ORIGINAL RESEARCH PAPER

General Medicine

A COMPARATIVE STUDY OF SUBCLINICAL RENAL DYSFUNCTION USING MICROALBUMINURIA IN RHEUMATOID ARTHRITIS PATIENTS

KEY WORDS: C- reactive protein, Erythrocyte sedimentation rate, Rheumatoid arthritis, Urine microalbuminuria, Constitutional symptoms.

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ABSTRACT

Background: In rheumatoid arthritis patients, subclinical renal dysfunction and microalbuminuria are common, especially in those with long standing disease and with severe disease activity. Further, it is the commonest form of chronic inflammatory arthritis and most often results in damage to joints, physical disability, morbidity, and mortality. Despite the high level of interest in microalbuminuria detection and its prognostic consequences, the determinants of increased urine albumin excretion have not been well investigated. This study was done to assess the subclinical renal involvement in Rheumatoid Arthritis (RA) patients. This study was designed to study and evaluate the subclinical renal dysfunction using microalbuminuria in Rheumatoid Arthritis patients and also to find its correlation with activity of disease as indicated by RA factor and DAS score, with inflammatory markers like ESR, CRP and with the total number of Tender and Swollen joint count.

Methods: This Observational Comparative study was undertaken on 150 patients (both Male & Female); 75 Subjects of the Case group were selected from patients attending Emergency/OPD or those who were admitted (IPD) seeking medical attention at SAIMS Hospital, Indore, M.P and diagnosed with RA by NEW 2010 ACR-EULAR criteria for RA while the 75 Subjects of the Control Group were selected by matching age and sex to the subjects of Case group.

Results: The mean age of Case group was 48.440 (10.483) and that of Control group was 48.333 (11.180), of them 73.3% were females and 26.7% were males in the Case group while 70.7% were females and 29.3% were males in the Control group. Of them, MA was found in 22 patients (29.3%) in Case group. In MA positive group, mean ESR was 37.864 ±13.970, mean CRP was 1.809 ±1.000, mean DAS Score was 5.978 ±0.727, mean TJC was 9.864 ±4.411, mean SJC was 14.727±5.073 and mean RA Factor was 265.091 ±281.444 as compared to 23.208 ±9.568, 1.077 ±0.754, 4.975 ± 0.605, 6.660 ±3.088, 10.453 ±3.755 and 99.642±156.851, respectively in MA negative group ($p < 0.05$ in all cases). Microalbuminuria was significantly correlated with ESR, CRP, TJC, SJC, RA factor and Constitutional symptoms. (p value <0.05).

Conclusions: Presence of microalbuminuria indicates severe disease activity and long-standing rheumatoid arthritis. Microalbuminuria was found to be significantly correlated with disease activity in rheumatoid arthritis as assessed by ESR, CRP, TJC, SJC, RA Factor and Constitutional symptoms.

INTRODUCTION

Rheumatoid arthritis (RA) is the commonest type of chronic autoimmune inflammatory disease of connective tissues with an unknown aetiology and is characterized by symmetric, peripheral polyarthritis which often results in damage to joints, physical disability, morbidity, and mortality[1]. It is typically characterized by joints which are warm, swollen, and painful. Most commonly, the hands and wrists are affected, with the same joints involved bilaterally i.e., on both sides of the body[2]. Although Rheumatoid Arthritis is principally a disease of joints, it also presents with a wide variety of extra-articular manifestations too involving cardiac, pulmonary, haematological, ocular and neurological systems. The most common systemic manifestations include subcutaneous nodules (rheumatoid nodules), anaemia, sicca symptoms e.g., dry eyes and pulmonary manifestations e.g., Interstitial lung disease, etc[1].

Globally, Prevalence of Rheumatoid arthritis is estimated to be between 0.3 to 1.5% using different types of classification criteria in the general population. According to the recent data in India, the prevalence was estimated to be around 0.65–0.75%. Overall, there is a 3:1 preponderance in females, but this excess is higher in younger people and the age-related incidence is insignificant or approximately equal in elder population with the peak age of onset raised to 50 years or more[3].

