A Study of Carotid Intimomedial Thickness as a Primary Marker of Atherosclerosis in Patients with Rheumatoid Arthritis.

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Rheumatoid arthritis (RA) is the most common inflammatory arthritis and affects a variety of organ systems including blood vessels and heart. RA is associated with disability, shortened life expectancy, and increased mortality as compared to the general population. Cardiovascular disease is the leading cause of mortality in RA. This increased cardiovascular risk in RA patients has been attributed to accelerated atherosclerosis which has been found to be independent of traditional cardiovascular risk factors. Inflammation, increased levels of homocysteine, homoeostatic imbalance, decreased mobility, low levels of

Highlights

Background
Atherosclerosis is a slowly progressive diffuse degenerative disease of arteries which can lead to various metabolic and cardiovascular complications. However, it can cause early and significant morbidity in patients with Rheumatoid Arthritis (RA) when compared to general population. Indirect evidence of accelerated atherosclerosis in RA comes from studies measuring carotid artery intima media thickness (CIMT). This present study aims to investigate the relationship between carotid intima-media thickness and clinical and metabolic features in rheumatoid arthritis (RA) patients.

Methods
In this prospective observational case control study, 34 patients with RA having a disease duration of more than 5 years were compared to 34 healthy matched controls. All the patients and controls were asymptomatic for atherosclerosis and had no traditional risk factors for atherosclerosis. Both groups underwent high frequency carotid ultrasound and Doppler examination for CIMT in addition to detailed history, physical examination and measurement of other metabolic parameters.

Results
The mean ages of RA group and the control group were 48±14.4 and 48.6±14.0 respectively with a female preponderance in the RA group. The groups were comparable for atherogenic biochemical risk indices such as body mass index (BMI), systolic and diastolic blood pressure, random blood sugar, and lipid profile. The RA group had a significant elevation of CRP as compared to the control group (88% vs 15%). The mean CIMT of the RA group was 0.86 ± 0.18 and that of the control group was 0.53 ± 0.15, a difference which was statistically significant (p<0.0001). As the severity of disease increased according to disease activity score (DAS 28), the CIMT in study group also showed an increasing trend.

Conclusions
RA is a chronic disease associated with chronic subclinical inflammation. In view of the consequent high risk of atherosclerosis seen in these patients CIMT may serve as an early surrogate marker of atherosclerosis. We can identify these high risk subgroups of patients with a simple, reliable, inexpensive, and non-invasive bedside carotid Doppler sonogram even in resource poor countries such as India. In our view physicians should be vigilant to identify and screen regularly for atherosclerosis with CIMT in RA patients, so that prompt early management can prevent the cardiovascular complications.

Keywords: Atherosclerosis, Carotid Intima Media Thickness, C Reactive Protein, Inflammation, Rheumatoid Arthritis

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antioxidants, side-effects of medication, and dyslipidaemia have all been suggested to cause accelerated atherosclerosis in RA. Amongst the above causes, inflammation has the strongest association with premature atherosclerosis in RA[1].

Carotid intima-media thickness (CIMT) is a simple, reliable, inexpensive, non-invasive marker that is increasingly being used to detect subclinical atherosclerosis and has been recommended by the American Heart Association (AHA), American Society of Echocardiography (ASE) and Society for Vascular Medicine (SVM) as a screening test for heart disease in apparently healthy individuals. CIMT has been used in several clinical trials as a surrogate end point for evaluating the regression and/or progression of atherosclerotic cardiovascular disease. Increased atherosclerosis in carotid arteries holds true for atherosclerosis for multiple vascular beds including coronaries, and so measurement of carotid IMT is an important marker of increased cardiovascular risk including acute coronary syndromes.

As an ethnic group, Asian Indians are predisposed to a high risk of metabolic syndrome, and premature atherosclerosis.[2] Thus, Indian patients with RA appear to be at a higher risk for developing atherosclerosis. However, sparse data are available regarding this suggestion. Therefore, the present study was designed to determine the presence of asymptomatic atherosclerosis in adult patients with RA by utilizing CIMT as a surrogate marker.

