

Correlation of Intima Media Thickness (As a Marker of Atherosclerosis) With Activity and Duration of Rheumatoid Arthritis Using Carotid Ultrasound

Dr. G. Balaraju, M.D^{*}, Dr. R. Nagamani, M.D^{**}, Dr. D. Sridhar, M.D^{***}, Dr. L. Muralidhar, M.D^{***}, Dr. K.S.Amrvathi, M.D^{***}, Dr. Mythili, M.D^{***}

^{*} Assoc. Prof. of Medicine

^{**} Prof. of Medicine

^{***} Asst. Prof. of Medicine

Abstract- Background: Inflammation has a strong association with increased atherosclerosis in RA. Indirect evidence of accelerated atherosclerosis in RA comes from studies measuring carotid artery intima media thickness (CIMT).

Aims of the study: To study the correlation, if any, between inflammation (severity and duration) to intima media thickness (As a marker of atherosclerosis).

Methodology: Carotid intima media thickness (CIMT) was measured in 30 patients of RA divided into three groups of thirty each based on duration of disease (less than two years, two to five years, and more than five years). Both common carotid intima media thickness (CCIMT) and total carotid intima media thickness (TCIMT, i.e., mean of values of CCA, ICA, and ECA). The values were compared to DAS-28 activity score. Thirty healthy subjects (age and sex matched) were taken as controls.

Results: The RA subjects had a CCIMT and TCIMT 0.798 ± 0.19 mm and 0.756 ± 0.17 mm respectively when compared to controls, i.e., 0.591 ± 0.11 mm and 0.57 ± 0.11 mm (p value < 0.001). Both CCIMT and TCIMT increased significantly with duration of disease but did not differ when compared to disease activity.

Conclusion: In view of relation to duration of disease, the physicians should regularly screen the established RA patients, so as to identify the evidence of atherosclerosis and manage it earlier.

Index Terms- Rheumatoid arthritis (RA), carotid artery intima media thickness (CIMT), intima medial thickness (IMT), common carotid artery (CCA), internal carotid artery (ICA) and external carotid artery (ECA).

I. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder involving the joints (nonsuppurative proliferative synovitis) along with other organ involvement including blood vessels and heart¹. RA is associated with disability, shortened life expectancy, and increased mortality².

Cardiovascular cause is the leading cause of mortality in RA³. This increased cardiovascular risk in RA patients has been attributed to accelerated atherosclerosis which has been found to be independent of the traditional risk factors⁴,

Inflammation⁵, increased levels of homocysteine, homeostatic imbalance⁶, decreased mobility⁷, low levels of antioxidants⁸, side-effects of medication⁹, and dyslipidaemia¹⁰ have been attributed to cause accelerated atherosclerosis in RA.

Amongst the above causes, inflammation has the strongest association with increased atherosclerosis in RA¹¹.

Indirect evidence of accelerated atherosclerosis in RA comes from studies using carotid artery intima media thickness (CIMT) as a marker of atherosclerotic burden and cardiovascular risk¹². CIMT measurement is a noninvasive and economical test which is quite reliable and sensitive for assessment of atherosclerosis¹³.

Increased atherosclerosis in carotid arteries holds true for atherosclerosis for multiple vascular beds including coronaries, and so measurement of carotid IMT is an important surrogate marker of increased cardiovascular risk including acute coronary syndrome¹⁴.

There are only a few studies available which have studied the relationship of disease activity and duration of disease in RA patients with carotid artery intima media thickness (a marker of atherosclerosis). So this study was planned to study the correlation, if any, between inflammation (activity and duration) to intima media thickness (a marker of atherosclerosis). Assessment of the carotid intima media thickness (CIMT) is the most widely used surrogate endpoint.¹⁵

II. AIMS AND OBJECTIVES

1. To assess carotid intima-media thickness in patients with Rheumatoid Arthritis by using Doppler Ultrasound.
2. To study the correlation between carotid intima-media thickness and the duration and severity of Rheumatoid Arthritis

III. METHODOLOGY

The study was performed on patients attending as outpatients and admitted as inpatients in the Departments of General Medicine and Orthopaedics of Osmania General Hospital. A total of 30 rheumatoid arthritis patients were enrolled and were compared with 30 age and sex matched control subjects. Total duration of the study was 2 years. i.e from September 2012 to September 2014. It is a cross-sectional study.

