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Original Research Article

Carotid intima media thickness as a marker of subclinical atherosclerosis in rheumatoid arthritis: a case control study

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ABSTRACT

Background: Increased cardiovascular morbidity and mortality has been observed in rheumatoid arthritis (RA) because of accelerated atherosclerosis. We measured carotid intima-media thickness (CIMT) as a surrogate marker of subclinical atherosclerosis in RA in this study.
Methods: In this study 40 cases of RA and 26 matched individuals were recruited. CIMT measurements were done using B-mode ultrasound. Disease activity was assessed using DAS28, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels.
Results: Mean age of the study groups was 52.45±7.43 years (range 41-69 years). Average disease duration was 9.34±4.18 years (range 5-20 years). Thirty two (32/40, 80%) cases of RA were RF positive. ESR was significantly higher in RA cases (51.75±24.13 mm Ist hr) compared to healthy controls (17.31±9.08 mm Ist hour, p <0.001). Significantly increased CIMT was observed in cases as compared to the control group (0.68 ± 0.06 mm versus 0.63±0.07; *P* 0.002). CIMT in the cases positively correlated with age (r = 0.500; 0.001), duration of disease (r= 0.594; *P* 0.001). CIMT negatively correlated with HDL (r = -0.345; 0.029).
Conclusions: Subclinical atherosclerosis (increase CIMT) is common in RA and correlated well with disease duration. So every patient of RA should be evaluated for development for atherosclerosis.

Keywords: Atherosclerosis, Intima-media thickness, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory, auto-immune disease of unknown origin with characteristic persistent symmetric polyarthritis (synovitis) and extra articular involvement of skin, heart, lungs and eye.

Cardiovascular mortality has been found to be increased in rheumatic diseases, which is attributed to accelerated atherosclerosis.[1-3] Chronic systemic inflammation is implicated as the driving force behind accelerated atherosclerosis in rheumatic diseases.[4-5] In RA, mortality due to coronary artery disease was found to be higher than general population indicating increased risk of atherosclerosis in RA patients.[6] The relation between atherosclerosis and RA was also shown in previous studies.[7-8]

Among the various screening methods, carotid intima media thickness (CIMT) has gained wide acceptance as a marker of atherosclerosis predicting future cardiovascular events.[9-10]

Due to paucity of Indian data regarding atherosclerosis in RA, this study was designed to assess subclinical

atherosclerosis in RA patients using CIMT as a surrogate marker of atherosclerosis.

METHODS

This study was conducted for one year at rheumatology clinic in a tertiary care center in North India among 40 cases of RA (diagnosed as per 1987 revised criteria for RA) having disease duration ≥5 years.[11] Twenty six healthy individuals matched for age and sex were recruited as control from hospital staff.

Exclusion criteria for both groups were diabetes mellitus, chronic kidney disease, coronary heart disease, cerebrovascular disease, peripheral vascular disease, hypertension, dyslipidemia, thyroid disorder, family history of premature symptomatic coronary heart disease, tobacco chewing, smoking, use of lipid lowering or antihypertensive drugs.[12] Written well-informed consents were obtained from participants of both groups. This study was in accordance with the declaration of Helsinki and was approved by the institutional ethics committee.

Sample size required was 16 subjects in each group at 95% confidence and 80% power to verify the minimum difference of 0.0142±0.137 in Carotid Intima Media Thickness of RA patients and healthy controls.[13]

All RA patients (40 cases) were on methotrexate either alone (19 patients) or with sulphasalazine (2 patients)/ hydroxychloroquine (10 patients). Nine RA cases were taking 3 DMARDs (methotrexate, sulphasalazine and hydroxychloroquine).

Clinical assessment

From each participant detailed history was taken and a complete rheumatological assessment was done.

Laboratory evaluation

After overnight fasting, venous samples of the patients were collected from left antecubital vein and evaluated for glucose, creatinine, ESR, CRP, Rheumatoid Factor and lipid profile. ESR was measured using Westergren method and lipid profile by colorimetry. Rheumatoid factor (RF) and C-reactive protein (CRP) levels were estimated by turbidimetry.

Disease activity was assessed according to disease activity score (DAS28).[14]

CIMT measurements[10]

CIMT measurements of both study groups were done. All measurements were made by a single examiner who was blinded to the study. Examination was done in a quiet, cool room (20-25˚C). A high resolution B-mode ultrasonography with a 10 MHz transducer was used to make the measurements. The subject was placed in supine position with the neck extended and the chin turned contralateral to the side being examined. The distance between the leading edge of the first bright line (the lumen-intima interface) of the far wall and the leading edge of the second bright line (collagen-containing upper layer of tunica adventitia) was taken as the IMT. IMT was measured at three points on the far walls of both the left and the right common carotid arteries (CCA) 10mm proximal to the carotid bulb. The IMT of these three locations was then averaged to produce the mean IMT for each side. The mean of IMT of each side was taken as the final CIMT.

