Evaluation of carotid artery intimo medial thickness and its correlation with severity of the disease in rheumatoid arthritis

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Abstract
Rheumatoid joint pain is an on-going incendiary infection with articular and extra articular signs. In rheumatoid arthritis increased mortality is observed due to cardiovascular diseases due to accelerated atherosclerotic process. CIMT can be used as a biomarker to evaluate subclinical atherosclerosis. This systematic study aims at correlating the coronary artery intimo medial thickness in rheumatoid joint pain patients to evaluate the seriousness of atherosclerosis in same patients. A prospective single-center study was conducted with a study group of 12 patients with RA and 12 stable, age and sex-matched controls. After applying inclusion and exclusion criteria and separating the patients into three gatherings dependent on term of the illness, the USG directed CIMT thickness was calculated and the findings were compared between different groups. There was a clear association between the duration of rheumatoid arthritis and intimo medial carotid artery thickness. There was no substantial association between disease occurrence and CIMT in cases of rheumatoid arthritis. An increase in CIMT should be promptly taken into consideration and appropriate preventive therapies on instituting can prevent and decrease the incidence of cardiovascular and cerebral events in rheumatoid arthritis.

INTRODUCTION
Rheumatoid arthritis is a chronic inflammatory condition of uncertain aetiology characterised by symmetrical polyarthritis. While primarily rheumatoid arthritis triggers joint cartilage and bone deterioration, it also has extra articular manifestations. The prevalence of rheumatoid arthritis in women is two to three times higher than in men, for unknown reasons. Genetics plays a key role in deciding both the risk of developing rheumatoid arthritis and the severity of the disease. Increased mortality is seen in rheumatoid arthritis patients, especially in patients with serious disease, where the estimated lifespan is shortened by 8-15 years. A 40% disability is observed within 3 years of onset of rheumatoid arthritis and 80% are moderately or severely disabled within 20 years (Ralston and McInnes, 2014). Cardiovascular involvement in rheumatoid arthritis is regarded as the main cause of mortality (Minaur et al., 2004).
related to the formation of atherosclerotic plaque. In rheumatoid arthritis, increased mortality due to cardiovascular involvement is due to an accelerated atherosclerotic phase. Rheumatoid arthritis is also known to be a typical independent risk factor for atherosclerosis (Turesson, 2004). The other factors responsible for the accelerated atherosclerosis in rheumatoid arthritis are inflammation, abnormal increased homocysteine levels (Ridker et al., 1997), imbalance in homeostasis (Wällberg-Jonsson et al., 2000, 1993), immobility (Superko et al., 1985), decreased antioxidant levels (Paredes et al., 2002) and side effects due to medications (Haagsma et al., 1999; Landewe et al., 2000). Inflammation is the major contributor for the accelerated atherosclerosis.

Carotid artery intimomedial thickness is a non-invasive, reliable, sensitive and economical biomarker for subclinical atherosclerosis (Schulte-Altedornenburg et al., 2001; Lorenz et al., 2007). Increased carotid artery atherosclerosis represents atherosclerosis in many vascular beds, including coronary arteries. As a result, CIMT measured tissue area beginning at the luminal-intimal interface and media adventitia interface of common carotid artery is an important surrogate marker for increased cardiovascular risk, including acute coronary syndrome (Singh et al., 2011). In RA patients, early diagnosis of atherosclerosis by CIMT measurement can help in establishing preventive measures against atherosclerosis, thereby reducing cardiovascular mortality. The ultimate aim of the present study is, to assess atherosclerosis by carotid artery intimomedial thickness in patients with rheumatoid arthritis and to correlate ultrasound findings with disease severity.

MATERIALS AND METHODS

Study Design

This prospective, single center, age and sex control study was performed in the department of general medicine, Vinayaka mission medical college, Karaikal, India. Informed consent was obtained from all participating patients after describing the study in their own language. Patients were recruited from all units in the hospital department.

Details of the study

Ethical details and Patient details

After approval by the ethical committee. After obtaining informed written consent from the patient 30 patients were screened with rheumatoid arthritis and 50 normal healthy volunteers were screened after applying inclusion and exclusion criteria, 12 cases of patients with RA and 12 healthy, age and sex matched controls sample selected. All patients’ routine investigation done along with USG guided (B-mode) carotid artery intimomedial thickness measurement. Found the carotid artery intimomedial thickness is significantly increased on comparing with the same age and sex healthy individuals.

Study group

The research group consists of 12 patients with RA and 12 stable, age and sex-matched controls.

Inclusion criteria

For cases adult patients over the age of 18 years and satisfying the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) criteria for RA are included in the study.