Rheumatoid arthritis features a progressive course with exacerbations and remissions being part of its history naturally. Its onset could be at any age, although it usually starts in the fourth decade of life. Subclinical renal dysfunction in the form of microalbuminuria is scarcely seen in patients with rheumatoid arthritis specifically in patients with long standing disease and with severe disease activity. Furthermore, there is a high chance of renal impairment with evident reduced glomerular filtration and tubular function and renal disease due to impairment is presumed to be a frequent reason of death in Ra[2].

Microalbuminuria also referred as Dipstick negative albuminuria is a relevant and sensitive screening tool used worldwide as an early maker of glomerular injury and widespread vascular damage as it detects early renal involvement, as compared to Dipstick urinalysis which although is a valuable screening tool for detecting and identifying urinary abnormalities like proteinuria, hematuria, leukocyturia and urinary specific gravity among other things, however fails in detecting early renal changes as it might be heralded by proteinuria ranging from 20-200mg/l (microalbuminuria)[4]. It can detect small quantities of small quantities of albumin the urine long before one obtains a positive urine test for protein using the albustix[5,6]. Microalbuminuria is defined as urinary albumin excretion between 30 and 300 mg/24 hour for timed 24 hours urine collections and between 20 and 200 mg/L for random samples.[7]

Various anecdotal studies[8-11] have shown that microal buminuria is associated with higher risk for renal and cardiovascular mortality and morbidity in patients with diabetes mellitus, hypertension, acute myocardial infarction

and elderly patients but the significance of microalbuminuria in rheumatoid arthritis (RA) and its correlation with activity of the disease is not well researched. In the rheumatoid arthritis CRP and ESR are nearly always elevated and reflect the disease activity. It is suggested that microalbuminuria and subclinical renal damage are frequently seen in rheumatoid arthritis [8, 9]. In most of the patients having microalbuminuria in RA, renal involvement is reversible, and the chances of developing end stage renal disease is scarce if timely intervention done.

In representation of same, the study was designed to study and evaluate the subclinical renal dysfunction using microalbuminuria in Rheumatoid Arthritis patients and also to find its correlation with activity of disease as indicated by RA factor and DAS score, with inflammatory markers like ESR, CRP and with the total number of Tender and Swollen joint count.

MATERIAL & METHODS

This Observational Comparative study was undertaken in the Department of General Medicine at Sri Aurobindo Medical College & PG Institute, Indore (MP) after valid approval of ethics committee of the institution between November 2019 to June 2021 on 150 patients (both Male & Female); 75 Subjects of the Case group were selected from patients attending Emergency/OPD or those who were admitted (IPD) seeking medical attention at SAIMS Hospital, Indore, M.P and diagnosed with RA by NEW 2010 ACR-EULAR criteria for RA while the 75 Subjects of the Control Group were selected by matching age and sex to the subjects of Case group.

INCLUSION CRITERIA: For Case Group: All patients aged >18 years satisfying the NEW 2010 ACR-EULAR criteria for RA were included in the study. For Control Group: Age and sex matched controls were taken who were not diagnosed with RA and also fulfilled the exclusion criteria. Patients who gave consent for the study were included in the study.

EXCLUSION CRITERIA: Patients with Cardiovascular Disease like Hypertension, Myocardial Infarction & congestive cardiac failure, Renal Dysfunction, Diabetes Mellitus and Urinary Tract Infection were excluded from the study. Pregnant patients and Patients confined to bed for more than 2 weeks were also excluded. Lastly, Patients who did not give consent for the study were excluded.

METHOD:

After taking pre-Informed written consent from the patient, a prestructured proforma was used to collect the desired baseline data. Detailed clinical examination was done and biochemical tests were done on all patients as per the protocol. A detailed history was taken from all the patients and age, sex, duration of Rheumatoid Arthritis (RA), presence of constitutional symptoms, list of joints which were tender/swollen, past history of medications, presence of any other systemic disease and presence of extra- articular manifestations of RA were recorded.

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. Calculation of Disease activity score (DAS28) was done for all of them by means of DAS28 calculator for ESR.