Materials And Methods

Study Design: This prospective observational case-control study was conducted in the Civil Hospital Ahmedabad, Gujarat, India. This study include 34 consecutive patients with RA attending the department of Internal Medicine for the treatment and routine follow up over a period between September 2013 and August 2014. The controls were selected from healthy relatives of the same sex attending with their RA patients to reduce the potential for confounding effects of familial predisposition and dietary factors.

Inclusion criteria:
- Patients more than 12 years of age.
- Fulfilling the American College of Rheumatology criteria for RA.[22]
- Having a disease duration greater than 5 years.

Exclusion criteria:
- Patients and control subjects exhibiting traditional risk factors such as hypertension (blood pressure >140/90 mm Hg), diabetes mellitus, and clinically overt atherosclerotic disease by way of coronary artery disease, peripheral vascular disease or cerebrovascular disease.
- Patients with age below 12 years.
- Disease duration less than 5 years.
- Features of other non-RA rheumatic diseases.
- History of smoking or alcoholism.
- Patients not willing to participate in the study.

Study procedure

Written and informed consent were obtained from both cases and controls prior to study enrollment. All the participants were subjected to clinical evaluation in the form of a detailed history and physical examination. The routine baseline laboratory investigations were carried out in all the subjects (both cases and controls) and included haemoglobin, total and differential white cell counts, platelets, ESR, blood glucose, liver and kidney function tests, serum lipid profile, Electrocardiogram (ECG), chest X-ray, urine analysis, C-reactive protein (CRP), rheumatoid factor and anti CCP antibody. Plain radiographs of the hands and wrists were also taken.

For measurement of CIMT - B-mode ultra sonography (USG) scan using a 7.5 MHz probe of the Toshiba Xario 200 scanner was used and a colour Doppler scan was used whenever required to visualize plaques, plaque ulceration and lumen stenosis. All subjects (including controls) underwent carotid sonography and carotid artery Doppler. The common carotid arteries were examined bilaterally up to the bifurcation. The intima media thickness, plaque characterisation (including echo texture, calcification, and cavitations) were noted – initially by gray scale 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.

All subjects included in the study were evaluated for their disease activity using Disease Activity Score[23], DAS 28 = 0.56,TJC + 0.28/SJC + 0.70 (logESR) + 0.014 GH, where, TJC is tender joint count, SJC is swollen joint count and GH is general health status as assessed by patient on visual analogue scale (VAS).

Statistical analysis

Data were recorded on a pre-designed proforma and managed using Microsoft Excel 2013 (Microsoft Corp). Descriptive statistics for the categorical variables were performed by computing the frequencies (percentages) in each category. For the quantitative variables, approximate normality of the distribution was assessed. Variables following normal distribution were summarized by mean and standard deviation. The association between two categorical variables was evaluated by Chi-square test or Fisher’s exact test as appropriate. Student’s ‘t’-test was used to compare the difference in mean values between the two groups for continuous variables that were normally distributed.

Results

1. Demographic profile
   a. Age
   The mean age of each group was comparable. (Cases 48.0 ± 14.4 and controls 48.6 ± 14.0)
   b. Gender
   There was female preponderance in the study group, with female: male ratio being 2.4:1.

2. Biochemical parameters
   a. Atherogenic Predisposition
   Both the groups were compared for various atherogenic biochemical risk indices and were comparable for the mean values of body mass index (BMI), systolic and diastolic blood pressure, random blood sugar, and lipid profile as shown in Table. 1.
   b. CRP
   The RA group had a significant elevation of CRP (>10 mg/dl) as compared to control group. (88% vs 15%)
3. Carotid intima media thickness (CIMT): Case vs. Control

The mean CIMT of the RA group was 0.86mm ± 0.18mm and that of control group was 0.53mm ± 0.15mm which was statistically significant (p<0.0001).

4. Relationship of intima media thickness with activity of RA

Based on DAS 28 i.e., disease activity score, group A (2.6 - 3.1); group B (> 3.2 to 5.1) and group C (> 5.1), disease activity correlated positively with increase in CIMT (Figure. 1 and Table. 2).

5. Comparison of the plaque positive with the plaque negative group

Carotid plaque was found more frequently among the cases (n=14 and 41%) compared with controls (n=6 and 17.6%). Of the sixty eight subjects, there was evidence of plaque in fourteen subjects. The CIMT was higher in plaque-positive group as compared to plaque-negative group in the RA group (0.90 ± 0.14 vs 0.82 ± 0.14) and it is statistically significant (p value<0.001). The CIMT was higher in plaque-positive group as compared to plaque-negative group in the control group (0.59 ± 0.09vs 0.48 ± 0.12) and it is also statistically significant (p value<0.001) (Table. 3).

