were not able to quantify the individual contribution of disease activity or nephrotoxic action of drugs in urinary albumin excretion.

Lastly an essential component of the study i.e the laboratory detection of microalbumin by latex immunoassay method was not performed blind. Had it been done, it could become the strength of the study.

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