Statistical analysis

Microsoft Excel and SPSS 17.0 for windows were used for data storage and analysis. Continuous variables were expressed as mean ± standard deviation. Student's t test and Chi-Square test were used to determine statistical difference between variables. Pearson's coefficient was used to investigate the correlation between the two variables. Statistical significance was set at P value ≤0.05.

RESULTS

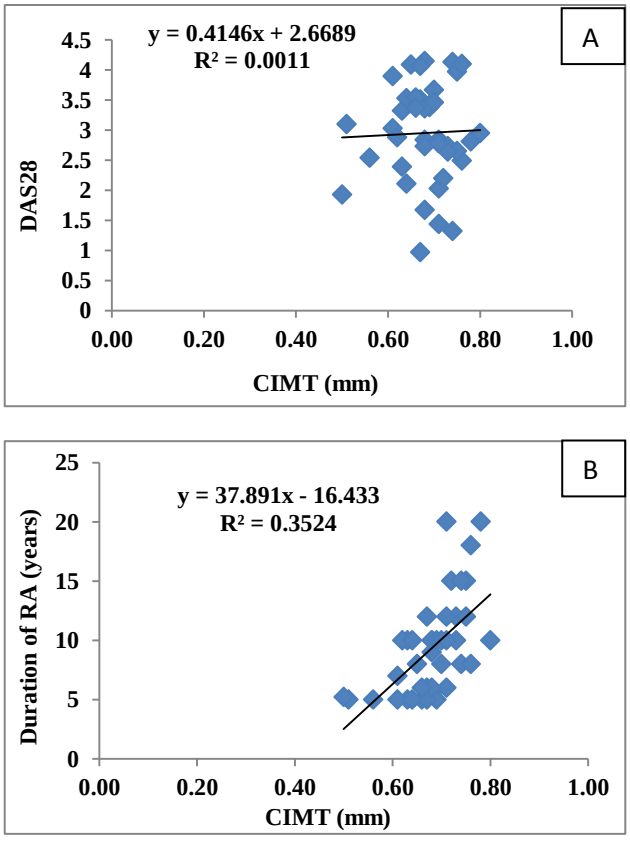

Figure 1: Correlation of Carotid intima media thickness with DAS28 (r 0.033, p>0.05); (A) and duration of RA (r 0.594 p 0.001) (B).

Mean age of the study groups was 52.45±7.43 years (range 41-69 years). Average disease duration was

9.34±4.18 years (range 5-20 years). Thirty two (32/40, 80%) cases of RA were RF positive. ESR, a marker of inflammation, was significantly higher in RA cases (51.75±24.13 mm Ist hour) compared to healthy controls (17.31±9.08 mm Ist hour, p <0.001). We observed a significantly increased CIMT in cases as compared to the control group (0.68±0.06 mm versus 0.63±0.07; *P* 0.002). Serum triglyceride was observed to be significantly lower in the cases as compared to control group (101.88 ± 36.19 mg/dl versus 127.33±37.88mg/dL; *P* 0.008). No significant difference was observed in levels of total cholesterol, low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL) in the two groups (Table 1).

Table 1: Characteristics of study subjects.

Variables	Cases of RA (n 40)	Healthy control (n 26)	P	Sig
Age (years)	52.45±7.43 (range 41-69)	50.88±7.78	>0.05	NS
Male : Female	10:30	10:16		
Disease duration (years)	9.34±4.18 (range 5-20)			
Duration of treatment (years)	6.12±2.99			
DAS 28	2.95±0.82 (range 1.32-4.15)			
RF positivity (n %)	32 (80.00)	00(00.00)		
CRP positivity (n %)	39 (97.5)	9 (34.6)	<0.05	Sig
BMI (kg/m^2)	23.50±4.08	25.1±3.27	>0.05	NS
Systolic blood pressure (mm Hg)	127.46±10.42	128.54±9.24	>0.05	NS
Diastolic blood pressure (mm Hg)	79.75±8.32	80.54±7.01	>0.05	NS
Mean arterial pressure (mm Hg)	94.33±8.24	96.15±7.06	>0.05	NS
ESR (mm Ist hr)	51.75±24.13	17.31±9.08	<0.001	Sig
CIMT (Right) (mm)	0.67±0.06	0.61±0.07	<0.001	Sig
CIMT (Left) (mm)	0.69±0.07	0.64±0.08	0.036	Sig
CIMT (mean) (mm)	0.68±0.06	0.63±0.07	0.002	Sig
Triglycerides (mg/dl)	101.88±36.19	127.33±37.88	0.008	Sig
Total cholesterol (mg/dl)	172.18±31.59	175.08±32.01	>0.05	NS
LDL (mg/dl)	102.65±23.48	108.96±25.80	>0.05	NS
HDL (mg/dl)	44.48±2.60	44.12±2.86	>0.05	NS

Table 2: Correlation of CIMT mean with various variables of RA cases.

