RISK OF SUBCLINICAL ATHEROSCLEROSIS IN PATIENTS WITH RHEUMATOID ARTHRITIS IN INDIA

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ABSTRACT: OBJECTIVE: Patient with rheumatoid arthritis (RA) has high cardiovascular morbidity and mortality as compared to the general population. Carotid intima media thickness (IMT) as measured by ultrasound is a validated surrogate marker of atherosclerosis. We studied the prevalence of subclinical atherosclerosis in Indian patients with RA. **METHODS:** Common carotid IMT (CCA IMT) was measured at the level of carotid bifurcation in 64 RA patient and 48 age and sex matched controls. Values of mean CCA IMT above mean $\pm$ 2 SD of the control group were defined as abnormal IMT. Variables of disease activity and severity were measured in RA patients. Patients and controls with known traditional cardiovascular risk factors were excluded from the study. Student-t test and chi-square test for proportion were used for statistical analysis. A logistic regression analysis was done to find out independent predictors of abnormal IMT. **RESULT:** Twenty-four RA patient (37.5%) and four controls (6.25%) had abnormal IMT values. RA patient had significantly increased mean CCA IMT (0.648 $\pm$ 0.142 mm) as compared to controls (0.316 $\pm$ 0.003 mm; P<0.0001). Age $\geq$ 46 years, duration of disease $\geq$ 6 years, and tender joint count $\geq$ 4 predicted increased risk of having abnormal CCA IMT in a logistic regression analysis. **CONCLUSION:** Nearly more than one third of RA patients in our study had subclinical atherosclerosis. Age, tender joint count and duration of disease were independent predictors of abnormal CCA IMT.

KEYWORDS: Rheumatoid arthritis. Atherosclerosis.

INTRODUCTION: Rheumatoid arthritis (RA) patients have a shortened life span,¹⁻³ in comparison to patients with non-rheumatoid arthritis, cardiovascular disease is the leading cause of mortality in patient with RA, with a relative risk of about 2 compared with age matched controls.⁴ Inflammation mediated vascular endothelial dysfunction leading to development of atherosclerosis is thought to be the major contributory factor for excess cardiovascular morbidity and mortality in RA.⁵ Increased carotid intima media thickness of the common carotid arteries (CCA IMT) as measured by ultrasound is an established indicator of atherosclerosis.⁶

Although there are several reports of increased prevalence of subclinical atherosclerosis in RA as assessed by carotid ultrasound from other countries.⁷⁻¹⁰ not much data is available from our country. In India the current prevalence of coronary artery disease (CAD) is nearly 10 times higher compared to 40 years ago.¹¹ and CAD in Indians occur prematurely.¹² Thus, we undertook this study to define the prevalence of subclinical atherosclerosis by carotid ultrasound in patients with RA attending our tertiary care hospital center.

MATERIALS AND METHODS:

Patients and controls: Sixty four patients with RA (American College of Rheumatology criteria, 1987).¹³ seen at the department of Internal Medicine between May 2012 and January 2015 were

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included in the study. Forty eight unrelated age and sex matched healthy individuals were recruited from the hospital. Informed consent was obtained. Patients and controls having known risk factor(s) for atherosclerosis were excluded. These included patients with diabetes mellitus as diagnosed according to World Health Organization criteria,¹⁴ with history of use of anti-diabetic medications, hypertension as defined by blood pressure >140/90mmHg or history of use of antihypertensive medication, history of ischemic heart disease or cerebrovascular events, past or present smokers, use of high dose of steroids (>10mg/day) in past 3 years, renal insufficiency, or atherosclerotic peripheral vascular disease.

Patient assessment included duration of disease, tender joint count (TJC), swollen joint count (SJC), joint deformities, extra-articular features, rheumatoid factor (RF) and disease modifying anti-rheumatic drug (DMARD) use. A composite disease activity score (DAS28) was calculated using 3 variables, SJC, TJC and Westergren erythrocyte sedimentation rate.¹⁵

Carotid ultrasound was performed using high resolution B-mode ultrasound (Philips HD 11) with a 10MHz linear transducer by a single investigator (RPS) who was blinded to the clinical information about the subject being evaluated. Measurement of IMT was assessed in the right and left common carotid artery at the level of carotid bifurcation.⁷ in the posterior wall, and the means of both values were calculated. All measurements were made manually on digitized still images that were obtained during ultrasound scanning. They were calculated as the average of measurement during 3 cardiac cycles at end diastole. An individual IMT value more than mean $\pm$ 2 standard deviation (SD) of the control group was taken as abnormal IMT. A plaque was defined as a distinct protrusion greater than 1.50mm into the vessel lumen.