Radiographic assessment

X-ray of both hands were taken in all patients to evaluate for rheumatoid activity, deformities and erosions.

IV. CAROTID DOPPLER

For measurement of IMT - B-mode USG scan using 7.5 MHz probe is used and whenever required to see plaques, plaque ulceration, lumen stenosis Colour Doppler scan is used.

All subjects (including controls) underwent carotid sonography. The common carotid arteries (CCA) were examined bilaterally upto the bifurcation (including proximal part of internal carotid artery (ICA) and external carotid artery (ECA). The intima media thickness (IMT), plaque characterisation (including echotexture, calcification, and cavitation) were assessed – initially by gray scale USG and then followed by colour flow imaging. All measurements were taken in diastole, measured in the phase when the lumen diameter is at its smallest and IMT at its largest.

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.

All subjects included in the study were evaluated for their disease activity using DAS-28 (disease activity score).

$$DAS\ 28 = 0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.70(\log ESR) + 0.014\ GH$$

where,

TJC is tender joint count

SJC is swollen joint count

ESR is erythrocyte sedimentation rate

GH is general health status as assessed by patient on visual analogue scale (VAS)

V. STATISTICAL ANALYSIS

The results obtained were subjected to student's unpaired t-test, chi-square test and linear regression for statistical analysis.

VI. RESULTS

Thirty patients of rheumatoid arthritis diagnosed by modified ACR criteria (1987) along with 30 age and sex matched controls were included in the study after they had fulfilled the inclusion and exclusion criteria.

1. Age and Sex distribution

The study group included 23 females and 7 males. The age and sex distribution of patients with RA is shown in Table 1 below. Equal number of age and sex matched controls were taken.

Table 1. Age and sex distribution

Age groups	No. of cases	Females	Males
21-30	3(10%)	3(10%)	0
31-40	9(30%)	8(26.6%)	1(3.3%)
41-50	15(50%)	10(33.3%)	5(16.6%)
51-60	2(6.6%)	1(3.3%)	1(3.3%)
61-70	1(3.3%)	1(3.3%)	0
Total	30	23(76.6%)	7(23.3%)

The patients were divided into three groups based on duration of disease.

	Range(yrs)	Mean (yrs)
Group 1	25-55	43.3
Group 2	29-57	42.8
Group 3	27-64	44.2
Controls	25-64	43.43

Table 2. Mean age in all groups

The mean age of all the groups and controls were comparable

Sex distribution group wise

Out of 30 subjects, 23 were females and 7 were males. Female:male ratio in this study was 3.28:1

	Females	Males	Total
Group 1	8	2	10
Group 2	7	3	10
Group 3	8	2	10
Total	23	7	30

Table 3. Sex distribution group wise

2. Duration of disease

The average duration if the disease in different groups were as follows

Groups	Duration (yrs)
Group 1	1 ± 0.47
Group 2	3.35 ± 0.65
Group 3	11.6 ± 3.68

Table 4. Mean duration of disease

3. Biochemical parameters

The groups were compared for various atherogenic biochemical risk indices. All groups were comparable – including the mean values of blood sugar and lipid profile.