Discussion

Rheumatoid arthritis (RA) is associated with increased cardiovascular morbidity and mortality predominantly due to accelerated and premature atherosclerosis[3]. Thus both men and women with RA are twice as likely to suffer from myocardial infarction as compared to general population [4]. The overall life expectancy in RA is significantly reduced, with standardized mortality rates ranging from 1.28 to 3.0 [5]. There is an independent association of RA and preclinical and overt cardiovascular disease and most of the time it is silent with an unfavourable outcome [6]. Another very important recent finding is the increased prevalence of heart failure with preserved ejection fraction with a lack of typical symptoms of heart failure in RA patients compared to non RA patients [7]. In this study Davis et al. found an increased incidence of diastolic dysfunction and a 1.9 fold increased mortality.

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 [8]. These circulating inflammatory cytokines causes repeated, continuous insults to the endothelial lining of the arteries, and this theory holds true for earliest event in atherogenesis by the “Response to Injury theory”. These circulating cytokines alter the function of distant tissues, including adipose tissue, skeletal muscle, liver etc. which can lead to dyslipidemia.

Accelerated atherosclerosis has been reported in RA to be independent of traditional risk factors. In the present study, diabetes mellitus, hypertension, and smoking were excluded from the study group, while the mean values of triglyceride, cholesterol, HDL, LDL, and VLDL were within normal range and were comparable between the RA and the control group, thus our study was free of the effects of these traditional risk factors and a selection bias for accelerated atherosclerosis. Studies by Chung et al. [9] and Mahajan et al. [10] did not find significantly correlated dyslipidaemia with accelerated atherosclerosis in RA patients, although Jonsson et al. [11] and Roman et al. [12] did show a correlation with dyslipidaemia. Moradet et al. showed decreased levels of HDL in women with RA [13].

According to Homa et al., the intima media thickness of the 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) [14]. The mean age of the present study (including control group) was 48.4 years. So the expected common carotid thickness was approximately 0.548 mm. In the present study, common carotid intima media thickness

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case (n=34)</th>
<th>Control (n=34)</th>
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<tr>
<td>Age (years)</td>
<td>48.0 ± 14.4</td>
<td>48.6 ± 14.0</td>
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<tr>
<td>Blood sugar (mg%)</td>
<td>95.7 ± 10.6</td>
<td>94.6 ± 9.2</td>
</tr>
<tr>
<td>Triglycerides (mg%)</td>
<td>127.7 ± 108.3</td>
<td>125.40 ± 103.0</td>
</tr>
<tr>
<td>Cholesterol (mg%)</td>
<td>176.7 ± 79.3</td>
<td>177.4 ± 74.2</td>
</tr>
<tr>
<td>HDL (mg%)</td>
<td>44.2 ± 16.1</td>
<td>46.1 ± 18.7</td>
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<tr>
<td>LDL (mg%)</td>
<td>112.6 ± 54.8</td>
<td>109.3 ± 56.8</td>
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<tr>
<td>SBP (mmHg)</td>
<td>124.8 ± 22.4</td>
<td>122.6 ± 20.1</td>
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<tr>
<td>DBP (mmHg)</td>
<td>79.4 ± 15.4</td>
<td>78.0 ± 14.2</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>22.8 ± 8.5</td>
<td>22.3 ± 9.4</td>
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</table>

<table>
<thead>
<tr>
<th>DAS 28</th>
<th>No. of case</th>
<th>Mean CIMT (mm)</th>
</tr>
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<tbody>
<tr>
<td>Group A (2.6 – 3.2)</td>
<td>8</td>
<td>0.78 ± 0.10</td>
</tr>
<tr>
<td>Group B (3.2 – 5.1)</td>
<td>16</td>
<td>0.84 ± 0.15</td>
</tr>
<tr>
<td>Group C (&gt;5.1)</td>
<td>10</td>
<td>0.92 ± 0.12</td>
</tr>
</tbody>
</table>

Table 1. Showing various atherogenic biochemical risk factors in case and control group.

