Early Atherosclerosis in Rheumatoid Arthritis: A case Control Study

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ABSTRACT

BACKGROUND: Atherosclerosis remains the major cause of death and premature disability in developed countries.

OBJECTIVES: To assess the prevalence of early (accelerated) atherosclerosis in Rheumatoid Arthritis (RA) patients in the absence of traditional risk factors and influence of various other parameters on it.

METHODS: The study was carried at a tertiary care university hospital in northern India (Kashmir) in year 2008-2009. Thirty nine patients in the age group of 25- 55 years with RA fulfilling the American College of Rheumatology (ACR) Modified criteria 1987 and a purposive sample of twenty healthy volunteers that served as controls were enrolled to judge any difference in the studied parameters. Subjects with other risk factors for atherosclerosis were excluded from the study. Disease Activity Score (DAS-28) was used to measure the disease activity. B-mode ultrasonography was used to measure carotid artery intima media thickness (CIMT) in both the groups.

RESULTS: RA patients presented with elevated CIMT in the age group of 41-50 years ($p = 0.665$) whereas volunteers had such tendency in the 5th decade of life ($p = 0.550$). Duration of disease greater than 5 years also positively influenced the development of increased CIMT in the patient group ($p = 0.64$). Patients in the RA group had a higher erythrocyte sedimentation rate (ESR) and mean CIMT as compared to the controls ($p = 0.000$). RA patients had lower hemoglobin concentration when compared to age and sex matched controls. Intergroup comparison in patients with normal and increased CIMT showed that increased BMI, elevated triglyceride (TG) concentration and raised ESR influenced the development of CIMT which on binary logistic regression showed that TG ($p = 0.043$) and BMI ($p = 0.053$) had influence in progression of CIMT.

CONCLUSION: Rheumatoid Arthritis patients have definite evidence of early (accelerated) atherosclerosis due to inflammation even in this ethnic population. BMI and serum triglycerides even in normal range have noteworthy influence in acceleration of atherosclerosis in them. B-mode ultrasonography is simple, non-invasive, and one of the sensitive methods to detect earlier atherosclerotic changes in them. JMS 2012;15(2):106-10

Key words: Rheumatoid arthritis, atherosclerosis, carotid intima media thickness, B-mode ultrasonography

Atherosclerosis remains the major cause of death and premature disability in developed societies.¹ It is now considered an immuno-inflammatory process. Apart from traditional risk factors like smoking, hypertension, diabetes mellitus, dyslipidemia, several novel inflammation related risk factors are currently implicated in the pathophysiology of

atherosclerosis. Among these novel risk factors, rheumatoid arthritis (RA) has been implicated to cause accelerated atherosclerosis and increased cardiovascular morbidity and mortality.²

Atherosclerosis is emerging as an important complication of rheumatoid arthritis with coronary artery disease as major cause of mortality. Patients with RA have reduced life expectancy and high cardiovascular morbidity and mortality as compared to that in the general population.³⁻⁷ Indian population is also at increased risk of developing atherosclerotic coronary artery disease. Indian data on this

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aspect of RA is sparse and there is no such study available in this ethnic population till date. Keeping this in mind, we conducted a prospective study to assess the prevalence of atherosclerosis in RA patients in the absence of traditional risk factors and influence of various other factors on it.

Methods

The study was carried at a tertiary care university hospital in northern India (Kashmir) from 2008-2009. Thirty nine patients in the age group of 20- 54 years with RA fulfilling the American College of Rheumatology(ACR) Modified criteria 1987 were taken up for the study.⁸ Besides; twenty healthy volunteers were enrolled to judge any difference in the studied parameters.

Smokers, males with age < 20 and ≥ 45 years, females <20 and ≥ 55 years and patients having a BMI of > 30 were excluded from the study. Besides patients having a history of coronary artery disease (CAD) or stroke, a history of CAD or stroke in first degree relatives in males > 55 years and females > 65 years, diabetes mellitus, hypertension (BP $\geq 140/90$ mmHg), hyperlipidemia (fasting total cholesterol of >200 mg/dL; fasting serum triglycerides > 150 mg/dL) were also excluded from the study.¹

Formal written consent was taken from the studied subjects prior to recruitment in the study. Also the study was approved by the hospital ethical committee. A detailed history and physical examination was performed in all the subjects. Disease Activity Score-28 (DAS- 28) was used to measure the disease activity with a DAS-28 score of ≥ 3.2 -<5.1 classified as mild and a DAS-28 score of ≥ 5.1 classified as severe disease.⁹ Patient was said to have diabetes mellitus if it was diagnosed by the physician, patient was taking anti-diabetic medications or had a fasting blood sugar ≥ 126 mg% or a 2 hour post 75 gram oral glucose load ≥ 200 mg% or a random blood glucose of ≥ 200 mg%. CAD was said to be present if the patient had a history of angina or myocardial infarction or if the patient had been put on anti-ischemic medication by the physician. History of stroke or transient ischemic attack (TIA) in the patient or his or her first degree relative was determined by historical evidence and previous records.