Biochemical parameters	Group 1	Group 2	Group 3
Blood sugar (mg%)	96	92	83
Triglycerides	150	155	148
Cholesterol	141	154	162
HDL	48	42	40
LDL	90	85	83
VLDL	30	36	41

Table 5. Comparison of Biochemical parameters

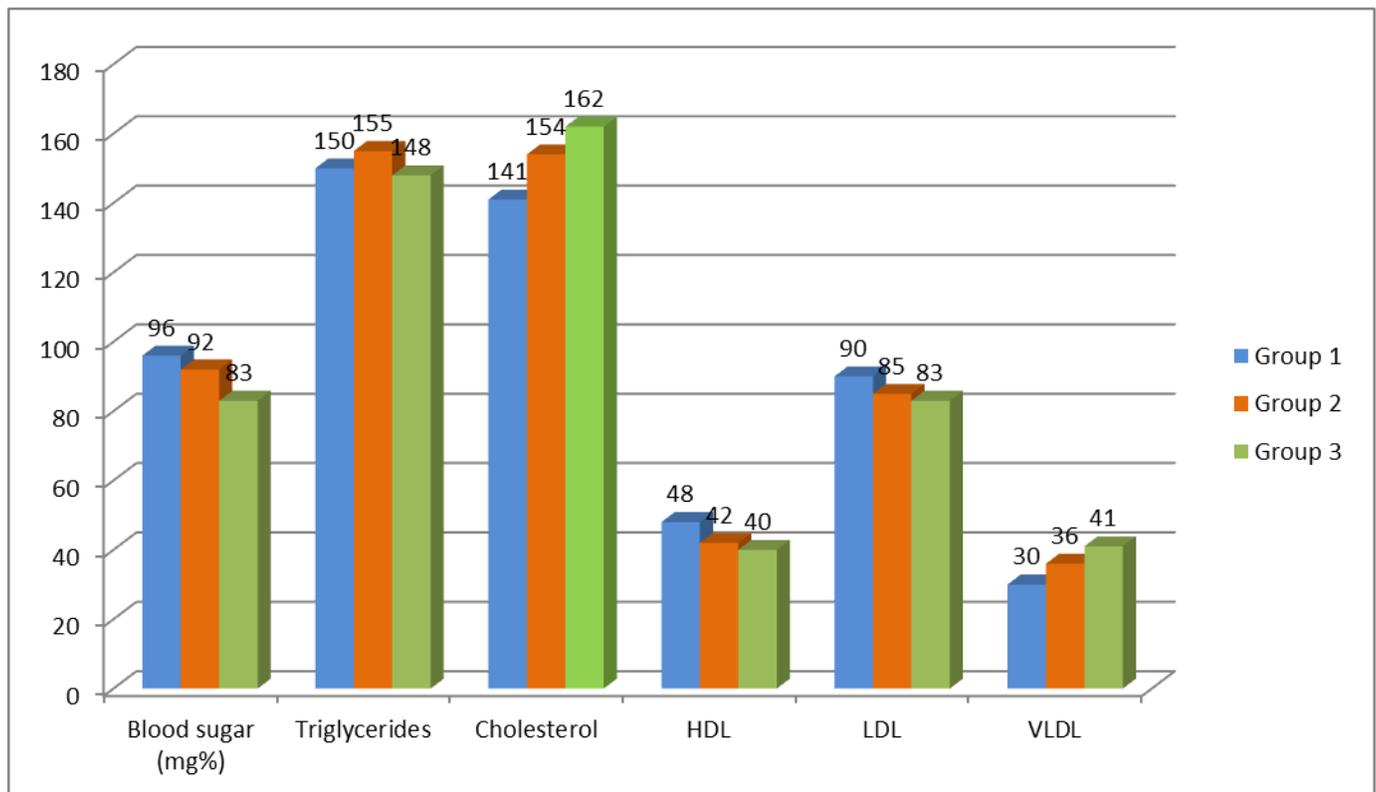


Figure 2. Comparison of Biochemical parameters

On investigations, the hemoglobin levels ranged from 9.5 to 13.5 gm% . The mean ESR in the study group was 33.03 and ranged from 10 mm to 80 mm/hour and in the control subjects the levels ranged from 10 to 40 mm/hour, with a mean of 24 mm/hour. Twenty-two patients (72.3%) were found to be rheumatoid factor (RF) positive.

Twenty-four patients (80%) were found to have CRP >6µg/L.

4. Disease duration and activity

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.

