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# STUDY OF ATHEROSCLEROSIS IN RHEUMATOID ARTHRITIS USING CAROTIDINTIMAL THICKNESS AS A SURROGATE MARKER

**KEYWORDS:** Atherosclerosis, rheumatoid arthritis, carotid

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**ABSTRACT**

Patients with rheumatoid arthritis (RA) have an increased morbidity and mortality due to cardiovascular disease (CVD). Traditional cardiovascular (CV) risk factors cannot fully explain the increase but inflammation has been shown to contribute to the increased CVD among these patients. This study was done to find out the early atherosclerotic changes in rheumatoid arthritis patients using carotid intimal thickness as a surrogate marker and to compare with healthy adult subjects and to study the relationship between carotid intimal medial thickness to C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and disease activity score in rheumatoid arthritis patients which are the most commonly assessed markers of inflammatory response in patients with rheumatoid arthritis.

**Methodology:** 50 patients who were identified to have rheumatoid arthritis in accordance with American college of rheumatology were compared with age and sex matched controls. The present study involved a total of 50 patients according to the inclusion and exclusion criteria. Patients with rheumatoid arthritis who satisfied the American college of rheumatology criteria1 were included in the study as cases. Patients with diabetes mellitus, hypertension, chronic kidney disease, smoking and alcoholism, dyslipidemia were excluded from the study. Investigations done in the study included complete hemogram, FBS,PPBS, ESR, Blood urea, Serum Creatinine , Urine routine, CRP, Lipid Profile, Ultrasound Doppler of the carotids for measurement of CIMT, RA factor, Anti CCP antibody, X rays. IMT of the CCA was measured 1cm proximal to the bulb, the IMT of the ICA was measured 1cm distal to the bifurcation of the CCA, the IMT of ECA was measured 1cm distal to the bifurcation of the CCA.

To provide a measure of RA disease activity that is more valid than the various existing disease activity variables individually, the disease activity score (DAS) is used.2,3 The DAS is based on an external standard of RA disease activity, and combines information from swollen joints, tender joints, the acute phase response and general health into one continuous measure of rheumatoid inflammation. The DAS28 is an index similar to the original DAS, consisting of a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), ESR, and an optional general health assessment on a visual analogue scale (range 0-10). Because of the use of reduced and non-graded joint counts, the DAS28 is easier to complete than the DAS. The DAS28 has a continuous scale ranging from 0 to 9.4, and usually shows a Gaussian distribution in RA populations. DAS and DAS28 values cannot be directly compared, but a formula to transform DAS28 into DAS values is available.4 The level of disease activity can be interpreted as low (DAS28 <3.2), moderate (3.2< DAS28 <5.1), or high (DAS28 > 5.1).4 The statistical methods included descriptive procedure, contingency coefficient test, independent samples t test, one way Anova, Scheffe's Post hoc test. All the statistical calculations were done through SPSS for windows (v 16.0).

## RESULTS

The present study included 50 patients with rheumatoid arthritis satisfying ARA criteria and were compared for CIMT with age matched and sex matched controls during study period admitted to JSS Hospital fulfilling the inclusion and exclusion criteria.

### 1.AGE DISTRIBUTION OF CASES AND CONTROLS

| | | | GROUPS | | Total |
|---|---|---|---|---|---|
| | | | Case | Ctrl | |
| AGES | <35 | Count | 3 | 3 | 6 |
| | | % of GROUPS | 6.0% | 6.0% | 6.0% |
| | 36-45 | Count | 19 | 19 | 38 |
| | | % of GROUPS | 38.0% | 38.0% | 38.0% |
| | 46-55 | Count | 17 | 13 | 30 |
| | | % of GROUPS | 34.0% | 26.0% | 30.0% |
| | 56-65 | Count | 6 | 8 | 14 |
| | | % of GROUPS | 12.0% | 16.0% | 14.0% |
| | 66-75 | Count | 5 | 7 | 12 |
| | | % of GROUPS | 10.0% | 14.0% | 12.0% |
| Total | | Count | 50 | 50 | 100 |
| | | % of GROUPS | 100.0% | 100.0% | 100.0% |

There was a preponderance of females (74%) and majority of the patients were in the age group of 35-55 years. The mean age of each group was comparable. The males and females were divided into two groups and were distributed according to their ages and the mean CCIMT and TCIMT values were matched with controls of respective ages and were found to significantly increased in cases compared to controls. In the study group, there were 12 males and 38 females, i.e., male:female ratio was 1:3.16. The control group also had a similar male: female distribution. The carotid intimal medial thickness between cases and controls were compared in accordance with the age and sex and was found to increased in the cases when compared with the controls.