B mode ultrasonography or color Doppler was used to measure CIMT in both the groups. A single expert radiologist conducted the test to exclude any individual bias in interpretation.

The subjects were examined in supine position in the bed. Common carotid arteries on both the sides were scanned along the three different planes in longitudinal axis and in a cross sectional axis. CIMT was measured on a longitudinal scan of the carotid artery at a point 10 mm proximal from beginning of the dilatation of the carotid bulb. This scan pattern was characterized by two echogenic lines separated by hypo-echoic and anechoic space. Outer line

corresponded to the medial-adventitial border and the inner line corresponded to the luminal-intimal border. Distance between two parallel lines represented the CIMT as the white area. Mean CIMT values ($\pm 2SD$) above the mean CIMT values of volunteers were taken as abnormal.^{9,10}

Statistical analysis: Data was described as mean $\pm$ SD and percentages. Univariate analysis was done by Student's t-test and Mann-Whitney's U test. The factors with *p* value of <0.05 on univariate analysis were subjected for multivariate analysis (Binary Logistic Regression) to evaluate best predictors in the study group. Statistical package SPSS-16.0 was used for data analysis.

Results

Age of patients ranged from 20- 50 years (37.7 ± 6.9) and in controls 21-53 years (36.1 ± 11.1). Females constituted 71.8% of cases and 40% of controls. Gender ratio of the respective two groups was 1:2.3 and 1.5:1 respectively. Duration of disease ranged from 1-20 years (mean 5.7 ± 4.1 years). 94.9% of patients were on some form of non-steroidal anti-Inflammatory drugs (NSAIDs), 48.7% on disease modifying anti-rheumatic drugs (DMARDs), 59% on steroids and 7.7% on ayurvedic medicines. Rheumatoid factor was positive in 34(87.4%) and 35(89.7%) tested positive for C - reactive protein (CRP). There was evidence of X-ray erosions in X-rays of hands in 14(35.9%). Mean CIMT was maximum in the age group of 41-50 years (*p* 0.665), but in the controls it was maximum in the age group of 51-60 years (*p*=0.55). Mean CIMT increased in patients after the age of 40 years and was higher in patients with disease duration of greater than 5 years (*p*=0.64). Gender difference was insignificant in cases (*p*=0.240) and controls (*p*=0.729).

Haemoglobin(Hb), erythrocyte sedimentation rate (ESR), mean CIMT and female gender showed statistically significant difference between study and control group (*p*<0.05) (Table 1).

Additionally, CIMT among the subjects in the study group was dichotomized into raised ($\geq 2SD$ from mean of controls) and normal (<2SD from mean of controls) groups. These two groups were then subjected to intergroup comparison. BMI, TG and ESR were found to be significantly different among the two groups.. The predicted three parameters were further evaluated by binary logistic regression that showed TG (*p*=0.043) and BMI (*p*=0.053) having statistically significant influence in progression of CIMT (Table 2).

DAS-28 scoring did not show any statistical influence on CIMT in RA patients (*p* 0.707). Rheumatoid factor (*p* =0.840), CRP status (*p*=0.540) and presence of radiological abnormalities (*p*=0.503) as well did not influence mean CIMT values. Patients taking NSAIDs, DMARDs and steroids showed no significant difference in mean CIMT in