	Duration(yrs)	Mean DAS28-Score	Range	<3.2 Mild	3.2-5.1 Moderate	>5.1 Severe
Group 1	1 ± 047	4.485	2.54-6.83	3	3	4
Group 2	3.35 ± 0.65	4.609	2.34-6.89	2	4	4
Group 3	11.6 ± 3.68	4.657	2.47-6.77	2	5	3

Table 6. Comparison of DAS28 Score in 3 groups

5. Carotid intima media thickness (CIMT): Case vs. control

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 significantly higher in the study group when compared to control group (p-value <0.001)

IMT(in mm)	Study group	Control Group	Pvalue
CCMIT	0.798	0.59	<0.001
Total CIMT	0.756	0.57	<0.001

Table 7. Comparison of CIMT & TCIMT of cases with controls

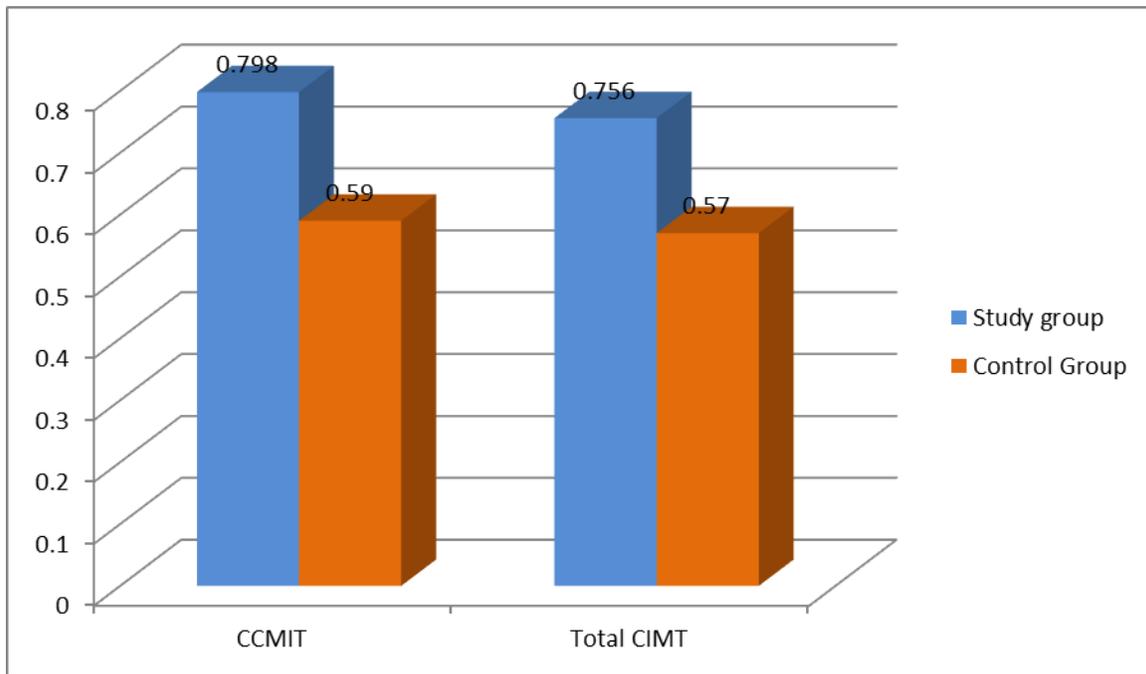


Figure 3. Comparison of CIMT & TCIMT of cases with controls

6. Relationship of intima media thickness with disease duration

Common carotid IMT (CCIMT) ranged from minimum of 0.56 mm to maximum of 1.4 mm, the mean value of group I as $0.703 \pm 0.15\text{mm}$; of group II was $0.79 \pm 0.16\text{ mm}$ and of group III was $0.903 \pm 0.21\text{ mm}$, the increase in CCIMT with duration was significant (p value <0.01)

	CCIMT		TCIMT	
	Mean	Range	Mean	Range
Group 1	0.703	0.56-0.94	0.678	0.53-0.89
Group 2	0.79	0.58-1.1	0.74	0.54-1.03
Group 3	0.903	0.68-1.4	0.85	0.64-1.25

