Section: Medicine

Original Research Article

STUDY OF SUBCLINICAL ATHEROSCLEROSIS BY MEASURING CAROTID INTIMA MEDIA THICKNESS IN PATIENTS OF RHEUMATOID ARTHRITIS IN A TERTIARY CARE CENTRE

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease manifesting as systemic and synovial joint inflammation. RA is a significant global burden as it leads to progressive joint damage and disability. Furthermore, due to systemic inflammation, there exists a significant relation between RA and subclinical atherosclerosis resulting in heightened cardiovascular risk. A critical aspect is role of RA in the development of subclinical atherosclerosis which serves as a precursor to more severe cardiovascular events including myocardial infarction and stroke. Hence this study has been conducted to establish relationship between these two factors which is otherwise scarcely documented. The aim is to establish relation between rheumatoid arthritis (RA) and subclinical atherosclerosis by measuring bilateral carotid intima-media thickness (CIMT). **Materials and Methods:** This is an observational, single-centre study and was conducted at the outpatient department/ ward / emergency wing of Department of Medicine, ESI-PGIMSR, Basaidarapur, New Delhi. This study included patients aged 18 to 60 years with a confirmed diagnosis of rheumatoid arthritis, based on the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria, who visited hospital between July 2022 and December 2023. Assuming an atherosclerosis prevalence of 10%, the sample size calculation was based on a 95% confidence level (Z = 1.96) and a margin of error of 5% (ME). Relevant data was collected which included demographic data, laboratory findings, disease states, and cardiovascular assessments. Clinical assessments of patients were done. Bilateral carotid intima-media thickness (CIMT) measurements were done in all patients along with other parameters such as anti-cyclic citrullinated peptide (anti-CCP) antibody levels and C-reactive protein (CRP) level. Statistical analyses employed were chi-square tests, Spearman correlation, Kruskal-Wallis tests, Wilcoxon-Mann-Whitney U tests, and Student's t-tests, with a p-value of <0.05 considered statistically significant. **Result:** The mean age of patients with CIMT <1 mm was 38.54 years, while for the CIMT >1 mm group, the mean age was 53.17 years. Patients with a CIMT ≥ 1 mm had a significantly longer duration of disease, longer durations of morning stiffness, and higher values of tender joint count (TJC) and swollen joint count (SJC) ($p<0.05$). Patients with mild to moderate DAS28 demonstrated a higher percentage of patients with CIMT less than 1mm. Conversely, those with moderate to high DAS-28 showed CIMT higher than 1mm ($p=0.046$). **Conclusion:** The study suggests a potential association between CIMT and RA disease severity as assessed by DAS-28. The patients with less than 1 mm CIMT belonged to mild and moderate R. A. While greater than 1 mm belonged to moderate and high RA. A positive correlation was also observed between SJC, TJC, and duration of morning stiffness, indicating a role of RA associated inflammation in the progression of CIMT.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease manifesting as systemic and synovial joint inflammation and is a significant global burden as it leads to progressive joint damage and disability. As per the reports of Global Burden of Diseases (GBD), approximately 18 million cases of RA were documented in 2019, primarily affecting the elderly population aged over 55 years.[1]

RA is known for its effects on the musculoskeletal system, however, it is increasingly recognized, that a systemic inflammation occurs that correlates with a heightened risk of cardiovascular disease (CVD).[2] A critical aspect of the associated cardiovascular risk in RA is its role in the development of subclinical atherosclerosis, which serves as a precursor to more severe cardiovascular events, including myocardial infarction and stroke. Progression of RA involves persistent inflammation damaging articular cartilage and bone, which exerts indirect effects on the vascular system. Recent literature indicates that RA-associated inflammation is not limited to joint tissues but has systemic effects such as promoting endothelial dysfunction and atherosclerosis.[3] This suggests the potential role of RA in increasing cardiovascular risks.