Criteria for the incorporation of controls 20 safe, age and gender-matched RA-free controls and free of conventional risk factors, such as smoking, hypertension (blood pressure >140/90 mm hg), diabetes mellitus, medical signs of atherosclerosis by way of cad, Peripheral Vascular Disease (PVD), cerebrovascular disease and appropriate patients considered to have dyslipidemia and on treatment.

Exclusion criteria

Hypertension (blood pressure >140/90 mm hg), smoking, diabetes mellitus, medical signs of atherosclerosis by way of CAD, Peripheral Vascular Disease (PVD), cerebrovascular disease, patients and controls considered to have dyslipidemia and on treatment. However, patients and controls that experience dyslipidemia after participation in the study will still be included in the study.

The patients included in the research as participants were classified into three classes depending on the duration of the disease. There are the following

Group -1: Those subjects who had less than 2 years of RA.

Group-2: Those subjects who had RA for 2 to 5 years.

Group-3: Those subjects that have had more than 5 years of RA.

Disease activity score was used for evaluating all patients with RA”Das28”. This score is determined using the following formula:

\[ DAS_{28} = 0.56 \sqrt{TJC} + 0.28 \sqrt{SJC} + 0.70 (\log ESR) + 0.014 GH \]

Where,

TJC: Tender Joint Count.

SJC: Swollen Joint Count.
GH: General Health Status as measured by the patient on a Visual Analogue Scale (VAS).

Evaluation of the carotid artery intimo-medial thickness of the control group using carotid ultrasonography was performed by a trained institution radiologist using ultrasonography on a grey scale and ultrasonography on a colour flow Doppler.

Carotid Artery Intima-Medial Thickness (CIMT) was measured in proximal, mid-and distal carotid on both sides. All measurements were taken in diastole, measured in phases where the diameter of the lumen is the smallest and the IMT at its largest. The maximum CIMT value between the right and the left was taken as the final CIMT for measurement.

Statistics
Statistical analysis was conducted using version 21 of the SPSS and the paired T-test was used for correlation.

RESULTS
Characteristics of the cases and controls included in the report

Gender Distribution of cases and controls
A total of 24 cases were enrolled in the study excluding a case and a control who were smokers. The case group has 12 individuals and the control group has 12 individuals. The case group has 25 % of males and control group had 25 % of males and the same with respect to females were 75 % and 75 % respectively. It is significant from the above table that in both the parameters the groups the majority are females. There was no statistically significant difference found in age between the two groups (Figure 1). (paired t-test applied, P-Value ≥ 0.05).

Age wise distribution of cases and Controls
Among the total cases, the groups (study group and control group) have the same distribution - 50 % belong to the age group 36 to 45 years, 42% belong to 46 - 55 years, 8 % belong to the age above 55 years (Table 1). Majority of the cases and controls belong
### Table 1: Age wise distribution

| Age (In Years) | No of cases | % | No of controls | % | P-Value |
|----------------|-------------|---|----------------|---|---------|
| 36 – 45        | 6           | 50| 6              | 50| 0.874   |
| 46 – 55        | 5           | 42| 5              | 42|          |
| > 55           | 1           | 8 | 1              | 8 |          |
| Total          | 12          | 100| 12             | 100|         |
| Mean Age       | 45.83       |    | 46             |   |         |

### Table 2: Duration of the symptoms in the case groups

| Duration of the Symptoms | No. of Cases | % |
|--------------------------|--------------|---|
| Group I (< 2 Years)     | 5            | 42|
| Group II (2 – 5 Years)  | 4            | 33|
| Group III (> 5 Years)   | 3            | 25|
| Total                    | 12           | 100|

### Table 3: DAS28 and duration of disease comparison

| Das          | Group I | Group II | Group III | Total |
|--------------|---------|----------|-----------|-------|
| Remission    | 1       | 0        | 0         | 1     |
| Low          | 0       | 0        | 0         | 0     |
| Moderate     | 3       | 2        | 2         | 7     |
| High         | 1       | 2        | 1         | 4     |
| Total        | 5       | 4        | 3         | 12    |

Figure 6: Comparisons of various biomedical parameters

Figure 7: Comparison of carotid artery intimomedial thickness at various levels

Figure 8: Comparison of left common carotid intimomedial thickness at different levels

Figure 9: Comparison of mean CIMT case vs Control group
Majority of the cases and controls belong to the 3rd and 4th decade of life. There was no statistically significant difference in age between the two groups. (Paired t-test applied, p ≥ 0.05) (Figure 2).