Table8. Comparison of CCIMT & TCIMT with the duration of disease

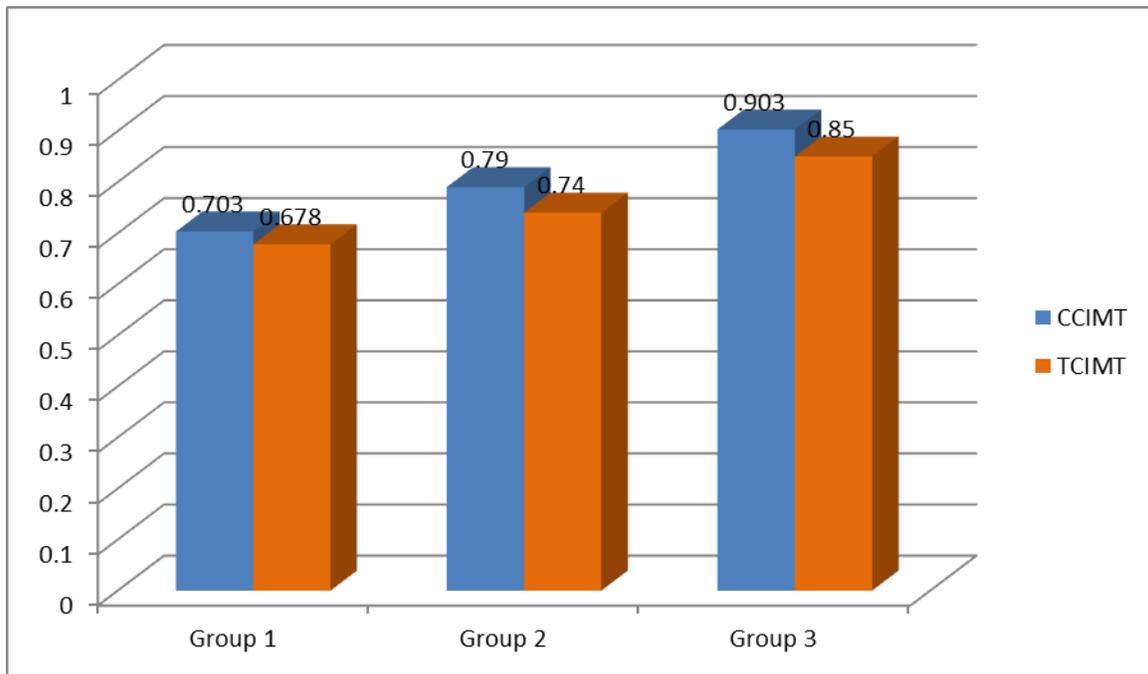


Figure 4. Comparison of CCIMT & TCIMT with the duration of disease

P Value : 0.0057

Deviation from horizontal significant

7. Relationship of intima media thickness with activity of RA

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). 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).

DAS 28	No. of Subjects	CCIMT(Mean) in mm	TCIMT(Mean) in mm
<3.2	7	0.77	0.74
3.2-5.1	12	0.78	0.76
>5.1	11	0.8	0.76