	Correlation coefficient (r)	p	Sig
CIMT and age at the time of study	0.500	0.001	Sig
CIMT and BMI	0.178	>0.05	NS
CIMT and disease duration	0.594	0.001	Sig
CIMT and DAS 28	0.033	>0.05	NS
CIMT and SBP	0.183	>0.05	NS
CIMT and DBP	0.164	>0.05	NS
CIMT and MAP	0.134	>0.05	NS
CIMT and ESR	0.152	>0.05	NS
CIMT and triglycerides	0.125	>0.05	NS
CIMT and total cholesterol	0.120	>0.05	NS
CIMT and LDL	0.146	>0.05	NS
CIMT and HDL	-0.345	0.029	Sig

CIMT in the cases positively correlated with age (r = 0.500; 0.001), duration of disease (r = 0.594; *P* 0.001). CIMT negatively correlated with HDL (r = -0.345; 0.029). No significant correlation was observed between CIMT and BMI, DAS 28, blood pressure, ESR, triglycerides, total cholesterol and LDL levels (Table 2).

DISCUSSION

Inflammation is a common pathogenic feature in both atherosclerosis and RA.[15] CIMT is a non-invasive, easy, reliable and relatively inexpensive tool for screening of atherosclerosis.[10]

A systemic review and meta-analysis of several studies encompassing the entire spectrum of rheumatic diseases had observed a significantly increased CIMT in these patients as compared to matched healthy individuals.[16]

In our study, we also observed significantly increased CIMT in RA cases (0.68±0.06 mm) compared to healthy controls (0.63±0.07mm) (p = 0.002). Previous studies also found significantly higher CIMT in RA cases compared to controls.[17-22] Similarly Adhikari et al also

found significantly higher CIMT in RA patients (0.50±0.16 mm) than in controls (0.44±0.09 mm) (P = 0.007).[17] In other Indian studies Singh et al and Mahajan et al also reported higher CIMT in RA compared to controls.[18,19] A similar observation has also been shown by Alkabbi et al and Gonzalez et al.[20,21]

As we excluded subjects with traditional risk factors for atherosclerosis (i.e. diabetes mellitus, chronic kidney disease, coronary heart disease, cerebrovascular disease, peripheral vascular disease, hypertension, dyslipidemia, thyroid disorder, family history of premature symptomatic coronary heart disease, tobacco chewing and smoking) from this study, the finding of increased CIMT among RA cases in this study assume added significance.

Significantly high ESR and CRP positivity among RA cases compared to age/sex matched healthy controls indicates that age alone is not enough to explain the increase in CIMT in RA cases, inflammation also had some role. Previous studies also observed inflammation as a contributing factor in development of atherosclerosis besides traditional cardio-vascular risk factors.[23-25] Elevated levels of ESR and CRP were found to be associated with excess cardio-vascular mortality in RA.[22,26] In one study, RA patients receiving tumour necrosis factor (TNF)-α blockers had reduction in CIMT probably by reduction in inflammation.[28] These reports support the role of inflammation as a contributing factor in the development of atherosclerosis (CIMT). Chronic inflammation also has the ability to induce endothelial cell dysfunction, wherein there is increased expression of leukocyte adhesion and signalling molecules on their surface. These changes are brought about by a complex interplay of inflammatory cytokines such as IL-6 and TNF-α, lipid molecules, and the endothelial cells.[32]

In our study triglycerides were significantly lower in RA cases. Cholesterol and LDL were also low and HDL was high in RA cases. This paradox of a seemingly beneficial lipid profile predisposing to accelerated atherosclerosis in rheumatic diseases was also seen previously.[3,29-30] The mechanism behind it is the ability of chronic inflammation to induce changes in the structural composition of the lipid molecules, making them more atherogenic.[31]

The correlation of disease duration with CIMT, found in our study, can be explained by the fact that it is chronic systemic inflammation which is driving atherosclerosis in these patients. The same was also reported in previous studies.[17-18,20,24]

No significant correlation of CIMT and ESR or DAS 28 was found in our study. It might be due to the fact that DAS28 and ESR levels often fluctuate in chronic inflammatory diseases and their measurement at a single point only can show the inflammatory burden at that point of time and fails to reveal the inflammatory burden of the entire disease duration. The same finding was also observed in previous studies.[16,32-33]

One of the limitations of our study was that it is cross-sectional and therefore we cannot assess the effect of atherosclerosis i.e. myocardial infarction. A follow up study can provide much information about the complication of atherosclerosis. Another limitation was the effects of drugs as all patients were on methotrexate either alone or with sulphasalazine/hydroxychloroquine but we tried to correlate the disease activity scores, achieved by these drugs and CIMT.

CONCLUSION

Subclinical atherosclerosis (increase CIMT) is common in RA and correlated well with disease duration. So every patient of RA should be evaluated for development for atherosclerosis.

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Ethical approval: The study was approved by the institutional ethics committee

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