Venous blood sample were obtained for Routine Investigations like CBC done by automated analysis method in Beckam coulter machine, Fasting Blood Sugar, Post Prandial Blood Sugar, Blood Urea & Serum Creatinine done by Vitros-5.1/FS machine, Erythrocyte sedimentation rate (ESR) was obtained by Wintrobe method (ESR), C-reactive protein (CRP) using ELISA technique and Rheumatoid factor (IgG) was measured by quantitative turbitometer. Urine Samples for Routine and microscopy were taken. Urine for Microalbumin- Dipstick (Immunoprecipitation tests) Microalbumin tests were used for detection. A value between 20 to 300mg/L is considered positive. Chest Xray was also done.

Activity of Disease measured by DAS-28 score (Disease Activity Scale Score): The DAS28 (Disease activity Score 28) is a system developed and validated by the EULAR (European League against Rheumatism) to measure the progress and improvement of Rheumatoid Arthritis. DAS 28 is often used in clinical trial for development of RA. It is assessed by patient on Visual Analog Scale (VAS). 28 stands for the number of different joints involved and are included in the measurement: Proximal Interphalangeal joints (10 Joints), Metacarpophalangeal joints (10), Wrists (2), Elbows (2), Shoulders (2), Knees (2). Both the no. of swollen and tender joints was counted. In addition, the ESR rate was also measured. Also, subjective assessment of disease activity on Visual Analogue Scale between 0 to 100 by the patients, where 0 is "no disease activity" and 100 is "highest disease activity possible" was also done.

DAS28 = 0.56 x $\sqrt{}$ (28TJC) + 0.28 x $\sqrt{}$ (28SJC) +0.70 x Ln (ESR) + 0.014 x VAS where, (TJC-Total tender joints SJC-Total swollen joints ESR-Erythrocyte Sedimentation Rate in mm/hr VAS/GH-Scale corresponding to their general health or global disease activity)

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 >5.110

STATISTICAL METHODS

The data was coded and entered in Microsoft excel 2010 (Microsoft corp.), analyzed using excel 2010 and SPSS 20.0 for Windows (SPSS inc). Prevalence of an outcome variable along with 95% confidence limits was calculated. A descriptive analysis of the population was carried out. The categorical or dichotomous variables were expressed as absolute values and percentages, and were compared with Pearson test. The continuous variables with a normal distribution were described as the mean (+/-SD). Variables were compared using Student T test/ANOVA test and those which will not present a Gaussian distribution were compared with the Mann-Whitney U test. The correlation between two quantitative variables was carried out by using Karl Pearson's/ Spearmen's coefficient of correlation. Association between the variables was determined by Chi Square test. A P value less than .05 was considered Statistically Significant whereas a p value > 0.05 will be taken as non-significant difference.

RESULTS

In this study, the mean age of the population was 48.440±10.483 years for Case Group & 48.333±11.180 for Control group. Among the participants, there were 55 females (73.3%) and 20 males (26.7%) in the Case group while there were 53 females (70.7%) and 22 males (29.3%) in the Control group, with a female to male ratio of 2.75:1. Maximum no. of 22 patients (29.3%) were in 36-45 years age group followed by 15 (20%), 11 (14.7%) & 5 (6.7%) patients in 46-55, 56-65, 26-35 & 66-75 years age group respectively (Table 1).

Of them, MA was found positive in 22 patients (29.3%) in Case group with 10 patients (45.5%) having symptoms > 10 years followed by 9 (40.9%) for 6-10 years and least 3 (13.6%) for <

5 years duration. While out of 53 patients having negative microalbuminuria in Case group, 41 patients (77.4%) were having symptoms for < 5 years of duration while least 2 patients (3.8%) had symptoms for 10 years.

In MA positive group, mean ESR was 37.864 ±13.970 which was significantly higher than that of MA negative group i.e.,23.208 ±9.568. Further, in MA positive group, mean CRP was 1.809 ±1.000, mean DAS Score was 5.978 ±0.727, mean TJC was 9.864 ±4.411, mean SJC was 14.727±5.073 and mean RA Factor was 265.091 ±281.444. A strong positive and statistically significant correlation (P<0.05) was found between microalbuminuria and ESR, CRP, TJC, SJC, RA factor, Constitutional symptoms, morning stiffness, weight loss, malaise status and Extraarticular manifestations. Fever had insignificant correlation with microalbuminuria. (Table 2)