TABLE 1. Baseline parameters in the study and control groups

	Study (n=39)	Control (n=20)	p value
Age(yrs)	37.7±6.9 (21,50)	36.1±11.1 (20, 53)	0.481
Female	28 (71.8)	0 (0.0)	0.000
NSAIDS	37 (94.9)	0 (0.0)	0.000
DMARDS	19 (48.7)	0 (0.0)	0.000
Steroids	23 (59.0)	0 (0.0)	0.000
Ayurvedic	3 (7.7)	0 (0.0)	0.000
BMI(kg/m ²)	24.6±2.5 (17.8, 28.6)	23.7±2.8 (19.0, 27.9)	0.324
Hb(g/dl)	11.1±1.8 (7.3, 15)	12.5±1.8 (9.1,15.5)	0.009
TLC(cumm)	7.7±2.6 (4.1,15.0)	6.7±1.8 (4.4,11.0)	0.112
ESR(mm/h)	41.6±18.2 (13, 92)	23.7±5.7 (13, 40)	0.000
CRP(mg/l)	35(89.7)	0(0.0)	0.000
RF(IU/ml)	34(87.2)	0(0.0)	0.000
BSF(mg/dl)	89.5±12.3 (61, 116)	91.7±17.2 (68, 146)	0.591
Urea(mg/dl)	35.0±9.0 (20, 58)	34.6±9.5 (23, 51)	0.888
Creatinine(mg/dl)	0.8±0.2 (0.4, 1.3)	0.8±0.1 (0.6, 0.9)	0.549
TG(mg/dl)	126.1±17.1 (90, 150)	126.4±13.3 (95, 144)	0.959
CHOL(mg/dl)	125.2±14.9 (98, 149)	127.3 ± 14.4 (95, 147)	0.632
Mean cIMT	0.6 ± 0.1 (0.4, 0.9)	0.5± 0.1 (0.3, 0.6)	0.000
Erosions	14 (35.9)	0 (0.0)	0.000

Note: Quantitative parameters are expressed as mean ± SD and the subsequent values separated by a comma within parenthesis represent greatest lower bound and least upper bound of the respective variable. Otherwise the numerals associated in parenthesis represent respective frequency and its percentage.

comparative analysis (Table 2). Results of multivariate analysis are shown in table 3.

TABLE 3. Results of multivariate analysis

	Score	Sig.
BMI	3.7583	0.053
ESR	2.5755	0.109
TG	4.106	0.043

Discussion

Forty percent of RA patients have extra articular manifestations of which 15% are severe.¹¹ Increasing attention is now paid to accelerated atherosclerosis in RA. Both traditional and inflammation related risk factors contribute to atherosclerosis in them. We sought evidence of atherosclerosis by B-mode carotid ultrasonography in patients of RA by measuring CIMT, which is simple, cost-effective and one of the sensitive methods although with some limitations in focal lesions. This non-invasive tool is

TABLE 2. Correlation of CIMT across respective parameters among the study group

	Raised CIMT (n=25)	Normal cIMT (n=14)	p value
Female	18 (72.0)	10 (71.4)	0.970
Duration(yrs)	5.4±4.0 (0,15)	5.1±5.7(0,20)	0.814
NSAIDS	24 (96.0)	13 (92.9)	0.674
DMARDS	12 (48.0)	7 (50.0)	0.906
Steroids	15 (60.0)	8 (57.1)	0.864
Ayurvedic	3 (12.0)	0 (0.0)	0.183
BMI(kg/m ²)	25.1±2.2 (18.7, 28.6)	23.3±2.8 (17.8, 26.7)	0.038
DAS- 28	6.6±1.2 (3.7, 8.4)	6.5±1.2 (4.1, 8.4)	0.707
Hb(g/dl)	10.8±1.6 (7.3, 14.8)	11.7±1.9 (9.2, 15.0)	0.121
TLC/μl	7.5±2.4 (4.1, 15.0)	8.2±2.9 (4.2, 14.5)	0.405
ESR(mm/h)	46.2±18.8 (13, 92)	33.2±14.3 (16, 60)	0.030
CRP(mg/l)	23 (92.0)	12 (85.7)	0.540
RF(IU/ml)	22 (88.0)	12 (85.7)	0.840
BSF(mg/dl)	88.7±10.2 (61, 109)	91.1±16.3 (61, 116)	0.603
Urea(mg/dl)	34.4±8.1 (20, 58)	36.4±11.3 (22, 55)	0.575
Creatinine(mg/dl)	0.8±0.2 (0.5, 1.3)	0.7±0.2 (0.4, 1.0)	0.153
TG(mg/dl)	130.3±11.2 (110, 150)	117.7±23.5 (90, 150)	0.044
CHOL(mg/dl)	125.0±14.4 (98, 149)	125.7±16.4 (101,148)	0.897
Erosions	8 (32.0)	6 (42.9)	0.503

Note: Quantitative parameters are expressed as mean ± SD and the subsequent values separated by a comma within parenthesis represent greatest lower bound and least upper bound of the respective variable. Otherwise the numerals associated in parenthesis represent respective frequency and its percentage.