Table 2. Showing correlation of DAS 28 severity score with CIMT.

Figure 1. Showing correlation of DAS 28 severity score with CIMT.
(CCIMT) in the control group was 0.534 ± 0.15 mm (almost
nearing the Homa equation) whereas the common carotid
intima media thickness in RA was higher, i.e. 0.862 ± 0.18
mm with p value of <0.001. A similar observation has also
been shown by Gonzalez et al. [15] and Alkabbi et al. [16]
in their respective studies. In an Indian study, Mahajan et al. have
shown similar observations [10]. All the studies (including the
present study) show a significantly higher value of CIMT in
RA subjects than the normal population (i.e., non-invasive
evidence of accelerated atherosclerosis).

The mean values of the common carotid IMT for mild, moderate
and severe activity sub-groups were 0.78 ± 0.10; 0.84 ± 0.15 and
0.92 ± 0.12 mm respectively; these values when compared with
each other were found to be statistically significant, suggesting
a correlation between disease activity at a particular time and
CIMT. However contradictory observations have been presented
by Jonsson et al. [11] and Roman et al. [12].

In the present study, when patients with plaque and those without
plaque were compared for variables such as demographic data,
disease activity, and traditional risk factors, CIMT was found to
have a significant association with plaque development (p value
< 0.001). Various studies have also shown an increased incidence
of plaque, especially normalised for age, and carotid intima
media thickness. [10,11,15,17] The presence of carotid plaque is
indicative of increased risk of atherosclerosis and cardiovascular
disease which may signify the need for more aggressive risk-
reduction interventions.

CIMT has been recommended to screen for heart disease
in normals. It is recommended as a surrogate end-point for
evaluating the regression and/or progression of atherosclerotic
vascular disease and as a predictor of the presence
of coronary atherosclerosis. Other surrogate markers of
vascular disease include flow-mediated dilatation. However, CIMT is a more appropriate tool for detecting structural
atherosclerotic disease. It has been observed that a correlation
between flow-mediated dilatation and CIMT may not be evident
in recent onset RA. A disease duration longer than seven years
was required to establish a correlation between flow-mediated
dilatation and morphological abnormalities expressed by
carotid ultrasound. CIMT also offers the advantage of wide
availability in developing countries such as India, low cost,
relative comfort and convenience for the patient as it is a non-
invasive investigation.

There are numerous evidence based studies highlighting
the cardio-protective effects of DMARDs particularly
methotrexate and biologics. Choi et al, have demonstrated that
methotrexate-treated patients had a 70% reduction in CV
mortality compared with those who did not receive a DMARD
[21]. However, the role of corticosteroids, COXIBs and most
NSAIDS remains controversial.

One of the limitations of our study was that it is cross sectional, we
would like to follow up these patients over a period of time to look
for clinical events such as myocardial infarction, cerebrovascular
accidents etc. Another drawback was our inability to comment
on the influence of drugs on atherosclerosis prevention.

<table>
<thead>
<tr>
<th>Number</th>
<th>CIMT (mm)</th>
<th>Number</th>
<th>CIMT (mm)</th>
</tr>
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<tbody>
<tr>
<td>Present</td>
<td>14 0.90 ± 0.14</td>
<td>6 0.59 ± 0.09</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>20 0.82 ± 0.14</td>
<td>28 0.48 ± 0.12</td>
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</table>

**Table 3.** Showing a comparison of the plaque positive with the plaque negative group and its correlation with CIMT.

**Conclusion**

We conclude that Rheumatoid Arthritis, which is 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
such as diabetes mellitus, hypertension & dyslipidemia. CIMT
measurement was found to be a safe, inexpensive, reproducible,
and repeatable strategy for detecting subclinical atherosclerosis.
We suggest that physicians should regularly screen the diagnosed
RA patients so as to identify the evidence of atherosclerosis
and target therapies 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 cardic
disease. It is attractive to consider the application of secondary
prevention guidelines to patients with RA. The treatment of the
underlying disease process, i.e., atherosclerosis, and preventing
its acute complications simultaneously present an enormous
challenge and opportunity.

**Conflicts of interest:**

The authors declare no conflict of interests.

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The authors state that they abide by the “Requirements for Ethical
Publishing in Biomedical Journals” [24].

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