Statistically significant correlation (P<0.05) was found between Microalbuminuria & DAS Score grades. Patients with MA positive status (22) showed higher percentage 77.3% (17) for high disease activity as compared to 22.7% (5) who had moderate disease activity. Whereas, in MA negative group, patients showed higher percentage for moderate disease activity i.e., 69.8% (37) followed by 30.2% (16) of patients for high disease activity. (Table 3)

A strong positive and statistically significant correlation (P<0.05) was found between microalbuminuria and RA Factor grades and status. Patients having microalbumin positive status showed highest percentage i.e., 86% (19) for high positive factor RA grade while only 4.5% (1) showed negative RA factor grades. Whereas, in MA negative group, 41.5% (22) patients showed highest percentage for high positive RA factor grade while 26.4% (14) showed Negative RA factor grades. (Table 3)

An overall incidence of 72% was reported for Constitutional symptoms with 54 cases out of 75 cases of RA having same. Out of 22 MA positive cases, 19 cases (86.4%) presented with Constitutional symptoms and remaining 3 (13.6%) had none. Whereas, for MA negative cases, 35 cases (66%) presented with Constitutional symptoms while 18 cases (34%) had none. Microalbumin positivity in RA was strongly associated with Constitutional symptoms in our study. (Table 4, Chart 2)

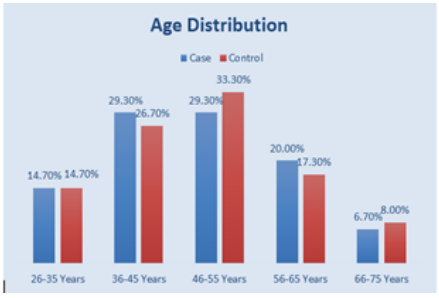

Chart 1: Association between Age Group and Study Groups

Table 1: Baseline characteristics of the Case and Control group

Study parameters	Case Group (N=75)	Control Group (N=75)	P Value
Age groups			
· **26-35 years**	11 (14.7%)	11 (14.7%)	
· **36-45 years**	22 (29.3%)	20 (26.7%)	
· **46-55 years**	22 (29.3%)	25 (33.3%)	
· **56-65 years**	15 (20%)	13 (17.3%)	
· **66-75 years**	5 (6.7%)	6 (8%)	
Age in years, Mean ± SD	48.440±10.483	48.333±11.180	**0.971* (Significant)**
Sex			**0.716 (Non-Significant)**
· **Male**	20 (26.7%)	22 (29.3%)	
· **Female**	55 (73.3%)	53 (70.7%)	
Microalbumin status			
· **Positive**	22 (29.3%)	4 (5.3%)	
· **Negative**	53 (70.7%)	71 (94.7%)	
Mean ± SD	32.389±38.210	12.099±5.553	**0.000*(Significant)**
Duration of Symptoms (years)	MA Positive	MA Negative	
5 Years	3(13.6%)	41(77.4%)	
6-10 Years	9(40.9%)	10 (18.9%)	
≥10 Years	10(45.5%)	2 (3.8%)	
			0.000*(Significant)

Table 2: Association of various variables with Microalbuminuria

Variables	MICROALBUMIN	N	Mean ± SD	T test	DF	P value	Results
ESR	Positive	22	37.864 ± 13.970	5.246	73	**0.000***	**Significant**
	Negative	53	23.208 ± 9.568				
CRP	Positive	22	1.809 ± 1.000	3.468	73	**0.001***	**Significant**
	Negative	53	1.077 ± 0.754				
DAS SCORE	Positive	22	5.978 ± 0.727	6.157	73	**0.000***	**Significant**
	Negative	53	4.975 ± 0.605				
TJC	Positive	22	9.864 ± 4.411	3.588	73	**0.001***	**Significant**
	Negative	53	6.660 ± 3.088				
SJC	Positive	22	14.727 ± 5.073	4.035	73	**0.000***	**Significant**
	Negative	53	10.453 ± 3.755				
RA Factor	Positive	22	265.091 ± 281.444	3.249	73	**0.002***	**Significant**
	Negative	53	99.642 ± 156.851				

Table 3: Association between Microalbumin Status and DAS Score grades & RA Factor