being increasingly employed as marker of early atherosclerosis and vascular risk.² The gold standard for measurement of atherosclerosis is Magnetic Resonance Imaging, which is neither freely available nor cost effective.¹²

Mean age of our patients and females which constituted 70% was similar to study done by Mahajan *et al.*¹³ Pattern of age and gender was similar to that seen in a study done in this population previously and worldwide.^{14,15-17} Mean duration of illness in our patients was 5.7 years while it was 8.03±5.48 years in earlier studies.^{10,13-14} Sero-positive patients constituted 87.2% being similar to an earlier study, though in some studies it was around 35%. Moreover percentage of patients on various medications was similar to other studies as well.¹⁶⁻¹⁷

Patients above 40 years and duration of illness >5 years had higher CIMT which is in accordance to the studies conducted earlier.¹⁸⁻¹⁹ Gender difference did not show any significant difference in CIMT between study and control group. There was no such study available for comparison. On subgroup analysis, BMI showed significant influence on

CIMT which was in contrast to that observed by Del Rencon *et al.*⁷ Various studies have shown significant increase in CIMT in patients with high DAS.^{1,16,20-21} But in our study there was no such influence observed, which is also in accordance to the observation made by Carotti *et al.*¹⁸ probably because of score recorded in the first week. Effect of erosions on CIMT was also insignificant in contrast to study done by Kumeda *et al.*²² This could be because of smaller size of our study or use of different method of documentation.

Marker of inflammation, ESR was found to be associated with increase in CIMT although this association could not be observed in subgroup analysis and association is conflicting in various other studies as well.^{20,23-26} CRP positivity in our study had no impact on CIMT in contrast to other studies,^{16,25,27-28} reason could be that high sensitivity CRP was not measured in our sample which could have shown the true reflection. Long half life of ESR as compared to CRP could also explain our observation. Serum triglycerides even in normal ranges showed positive correlation with CIMT in our patients as was also observed by Cuomo, *et al.*²⁹ This observation needs further study. In our study, it could probably be because of steroids or DMARDs use or female preponderance in whom there is lesser burden of atherosclerotic cardiovascular disease. This observation might point to the fact that even normal levels are not protective.

Patients on NSAIDs had higher CIMT although not statistically significant (p 0.674). This has been seen in earlier studies as well implicating that this could lead to increased risk of cardiovascular disease, infarction and heart failure.³⁰⁻³¹ Kumeda, *et al* observed no difference on CIMT in patients on various medications.²² There was no effect of DMARDs in our study as compared to previous study,¹⁶ possibly we took all drugs as one category. Patients on ayurvedic medications had higher CIMT; however, no study was available for comparison.

Twenty four(60%) of our patients had significantly abnormal CIMT as compared to controls. Only one (5%) control had abnormal CIMT. The frequency of abnormal CIMT in our patient population was much higher than that observed by Grover, *et al* (33.4%),¹⁰ and Mahajan, *et al* (21%).¹³ This higher incidence could be explained by geographical variation and our patients being mostly referred with severe disease than those in the community. This could also be because of higher age at the time of enrollment and greater duration of disease; this observation needs further study in our population. Tyrrel, *et al* in his meta-analysis observed significantly increased CIMT in autoimmune disorders including rheumatoid arthritis patients.³² Similar observation of increased prevalence and higher severity of CIMT especially in bulb-ICA (Internal Carotid Artery) was made by another study as well.³³

The studies that failed to show an increase in carotid atherosclerosis in RA in past were relatively small and used

varying methods.^{22,26} One study even large enough took more men, age >60 years, having severe hypertension, diabetes mellitus (10%) and hypercholesterolemia (13%).³¹

In conclusion, rheumatoid arthritis patients have definite evidence of accelerated atherosclerosis in absence of traditional risk factors owing to inflammation. This is comparable to what is seen in other populations' globally. BMI and serum triglycerides even in normal range showed significant influence in acceleration of atherosclerosis in these patients. Various other factors like age >40 years, male gender, longer duration of disease, BMI, elevated DAS-28 score, ESR, CRP positivity and erosions showed positive correlation though not statistically significant. B-mode ultrasonography is simple, non-invasive, and one of the sensitive methods to detect earlier atherosclerotic changes in them.

Conflict of interest:

The authors declare that they have no conflicting interest, support or funding from any agency.

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