Statistical analysis. Student t test was used for continuous variables and chi-square was used for proportional analysis. A P value <0.05 was considered statistically significant. Multivariate analysis using forward logistic regression was performed to determine the best model for predicting increased carotid IMT. All statistical analysis was performed using SPSS statistical software, Version 9.

RESULTS:

Clinical characteristics of patients with RA: There were 58 women with an average age of 44.26 $\pm$ 8.53 Years. Assessment of disease activity variables is shown in Table 1. Forty- eight patients (75.00%) were RF positive, 38(59.37%) had joint deformities, 24(37.5%) had extra-articular features like subcutaneous nodules, secondary Sjogren's syndrome, or interstitial lung disease. All except 2 patients were receiving one or more DMARD; 49(76.56%) were taking methotrexate alone, while 3 were receiving it in combination with hydroxychloroquine, sulfasalazine, or leflunomide.

Patients and controls were well matched with respect to age, sex and lipid values, except cholesterol level, which was significantly higher in patient with RA (Table 2) The IMT of right, left and mean of both sides was significantly greater in patients compared to controls (figure 1). Taking the mean $\pm$ 2 SD of the control group (0.585mm) as the upper limit of normal CCA IMT, 24 RA patients (37.5%) and 4 controls (6.25%) had abnormal mean CCA IMT (p<0.001). Carotid plaque was found in 6 RA patients (9.37%) but in none of the controls.

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Variables	Score (Mean $\pm$ SD)
Tender joint count	7.09 $\pm$ 5.50
Swollen joint count	3.51 $\pm$ 2.97
DAS28*(n=48)	4.40 $\pm$ 1.32

Table 1: Disease activity variables of 64 patients with RA

DAS28; Disease Activity Score 28.

* For tender and swollen joint counts and ESR.

Variable	Patients (n=64)	Controls (n=48) P	p
Age, Yrs.	44.26 $\pm$ 8.53	42.73 $\pm$ 7.60	0.22
Female ,N	58	42	0.46
Cholesterol, mg/dl	176.54 $\pm$ 40.41	158.45 $\pm$ 32 $\pm$ 32	0.020
Triglyceride, mg/dl	119.43 $\pm$ 32.45	112.21 $\pm$ 54.76	0.39
LDL, mg/dl	112 $\pm$ 38.43	101.65 $\pm$ 21.65	0.08
HDL, mg/dl	39.05 $\pm$ 6.44	39.42 $\pm$ 5.64	0.64
VLDL, mg/dl	24.78 $\pm$ 9.16	23.56 $\pm$ 11.31	0.21

Table 2: Age, Sex age serum lipid levels in patients and controls

LDL: Low density Lipoprotein; HDL: High density lipoprotein; VLDL: Very low density lipoproteins.

Correlation with carotid IMT and clinical variables in patients: A statistically significant correlation was observed between increased IMT and age of the patients, duration of disease and tender joint count. However, there was no correlation between increased carotid IMT and swollen joint count, DAS 28, serum cholesterol, or any other lipid component (Table 3). There was no significant correlation between age of the patients and the duration of disease (Correlation coefficient =0.169, 2 tailed significance =0.178). Further, there was a significant association between the presence of joint deformity ($p < 0.05$) and increased carotid IMT, while no such association of the latter was found with sex, presence of extra-articular features, erosions, RF positivity or history of methotrexate use (Table 4)

Predictive model for increased carotid IMT in patients by logistic regression analysis: A forward logistic regression analysis was done to assess whether demographic or clinical features would predict increased carotid IMT in RA patients. Included in the analysis were all variables that had shown a statistically significant association or correlation with increased carotid IMT. Analysis showed TJC, age, and duration of disease to be independent risk factors for abnormal IMT. In a predictive model analysis, TJC ≥ 4 , age ≥ 46 years and disease duration ≥ 6 years increased the risk of having abnormal IMT by 5.64, 5.86 and 6.23 times, respectively. The overall predictive value of the model was 77.2 % (Table 5)

DISCUSSION: We found subclinical atherosclerosis as indicated by increased CCA IMT in more than one third of Indian patients with RA as compared to age and sex matched controls. Abnormal IMT correlated with age, duration of disease, TJC and joint deformity, but by logistic regression analysis

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only age, duration of disease, and TJC were significant independent predictors of subclinical atherosclerosis.