Table.9

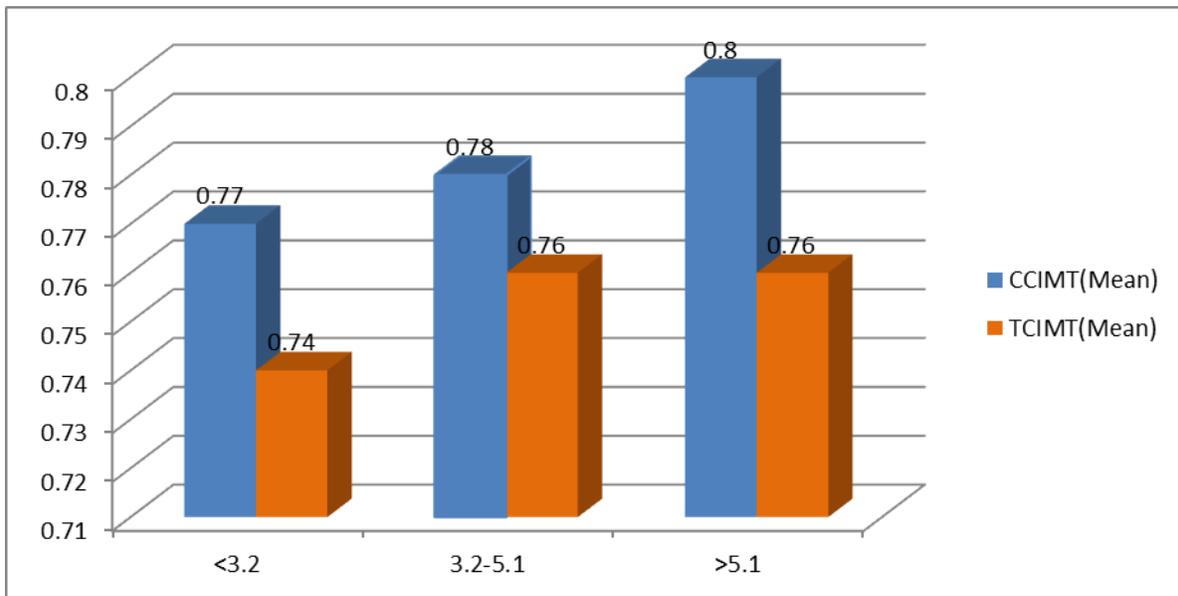


Figure 5. Comparison of CCIMT and TCIMT with DAS 28 Score, P Value : 0.8520

8. Comparison of plaque positive with plaque negative group

Of the thirty subjects, there was evidence of plaque in ten subjects.

	CCIMT(mm)	TCIMT(mm)
Plaque positive	0.984	0.923
Plaque negative	0.706	0.672

Table 10. Comparison of plaque positive with plaque negative group

P value<0.0001. The difference is statistically significant

VII. DISCUSSION

Atherosclerosis is an inflammatory disease and so there are striking parallels between the inflammatory and immunological mechanism operating in atherosclerotic plaque and in 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- CRP, serum amyloid A, ESR, fibrinogen, and secondary phospholipase 2¹⁶.

The accelerated atherosclerosis has been reported in RA to be independent of traditional risk factors. In the present study, diabetes mellitus, hypertension, and smoking were exclusion criteria while the mean values of triglyceride, cholesterol, HDL, LDL, and VLDL were within normal range, thus this study was free of the effects of these CIMT is a reliable marker for coronary atherosclerosis and peripheral vascular disease¹⁷.

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)¹⁸.

The mean age of the present study (including control group) was 43.4 years. So expected common carotid thickness was approximately 0.521 mm. In the present study, common carotid intima media thickness (CCIMT) in the control group was 0.591 ± 0.113 mm (almost nearing the homa equation, i.e., 0.521 mm) whereas the common carotid intima media thickness in RA was higher, i.e., 0.798 ± 0.19 mm with p value of <0.01(0.0057).

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. The mean of total carotid intima media thickness in RA study group was 0.756 ± 0.17 mm when compared to the control group, i.e., 0.586 ± 0.104 mm (p value <0.001).

A similar observation has also been shown by Gonzalez *et al*¹⁹ and Alkabbi *et al*²⁰ in their respective studies. In a recent Indian study, Mahajan *et al* have similar observations.

All the studies (including the present study) show 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 > 10 years) when compared to group I and II (p value < 0.001), thus suggesting that increasing carotid IMT increased 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 disease¹⁹.

Del Rincon *et al*²¹ and Mahajan *et al* also had similar observations. This may be due to more years of exposure to increased inflammation, and other factors like increased arterial stiffness²¹ and prothrombotic marker in RA patients²². Role of inflammation as a basic pathogenic mechanism in atherosclerosis is well known²¹.

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 vasculitis²³.

Shared immunological disease mechanisms in systemic autoimmune disorders and coronary vascular disease such as clonally expanded CD4+ and CD28 T-cells²³, systemic endothelial activation²⁴ and circulating immune complex²⁵, 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 RA²⁶.