The disease activity, as per DAS 28, was comparable in all three groups (p value > 0.05). Although the mean values of DAS 28 were comparable across all the groups but on further subdivision, i.e., Group A – mild disease (DAS 28 = 2.6 - 3.2); group B – moderate disease (DAS 28 > 3.2 - 5.1) and group C – severe (DAS 28 > 5.1). These groups were not comparable in number. Based on DAS 28 i.e., disease activity score, each group was further studied as group A (2.6 - 3.1); group B (> 3.2 to 5.1) and group C (> 5.1). In these sub-groups the relationship of activity of RA with intima media thickness of carotids was studied. On comparison of various sub-groups A, B, and C to each other, the CCIMT and TCIMT were found to be statistically non-significant (p value > 0.05 in each). The mean value of common carotid intima media thickness (CCIMT) and total carotid intima media thickness (i.e., mean of total CIMT of CCA, ICA, and ECA) were correlated with the ESR and CRP between cases and were found to statistically not significant (p value >0.05)

a. Common carotid IMT (CCIMT)

The CCIMT ranged from minimum of 0.54 mm to maximum of 1.4 mm, the mean value of group I was 0.5514 ± 0.109mm; of group II was 0.691 ± 0.128 mm and of group III was 0.79305 ± 0.204 mm, the increase in CCIMT with duration was significant (p value <0.001).

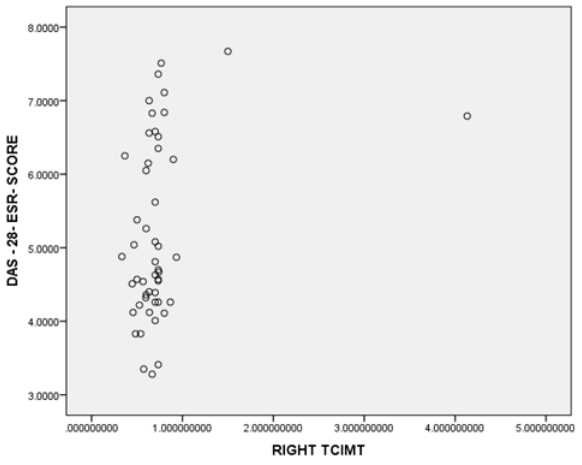
b. Total carotid intimal medial thickness

The TCIMT ranged from minimum of 0.53 mm to maximum of 1.45 mm, the mean value of group I was 0.5518 ± 0.107mm; of group II was 0.0.69 ± 0.128 mm and of group III was 0.79 ± 0.204 mm, the increase in CCIMT with duration was significant (p value <0.001).

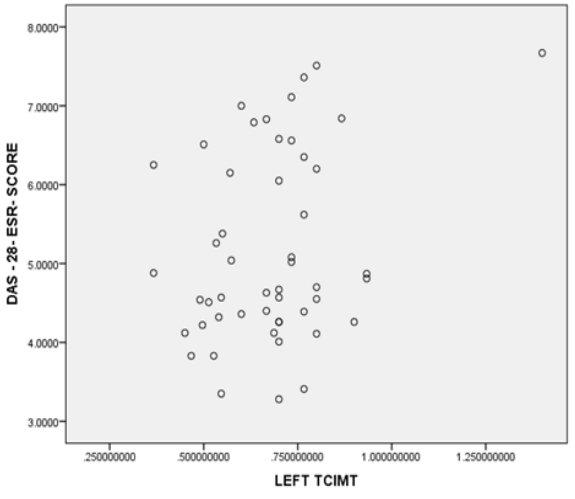
**3.COMPARISON BETWEEN CASES AND CONTROLS ,CIMT VALUES**

| | | | | | |
|---|---|---|---|---|---|
| RT_CCA | Case | 50 | 0.7798 | 0.77261 | 0.10926 |
| | Ctrl | 50 | 0.534 | 0.06154 | 0.0087 |
| R_TCIMT | Case | 50 | 0.7418 | 0.51931 | 0.07344 |
| | Ctrl | 50 | 0.5344 | 0.05458 | 0.00772 |
| LT_CCIMT | Case | 50 | 0.6758 | 0.18462 | 0.2611 |
| | Ctrl | 50 | 0.536 | 0.05689 | 0.00805 |
| LT TCIMT | Case | 50 | 0.6791 | 0.17112 | 0.0242 |
| | Ctrl | 50 | 0.5308 | 0.05374 | 0.0076 |