DAS		MICROALBUMIN		Total
		Positive	Negative	
Moderate Disease Activity		5 (22.7%)	37(69.8%)	42 (56%)
High Disease Activity		17 (77.3%)	16 (30.2%)	33 (44%)
Pearson Chi-Square	Value	Df	P Value	Result
	13.988a	1	0.000	Significant
RA Factor		**MICROALBUMIN**		**Total**
		Positive	**Negative**	
Negative		1 (4.5%)	14 (26.4%)	15 (20%)
Low Positive		2 (9.1%)	17 (32.1%)	19 (25.3%)
High Positive		19 (86.4%)	22 (41.5%)	41 (54.7%)
Pearson Chi-Square	Value	Df	P Value	Result
	12.682b	2	0.002	Significant

Table 4: Association between Microalbumin Status and Constitutional symptom

Constitutional Symptoms	MICROALBUMIN		Total
	Positive	Negative	
Absent	3 (13.6%)	18 (34%)	21 (28%)
Present	19 (86.4%)	35 (66%)	54 (72%)

Pearson Chi-Square	Value 3.186a	Df 1	P Value 0.074	Result Non-Significant
Morning Stiffness		**MICROALBUMIN**		**Total**
		Positive	**Negative**	
Absent		4 (4.5%)	23 (26.4%)	27 (36%)
Present		18 (81.8%)	30 (56.6%)	48 (64%)
Pearson Chi-Square	Value **4.290a**	Df **1**	P Value **0.038**	Result **Significant**
Weight loss		**MICROALBUMIN**		**Total**
		Positive	**Negative**	
Absent		14 (63.6%)	48 (90.6%)	62 (82.7%)
Present		8 (36.4%)	5 (9.4%)	13 (17.3%)
Pearson Chi-Square	Value **7.868a**	Df **1**	P Value **0.005**	Result **Significant**
Malaise		**MICROALBUMIN**		**Total**
		Positive	**Negative**	
Absent		6 (27.3%)	28 (52.8%)	34 (45.3%)
Present		16 (72.7%)	25 (47.2%)	41 (54.7%)
Pearson Chi-Square	Value **4.098a**	Df **1**	P Value **0.043**	Result **Significant**
Fever		**MICROALBUMIN**		**Total**
		Positive	**Negative**	
Absent		19 (86.4%)	44 (83.0%)	63 (84%)
Present		3 (13.6%)	9 (17%)	12 (16%)
Pearson Chi-Square	Value **.129a**	Df **1**	P Value **0.719**	Result **Non-Significant**

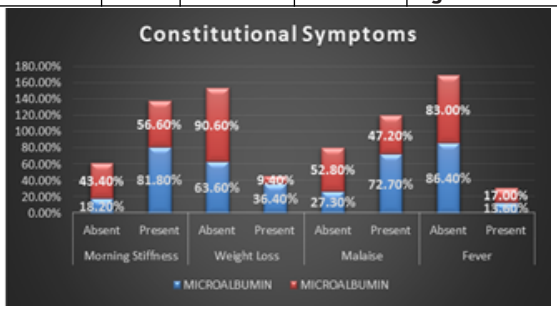

Chart 2: Proportion comparison of Association between Microalbumin Status and Constitutional symptoms

DISCUSSION

Microalbumin and subclinical damage are frequent in RA, particularly in those with long standing disease. A subclinical renal involvement may not be revealed by routine laboratory tests such as serum creatinine. The results of the present study confirms the occurrence of pathological albuminuria in several RA patients without any history suggestive of renal dysfunction, diabetes or hypertension. However, the long term renal prognosis in patients with microalbuminuria in RA, the problem is reversible and rarely develops to end stage renal failure provided timely interventions. Microalbuminuria is a sensitive predictor of renal dysfunction in patients of RA. Its measurement may serve as a useful tool for the management of patients with Ra but without clinical neuropathy.

A higher prevalence of RA was found in the fourth decade with 29.3% patients in both 36-45 and 46-55 age groups. The results found in our study were similar to the findings of study done by Akil M et al[9] while in contrast with findings of studies including Rai et al[10] and Pederson et al[11] who observed a higher incidence of same (45%) in patients of 25-40 age group.