An increased carotid IMT in patients with RA in our study provides valuable confirmation to earlier reports in Korean, Japanese, British, and Spanish studies ⁷⁻¹⁰ using similar methodology.

Continuous Variable	Correlation Coefficient	P
Age at time of study (yrs.)	0.584	<0.0001
Duration of disease at time of study (yrs.)	0.675	<0.0001
Tender joint count	0.404	0.023
Swollen joint count	0.164	0.196
DAS 28	0.187	0.200
Serum cholesterol	-0.065	0.691
Serum LDL*	-0.051	0.755
Serum VLDL*	0.128	0.430
Serum HDL*	-0.262	0.116
Serum triglycerides	0.121	0.496

Table 3: Correlation between selected measures in RA Patients and Mean CCA IMT

*For definition see table 2

Reports.⁷⁻¹⁰ similar to our cohort had variable duration of disease ranging from 8 years to 15 years in 2 earlier studies.⁸⁻⁹ The younger age of the patients in this study may account for a lower mean carotid IMT in our study as compared to earlier ones, as age is an important characteristic that influences IMT.^{7,8} The IMT value of controls in our study is comparable to an earlier study where the average age was 34 years.¹⁶ Both age and duration of disease were significantly correlated with carotid IMT, which was also observed by Kumara, et al in Japanese patients.⁷ Further, Gonzales Juanatery et al.⁸ revealed that age and duration of disease was predictive for the development of carotid plaques in patients with RA in northwestern Spain. The duration of RA in their patients was much longer (15.5±8.5) as compared to our study (8.03±5.48). This may be the reason for observation of a more severe expression of subclinical atherosclerosis in the form of plaques in their study.

Categorical Variables	n	IMT (mm) mean ± SD	P
Sex Female Male	58 6	0.540±0.005 0.583±0.004	0.164
Rheumatoid Factor Positive Negative	48 16	0.556±0.003 0.512±0.002	0.465

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Deformed Joints			
Yes	38	0.601±0.002	0.015
No	26	0.521±0.001	
Extera-articular features			
Present	24	0.613±0.003	0.474
Absent	40	0.522±0.001	
Methotrexate use			
Yes	52	0.556±0.001	1.001
No	12	0.553±0.003	

Table 4: Association between clinical feature of RA patients and mean CCA IMT

Variables	OR	95% CL	P
Tender Joint Count $\geq 4^*$	5.64	1.54-23.82	0.005
Age ≥ 46 Year**	5.86	1.24-29.32	0.039
Duration of disease ≥ 6 years ***	6.23	1.30-29.20	0.032

Table 5: Best predictive model for increased CCT IMT (>0.685) in RA patients

Reference categories: * tender joint count < 4; ** Age < 46 years *** duration of disease <6 years.

Total cholesterol was increased in RA patients compared to controls, which has also been observed.¹⁷ However, a majority of studies have found low total and low HDL cholesterol levels.⁵ and higher small density LDL levels.¹⁸ in RA patients as compared to controls. In migrant Indians, raised triglycerides are associated with CAD, whereas in native Indians raised cholesterol, raised LDL cholesterol/HDL cholesterol ratio show the same association. However, low HDL cholesterol is a common lipid abnormality among all Indians.¹⁹ As there are no other studies looking at lipid abnormalities in RA from our country, the increased cholesterol levels need confirmation in larger sample size. Moreover like earlier studies, RA cholesterol levels did not correlate with increased IMT.

Logistic regression analysis revealed that TJC, age, and duration of disease are independent risk factors for abnormal IMT. Both TJC and duration of disease signify the inflammatory burden of disease. Since the pathogenic mechanism of atheroma formation is immunoinflammatory, it is not surprising that both these disease variables are associated with carotid IMT. DAS 28 was not found to be associated with carotid IMT. This does not necessarily mean an athermanous spot, but it could be an inflamed endothelial lining and thus be a rheumatoid arteriopathy. On the other hand, the correlation of age with carotid IMT in our study has been observed by previous investigator in regression analysis.^{9,10} Kumeda et al.⁷ in addition to age found duration of disease, Larsen score, and the modified HAQ to be significant independent predictors for subclinical atherosclerosis. By univariate analysis, the presence of joint deformity was a significant factor associated with carotid IMT. The presence of extra-articular features was also associated with an increased carotid IMT, but was not statistically significant.