**Comparison of various parameters with the case groups**

**Duration of the symptoms**
Among the case group, 42% had the symptoms for nearly 2 years, 33% had the symptoms from 2 years to 5 years and 25% had the symptoms for duration more than 5 years (Table 2 and Figure 3).

**Comparison of age among case groups**
With reference to the age distribution among the groups, 3 were from group i, 1 was from group ii, 2 were from group iii in the age group 36 – 45 years. 1 was from group i. 3 were from group ii & 1 was group iii each in the age group 46 – 55 years, 1 was from group i & group iii in the age above 55 years (Figure 4).

**Comparison of gender among the case groups**
The study group was compared with gender and it showed that 1 male was from all the three groups. Also 4 females were from group i, 3 were from group ii and 2 were from group iii (Figure 5).

**Comparison of the various biochemical parameters with the case groups and controls**
Both classes were comparable – including mean values for the sugar and lipid profile (atherogenic biochemical risk indices) (Figure 6).

**Das 28 and duration of disease comparison**
Group i had 1 case with remission score, no case with low score, 3 cases with moderate score and 1 case with high score. Group ii had no case with remission score, 0 cases with low score, 2 cases each with moderate score and high score (Table 3). Group iii had no case with remission score, no case with low score, 2 cases with moderate score and 1 case with high score.

**Comparison of carotid artery intimo medial thickness**
Comparison of carotid artery intimo medial thickness at various levels on the same side right proximal common carotid Vs right mid common carotid Vs right distal common carotid. The study group intimomedial thickness on the right side was compared and the result proved that there was a positive correlation among the three parameters and right distal common carotid intima medial thickness proves to be statistically significant with high correlation (Figure 7).
Left proximal common carotid Vs left mid common carotid Vs left distal common carotid

The study group intimomedial thickness on the right side was compared with respect to left proximal common carotid, left mid common carotid, left distal common carotid and the result proved that there was a positive correlation among the three parameters (Figure 8). Left mid common carotid proves to be statistically significant with high correlation.

Carotid artery intima medial thickness: cases Vs controls

The study group was compared with respect to maximum CIMT of case group and maximum CIMT of control group and the result proved that there was statistical evidence that both the parameters were not equal. Since p-value < 0.05, it is statistically evident that the maximum CIMT of case group is higher when compared to maximum of control group (Figure 9).

Comparison of CIMT with the duration of the disease

Carotid artery intimomedial thickness vs DAS 28

The study group was compared with respect to carotid artery intimomedial thickness & DAS 28 and the result proved that there was a negative correlation between both the parameters (Figure 10). CIMT vs ACCP: the study group was compared with respect to maximum & ACCP and the result proved that there was a negative correlation between both the parameters. j. CIMT with rheumatoid factor: the study group was compared with respect to maximum & RF and the result proved that there was a negative correlation between both the parameters (Figure 11).

Comparison of disease activity score with various parameters

DAS score wise distribution of mean CIMT

The mean CIMT of remission score of das28 was 0.1, mean CIMT of moderate score of DAS28 was 0.0871 mean CIMT of high score of DAS28 was 0.1025 (Figure 12).

Mean duration of disease Vs DAS in various groups

The mean duration of disease and das with respect to the groups are: group I had an average duration of disease of 0.61 years and the mean das score was 2.61.

Group II had an average duration of disease of 3.50 years and the mean das score was 4.97.

Group III had an average duration of disease of 7.67 years and the mean das score was 4.23 (Figure 13).

DISCUSSION

Atherosclerosis is an inflammatory disease of the arterial system of the body in which, due to the accumulation of cholesterol and other lipids, inflammatory cells and calcium, the wall of the blood vessels is thickened and hardened by plaques. Inflammatory and immunological processes in atherosclerotic plaque and rheumatoid synovitis have remarkable similarities. The abundance of activated macrophages that release or trigger the release of inflammatory mediators, including cytokines (e.g., IL-1 and TNF), matrix metalloproteinase adhesion molecules, growth factors and t-cell infiltrates, are typical pathophysiological features in the affected tissues. Elevated levels of acute phase reactants, C - reactive protein (CRP), serum amyloid A, ESR, fibrinogen and secondary phospholipase are associated with both atherosclerosis and Rheumatoid arthritis. Atherosclerosis has various modifiable and non-modifiable risk factors. In various studies it has been proved that one of the many independent risk factors for atherosclerosis being rheumatoid arthritis leading to mild to debilitating complications.