The mean values of common carotid IMT for mild, moderate and severe activity sub-groups based on the DAS 28 Score were 0.77 ± 0.14 ; 0.78 ± 0.15 and 0.8 ± 0.17 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.

One of the limitations of my study was that it is cross-sectional. It would be worthwhile to follow up these patients over a period of time to look for clinical events like myocardial infarction etc. Another lacuna was my inability to comment on the influence of drugs. Many of the patients of RA were on methotrexate and the vast majority had received corticosteroids at some point of time in their disease course in varying doses for variable periods of time.

VIII. SUMMARY

The study was carried out in Osmania General Hospital from September 2012 to September 2014. Thirty patients of rheumatoid arthritis (23 females and 7 males) diagnosed by modified ACR criteria (1987) along with 30 age and sex matched controls were included in the study.

1. The mean age of the present study (including control group) was 43.4 years.

2. The mean common carotid intima media thickness (CCIMT) in the RA study group was 0.798 ± 0.19 mm when compared to the control group, i.e. 0.591 ± 0.11 mm with p value of <0.01(0.0057)
3. The mean of total carotid intima media thickness in RA study group was 0.756 ± 0.17 mm when compared to the control group, i.e., 0.57 ± 0.11 mm (p value <0.001)
4. The mean common carotid IMT was significantly higher in group III (disease > 10 years) when compared to group I and II (p value < 0.001), thus suggesting that increasing carotid IMT increased with duration of disease.
5. The mean values of common carotid IMT for mild, moderate and severe activity sub-groups based on the DAS 28 Score were 0.77 ± 0.14 ; 0.78 ± 0.15 and 0.80 ± 0.17 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.

IX. CONCLUSION

Rheumatoid arthritis, a chronic inflammatory disease mainly involving joints has been found to have accelerated atherosclerosis when compared to age and sex-matched controls. This effect of accelerated atherosclerosis in RA was found to be independent of traditional risk factors like diabetes mellitus, hypertension, smoking and dyslipidaemia.

The study also shows a significant, i.e., directly proportional relation between carotid intima media thickness to longer duration of disease, but no significant relationship between activity of disease and carotid intima media thickness.

In view of relation to duration of disease, the physicians should regularly screen the established RA patients, so as to identify the evidence of atherosclerosis and manage it earlier. Thus, prevention of cardiovascular disease in RA requires a combined approach incorporating cardiovascular risk factors screening and management, effective and sustained control of RA disease activity, a high index of suspicion and prompt investigation of suspected cardiac disease.

REFERENCES

- [1] Rosenberg A. Rheumatoid Arthritis. In: Robbins Pathologic basis of disease. Abbas AK, Fausto N, Kumar V, editors. Philadelphia; WB Saunders Company. 7th edition; p.1305-9.
- [2] Cobb S, Anderson F, Baver W. Length of life and cause of death in rheumatoid arthritis. *New Engl J Med* 1953; 249: 553-6.
- [3] Minapur NJ, Jacoby RK, Cosh JA et al. Outcome after 40 years with rheumatoid arthritis; A prospective study of function, disease activity and mortality. *J Rheumatol* 2004; 31: 3-8.
- [4] Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis; results from a community based study. *Ann Rheum Dis* 2004; 63: 952-5.
- [5] Ridker PM, Cushman M, Stampfer MJ et al. Inflammation, Aspirin and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336: 973-9.
- [6] Wallberg Jonsson S, Dahlen G, Nilsson TK et al. Tissue plasminogen activator, plasminogen activator inhibitor-1 and Von Willebrand factor in rheumatoid arthritis. *Clin Rheumatol* 1993; 12: 318-24.