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Our study on Indian patients with RA confirms earlier observations of subclinical atherosclerosis in RA. More importantly, it reveals subclinical atherosclerosis at a much younger age which was independently associated with duration of disease and tender joint count.

Only long-term follow-up studies can determine whether subclinical atherosclerosis increases the risk for cardiovascular events in patients with RA. Further exploration of the potential benefits of stricter control of RA disease activity on long-term atherosclerotic risk modification may open new ways to improve lifespan in patients with RA.

REFERENCES:

1. Princus T callahan LF, sale WG .severe functional decline, work disability and incre4ased mortality in seventy five rheumatoid arthritis patients' studies over nine years. *Arthritis Rheum* 1984; 27:864-72.
2. Mitchell DM, Spitz PW, Young DY Bloch DA Mcshane DJ fries JF. Survival Prognosis and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1993; 36:1045-53.
3. Wolf P, Mitechell DM, sibley JT et al. The mortality of rheumatoid arthritis *Arthritis Rhum* 1994; 37:481-94.
4. Del Rincon ID, Williams K stern MP. Freeman GL Escalante A. High incidance of cardiovascular events in rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; 44:2737-45.
5. Sattar N, MC carey DW, Cape II H, MC Innes IB .Explaining how high grade systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003; 108:2957-63.
6. Heiss G ,Sharret AR, Barnes R, Chambless LE, Szklo M, Alzola C. Carotid atherosclerosis Measured by B- mode ultrasound in populaoation; associations with cardiovascular risk factor in the ARIC study,. *am J Epidemiol* 1991; 1354:150-6.
7. Kumeda Y, Inaba M, Gota H et al. Increased thickness of the arterial intima media deterted by ultrasonography in patients with rheumatoid artritis. *Artritis Rheum* 200; 46:1489-97.
8. Gonzales Junanatory C, Llorca J, Testa A, Revuelta J, Garcia Porrua C.atherosclerotic finding in ling term treated rheumatoid arthritis patient without clinically evident atherosclerotic disease. *Medicaine* 2003; 82:407-13.
9. Alkaabi JK, Ho M, Levison R, Pullar T, Belch JFF. Rheumatoid arthritis and macro vascular disease. *Rheumatlogy oX ford* 2003; 43:292-7.
10. Park YB, Ahn CW, Choi HK et al. Atherosclerois in rheumatoid arhritis; morphologic evidence obtained by carotic ultrasoun. *arthrtis Rheum* 200; 46:1714-9.
11. Mohan V. Deepa R. Risk factors for coronary artery disease in Indians J assoc physician Inia 2004; 52:95-7.
12. Enas EA, Yusuf S, Mehta JL. Revalence of coronary artery disease in Asian Indians *AM J cardiol* 1992; 70:945-9.
13. Arnett FC, Edworthy SM, BlochDA, et al. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31:315-24.
14. World health organization study froup on diabeties mellitus. Report of a who study group geneva world health organization 1985.

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15. Prevoo MLL, van't Hof MA, kuper HH van leeuwen MA van de putte LBA van riel PLCM. Modified disease activity scores the include twenty eight joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
16. Ames PRJ, Margarita A, Sokoll KB, weston M, Brancaccio V. Premature atherosclerosis in primary anti phospholipid syndrome; preliminary data *ann rheum dis* 2005; 64:315-7.
17. Vaudo G, Marchesi S, gerli R et al. Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. *ann rheum dis* 2004; 63:31-5.
18. Camjo EH, paredes S, masana L et al. Elevated levels of small low density lipoprotein with high affinity for arterial matrix components in patients with rheumatoid arthritis; possible contribution of phospholipid A1 to this atherogenic profile *arthritis rheum* 2001; 44:2761-7.
19. McKeigue PM, Miller GJ, marmot MG. Coronary heart disease in south Asians overseas: review. *J clin epidemiol* 1989; 42:597-609.

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