In our study the major and common atherosclerotic risk factors like hypertension, diabetes mellitus and hyperlipidemia were excluded. One of the patients in the case group was an elderly smoker, which in turn is a risk factor for atherosclerosis is excluded from the study. The atherogenic biochemical parameters (such as blood sugar, urea, creatinine, total cholesterol, triglycerides, LDL, and HDL) measured in our study subjects were within the usual range. The research was free from the conventional risk factors for atherosclerosis and therefore associated only rheumatoid arthritis with atherosclerosis by evaluating the intimomedial carotid artery thickness. CIMT is a reliable marker for coronary atherosclerosis and peripheral vascular diseases. Our observations in comparison with the results shown by Alkaabi (2003) in their respective studies were higher i.e. the CIMT was higher in
our studies. In a recent Indian report, Mahajan et al. had similar observations (Mahajan et al., 2008). All studies (including the present study) showed a significantly higher value of CIMT in RA subjects than in the normal population.

The mean CIMT was substantially higher in group-2 (a condition aged 2-5 years) relative to group-1. This clearly shows that CIMT increases with an increase in the duration of rheumatoid arthritis. In their analysis, Gonzales et al. considered the duration of the disease to be one of the best predictors for the production of extreme morphological expression of atherosclerotic disease (Gonzalez-Juanatey et al., 2003). Delrincon et al. (2005) and Mahajan et al. (2008) have made similar observations. This may be attributed to more years of exposure to elevated inflammation (Turesson, 2004; Ridker et al., 1997; Paredes et al., 2002) and other factors such as increased arterial stiffness (Alkaabi, 2003) and prothrombotic markers in RA patients (McEntegart, 2001). The role of inflammation as a basic pathogenic mechanism of atherosclerosis is well known (Gonzalez-Juanatey et al., 2003). However, the mean CIMT of group 3 (a disease of more than 5 years of age) is less than that of group 2. This is at odds with our analysis. This can be attributed to a single case in group 3 and 5 patients in group 2 in our sample.

Mean CIMT values for remission, moderate and high disease activity subgroups were 0.1 cm; 0.0871 cm and 0.1025 cm, respectively. There were no cases in the low disease activity category in our study. These values, when compared with each other, were found to be statistically non-significant, indicating no association between disease activity at a given time and carotid intima media thickness. Similar observations were made by Jonsson et al. (2001) when CIMT was associated with rheumatoid factor and anti-CCP in RA cases, mean CIMT was relatively higher in RF-positive cases than in RF-negative patients and there was no important association between CIMT and ACPP. The p-value was found to be greater than 0.05, which is not statistically important. Rheumatoid arthritis, a chronic inflammatory condition primarily affecting joints, has been shown to have accelerated atherosclerosis relative to age and sex-matched controls. The study also shows an important, i.e., directly proportional relationship between carotid intima media thickness and longer duration of disease. There was no significant relationship on comparing the CIMT of right and left side. The right side CIMT was not equal to the left side CIMT. This comparison is not done in any Indian studies. There was no significant relationship observed between various parts of the common carotid on measuring the CIMT at the proximal, mid and distal common carotid. There was no significant relationship observed between the disease activity and various atherogenic parameters like total cholesterol, triglycerides, LDL-c. The disease activity did not show any positive correlation with the rheumatoid factor. But a positive correlation was observed between anti-CCP and disease activity. Thus showing that both anti-CCP and DAS28 can be used for the disease prognosis and the treatment response marker. But this study did not indicate a major association between disease behaviour and carotid intima media thickness.

However, in view of the connexion to the length of the disorder, physicians should routinely track existing RA patients to detect and treat signs of atherosclerosis sooner. Preventing cardiovascular disease in RA involves a combined. Strategy that includes cardiovascular risk factors for screening and treatment, efficient and continuous monitoring of RA activity, a high degree of suspicion and prompt examination of suspected heart disease.

CONCLUSION

In this single center, age and sex control study on rheumatoid arthritis and carotid artery intima-media thickness, it is found that in rheumatoid arthritis patients, the carotid artery intimo medial thickness is significantly increased on comparing with the same age and sexed healthy individuals. Thus this shows that rheumatoid arthritis is an independent risk factor for accelerated atherosclerotic process. There was no significant correlation between the disease activity and the carotid artery intimo medial thickness in Rheumatoid arthritis cases. There was direct relationship between the duration of rheumatoid arthritis and the corresponding carotid artery intimo medial thickness. To conclude, in Rheumatoid arthritis patients, an early evidence and identification of an undesired vascular profile such as increase in carotid artery intimomediaal thickness should be promptly taken into consideration and appropriate preventive therapies on instituting can prevent and decreased the incidence of cardiovascular and cerebrovascular events in Rheumatoid arthritis.

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**Conflict of Interest**

The authors declare that there is no conflict of interest for this study.

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