**4.A.DISEASE ACTIVITY AND RIGHT TCIMT VALUES.**




**4.B.DISEASE ACTIVITY AND LEFT TCIMT VALUES**




## DISCUSSION

Atherosclerosis is a chronic inflammatory disease with striking parallels between the inflammatory and immunological mechanism operating in atherosclerosis and rheumatoid synovitis. The common pathogenic features in the affected tissues include an abundance of activated macrophages which release or induce inflammatory mediators, including cytokines (e.g., interleukin 1 and TNF), growth factors, adhesion molecules with matrix metalloproteinases, and an infiltrate of T-cells. RA and atherosclerosis are associated with elevated levels of acute phase reactants – C-reactive protein (CRP), serum amyloid A, erythrocyte sedimentation rate (ESR), fibrinogen, and secondary phospholipase 2.5 The accelerated atherosclerosis, reported in RA is independent of traditional risk factors. In the present study, diabetes mellitus, hypertension, smoking and dyslipidemia were the exclusion criteria and thus our study was free of the effects of these on atherosclerosis. CIMT is a reliable marker for coronary atherosclerosis and peripheral vascular disease.5. According to Homa et al, the intima media thickness of common carotid artery (measured at areas devoid of plaque) increases linearly with age from 0.48 mm at 40 years of age to 1.02 mm at 100 years of age (following a formula 0.009 x age + 0.116 mm). The mean age of the present study (including control group) was 49 years. So expected common carotid thickness was approximately 0.557 mm. In the present study, common carotid intima media thickness (CCIMT) in the control group was 0.5344 ± 0.113 mm (almost nearing the homa equation, i.e., 0.557 mm) whereas the common carotid intima media thickness in RA was higher, i.e., 0.7278 ± 0.154 mm,p value < 0.001.

The mean total carotid intima media thickness (TCIMT) was calculated by taking the mean of all three dimensions of carotid, i.e., common, internal, and external on both sides.6

The mean of total carotid intima media thickness in RA study group was 0.7104 ± 0.184 mm when compared to the control group, i.e., 0.5326 ± 0.104 mm (p value < 0.001). A similar observation has also been shown by Gonzalez et al7 and Alkabbi et al8 in their respective studies. In a recent Indian study, Mahajan et al have similar observations.8 All the studies (including the present study) showed a significantly higher value of CIMT in RA subjects than the normal population (i.e., noninvasive evidence of accelerated atherosclerosis). The mean common carotid IMT was significantly higher in group III (disease > 4 years) when compared to group I and II (p value < 0.001) ,thus suggesting increasing carotid IMT with duration of disease. Gonzales et al in their study had found disease duration as one of the best predictor for the development of severe morphologic expression of atherosclerotic disease.7 DelRincon et al10 and Mahajan et al8 also had similar observations. This may be due to more years of exposure to increased inflammation,11-14 and other factors like increased arterial stiffness9 and prothrombotic markers in RA patients.14 Role of inflammation as a basic pathogenic mechanism in atherosclerosis is well known.9 Liuzzo et al found increased levels of unusual subsets of T-cells – CD4+, CD28 in 65% of patients with unstable angina, but not in patients with stable angina. These lymphocyte subpopulations were originally described in patients with RA and have been associated with presence of extraarticular especially vasculitis.15 Shared immunological disease mechanisms in systemic autoimmune disorders and coronary vascular disease such as clonally expanded CD4+ and CD28 T-cells,15 systemic endothelial activation16 and circulating immune complex,17 may be involved in the development of cardiovascular comorbidities in RA patients.

The presence of decreased insulin sensitivity and increased ceruloplasmin levels (antioxidant factor) have been attributed to atherosclerosis in RA.18 The mean values of common carotid IMT for moderate and severe activity sub-groups were 0.6553 ± 0.138 and 0.709 ± 0.228 mm respectively; these values when compared with each other were found to be statistically non-significant (p value > 0.05), suggesting no correlation between disease activity at a particular time and carotid intima media thickness. Similar observations were presented by Jonsson19 and Roman et al.20

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