Maximum no. of patients i.e., 73.3% (55) in our study were females whiles males comprised only 26.7% (20) out of 75 patients with RA. Male to female ratio was 1:2.75 which was similar to findings of Turesson C et al[12] who reported a ration of 1:2.71.

The prevalence of microalbuminuria in rheumatoid arthritis was found to be 29.3% i.e., 22 out of 75 cases in RA patients while in Control Group it was 5.33% in our study. This was in concordance with the findings obtained in other studies including Pederson L M et al [11]& Bhatt et al[13]. According to Pederson L M et al[11] the prevalence of microalbuminuria in Rheumatoid Arthritis was 27.7%. Bhatt et al[13] observed the prevalence of microalbuminuria to be 30%. In the study done by Monica Verma et al[14] the relative occurrence of microalbuminuria in rheumatoid arthritis patients was 26%. Sihvonen et al[15] saw that microalbuminuria was present in 34 out of 600 rheumatoid arthritis patients.

The reports in our study confirms the presence of MA in many RA patients without a past history of renal dysfunction, hypertension, or diabetes mellitus. These findings are found to be consistent with the previous reports concerning Subclinical renal dysfunction in RA.

In our study, it was found that there was strong positive correlation between microalbuminuria and ESR. Results in our study showed that MA increases with increasing ESR levels. According to Monica Verma et al[14] statistically significant relationship observed between MA and ESR ($p < 0.05$). Pederson L M et al[11] observed no statistically significant association between ESR and MA in patients with rheumatoid arthritis, even though elevated ESR levels were observed among RA 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.

In the present study, significantly elevated levels of CRP were observed in patients having MA ($p < 0.05$). As elevated ESR and CRP are markers of severe disease, microalbuminuria also suggests a severe disease. Pederson L M et al[11] study also got similar results, they observed that CRP was significantly associated with urine albumin creatinine ratio (UACR). Statistically significant relationship between MA and CRP was also noted by Ganesan et al[16] and Monika Verma et al[14].

In this study, a statistically significant association was observed between RA factor and microalbuminuria ($p<0.05$). Similar results were also obtained by Ganesan et al[16] microalbuminuria was significantly associated with RA factor ($p<0.001$). These results suggest that microalbuminuria is significantly associated with disease activity in rheumatoid arthritis patients.

Microalbuminuria was found to statistically significant associated ($p<0.05$) with markers of disease activity i.e., DAS28 Score, RA factor, ESR, CRP, No. of tender joint count and no. of swollen joint count. A strong association was also observed with the presence of Constitutional symptoms and Extraarticular manifestations. Amongst the constitutional symptoms, Morning stiffness, weight loss and malaise showed a significant correlation ($p<0.05$) with Microalbuminuria positivity while fever had insignificant correlation.

CONCLUSION

Microalbuminuria is seen frequently in patients with rheumatoid arthritis about one third of the patients having rheumatoid arthritis were seen to have microalbuminuria. Presence of Microalbuminuria indicates severe disease activity and long-standing rheumatoid arthritis. Microalbuminuria was found to be significantly correlated with disease activity in rheumatoid arthritis as assessed by the markers like ESR, CRP, RA factor. RA was once considered mainly a disease of synovial linings of the distal joints, the overtly systemic impact of RA on all major systems of the body is becoming more realized. The overall findings of our study points towards adopting a holistic, multifaceted, and inter professional approach towards the early suspicion, evaluation and treatment of RA. As an autoimmune disease with multisystem involvement, RA's elaborate impact

on the body can be life altering and harmful. By increasing awareness of the fundamental and unparalleled components of this disease, there is a hope that future research will be directed towards expanding treatment options and improving the experiences and wellbeing of patients with RA. In most of the patients having microalbuminuria in RA, renal involvement is reversible, and the chances of developing end stage renal disease is scarce if timely intervention done.

Limitations

The major part of the study was undertaken in the Covid-19 pandemic era. Covid -19 infection itself presents had a multisystem involvement. Other than this most of the patients were under medication prophylactically or therapeutically like steroids, multivitamins, analgesic, antipyretics, ayurvedic and homeopathic medications, etc, some of which could have impact on disease activity.

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