- [7] Superko HR, Haskell WL, Wood PD. Modification of plasmacholesterol through exercise. *Post Grad Med* 1985; 78: 65-75.
- [8] Paredes S, Girona J, Camejo EH et al. Anti-oxidant vitamins and lipid peroxidation in patients with rheumatoid arthritis; association with inflammatory markers. *J Rheumatol* 2002; 29: 2271-7.
- [9] Haagsma CJ, Blom HJ, Van Riel PL et al. Influence of Sulfasalazine, Methotrexate and combination of both on plasma homocysteine concentrations in patients with rheumatoid arthritis. *Ann Rheum Dis* 1999; 58: 79-84.
- [10] Heldenberg D, Caspi D, Levto O et al. Serum lipids and lipoprotein concentration in women with RA. *Clin Rheumatol* 1983; 2: 387-91.
- [11] Libby P. The pathogenic, prevention and treatment of atherosclerosis. In: Fauci, Braunwald, Kasper et al. *Harrison's principles of internal medicine*. 17th edition. New York, McGraw Hill Company 2008; 2: 1501-9.
- [12] Hoskote SS, Joshi SR. Carotid intimomedial thickness – a non invasive index of vascular health. *IAPI* 2008; 56: 577-8.
- [13] Lorenz MW, Markus HS, Bots ML et al. Prediction of clinicalcardiovascular events with carotid intima-media thickness; a systematic review and meta-analysis. *Circulation* 2007; 115: 459-67.
- [14] Del RI, Freeman G, Hass R et al. A escalante – abstract 1901. Effects of carotid atherosclerosis on the incidence of acute coronary syndromes in rheumatoid arthritis. *Arthritis Rheum* 2005; 52: 3413-23
- [15] Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis* 2007;23(1):75-80.
- [16] Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; 340: 115-26.
- [17] Revkin JH, Shear CL, Pouleur HG et al. Biomarkers in the prevention and treatment of atherosclerosis; need, validation and further. *Pharmacol Rev* 2007; 59: 40-53.
- [18] Homa S, Nobuyoshi H, Ishida H. Carotid plaque and intima-media thickness assessed by B-mode sonography in subjects ranging from young adults to centenarians. *Stroke* 2001; 32: 830-5.
- [19] Gonzalez JC, Llorca J, Terta A et al. Increased prevalence of severe sub-clinical atherosclerosis findings in long-term treated RA patients without clinically evident atherosclerotic disease. *Medicine (Baltimore)* 2003; 82: 407-13.
- [20] Alkaabi K. Rheumatoid arthritis and macrovascular disease. *Rheumatology* 2003; 42: 292-7.
- [21] DelRincon I, Freeman GL, Hass RW et al. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestation to atherosclerosis. *Arthritis Rheum* 2005; 52: 3413-23.
- [22] McEntegart A, Capell HA, Creran D et al. Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. *Rheumatology (Oxford)* 2110; 40: 640-4.
- [23] Liuzzo G, Kopecky SL, Frye RL et al. Perturbation of the T-cell repertoire in patients with unstable angina. *Circulation* 1999; 100: 2135-9.
- [24] Turesson C, Englund P, Jacobsson LT et al. Increased endometrial expression of HLA-DQ and interleukin I alpha in extra-articular arthritis. Results from immunohistochemical studies of skeletal muscle. *Rheumatology (Oxford)* 2001; 40: 1346-54.
- [25] Mustafa A, Nityanand S, Berglund L et al. Circulating immune complexes in 50-year-old men as a strong and independent risk factor for myocardial infarction. *Circulation* 2000; 102: 2576-81.
- [26] Louro MO, Cocho JA, Mera A, Tutor JC. Immunochemical and enzymatic study of ceruloplasmin in rheumatoid arthritis. *J Trac Elem Med Bil* 2000; 14: 174-8.

AUTHORS

First Author – Dr. G. Balaraju, M.D., Assoc. Prof. of Medicine
Second Author – Dr. R. Nagamani, M.D., Prof. of Medicine
Third Author – Dr. D. Sridhar, M.D., Asst. Prof. of Medicine
Fourth Author – Dr. L. Muralidhar, M.D., Asst Prof. of Medicine
Fifth Author – Dr. K.S.Amrvathi, M.D., Asst. Prof. of Medicine
Sixth Author – Dr. Mythili, M.D., Asst. Prof. of Medicine