Notably, great advancements have been made in the diagnostic techniques and management strategies for RA, translating to improved patient outcomes and CVD risks. Diagnosis of RA requires an integrated approach combining clinical evaluation, laboratory analyses, and imaging techniques. Key diagnostic indicators are joint swelling, pain, and stiffness, in addition to the elevation of serum markers, such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. New-generation imaging modalities, such as ultrasound and magnetic resonance imaging (MRI) further assess the disease activity and joint damage with high precision.[4]

Effective management of RA focuses on reducing inflammation, preserving joint function, and improving quality of life using a multidisciplinary strategy. Pharmacological therapy with disease-modifying antirheumatic drugs (DMARDs) has revolutionized the treatment of RA, with methotrexate being the mainstay therapy. Furthermore, bioactive compounds that target specific inflammatory pathways are supplemented with DMARDs. Non-pharmacological interventions include physical therapy and lifestyle changes, which are crucial to managing RA.

While significant advances are made in understanding the cardiovascular risks associated with RA, the specific relationship between RA and subclinical atherosclerosis remains scarcely documented. To address this research gap, the present study aims to determine whether RA increases the risk of subclinical atherosclerosis, measured using bilateral carotid intima-media thickness (CIMT). By providing real-world evidence, the objective of the study is to expand current knowledge of cardiovascular disease in RA patients, supporting efforts for timely detection and targeted intervention strategies.

MATERIALS AND METHODS

The present study was an observational single-center study done from July 2022 to December 2023 with patients visiting the Rheumatology Clinic /ward/emergency of the Department of Medicine at ESI-PGIMSR, Basaidarapur, who were diagnosed with rheumatoid arthritis. The patients were included in the study after taking due clearance from ethical committee and scientific committee of ESI PGIMSR Basaidarapur Delhi. The study posed no risk to the participants. Signed informed consent were obtained from each patient after providing a thorough understanding of the study. Data confidentiality was maintained throughout the study, with data access available only to authorized personnel.

Inclusion Criteria

Adult patients aged between 18 and 60 years, and Diagnosis of rheumatoid arthritis according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria.[5]

Exclusion Criteria

Patients with diabetes mellitus, hypertension, dyslipidemia, or a history of smoking were excluded as these conditions are risk factors for atherosclerosis.

Sample size calculation: Based on an assumed atherosclerosis prevalence of 10%, the sample size calculation employed a confidence level of 95% (Z = 1.96) and a margin of error of 5% (ME). The calculation formula was as follows: N = Z2 (P(1-P)) / (ME)^2 whereN represents the sample size, Z is the Z-score corresponding to the confidence level, P is the estimated prevalence of atherosclerosis, and ME is the margin of error. Using these values, the minimum required sample size for this study was determined to be 140 participants.

Study procedure: The patients were taken detailed history of presenting complaints in chronological order, specific past history, known comorbidities, personal history, medication history, family history. A ssdetailed general and systematic examination was done . Specific laboratory investigations were also done. The complaints were addressed according to the duration of RA, presence or absence of morning stiffness. The diseased state of RA was determined after the systemic examination of all joints to assess RA activity, including tender joint counts (TJC) and swollen joint counts (SJC). A simplified 28-joint articular index was employed to assess disease activity. The joints covered under this index were 10 proximal interphalangeal joints, 10 metacarpophalangeal joints, and wrist, elbow, shoulder, and knee joints on both, the left and right sides. Disease severity was measured using the DAS-28 score.

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Several laboratory parameters were assessed. Blood pressure, random blood sugar, and serum lipid profile were measured. Erythrocyte sedimentation rate (ESR) was evaluated using the Westergren method, and rheumatoid factor was assessed with a quantitative latex fixation laboratory kit. The levels of anti-cyclic citrullinated peptide (anti-CCP) antibodies and C-reactive protein (CRP) were measured. Routine investigations included complete blood count with hemoglobin, blood urea, serum creatinine, liver and kidney function tests, and serum electrolytes.

CIMT was measured under controlled conditions to ensure accuracy, in a dimly lit room with a temperature maintained between 22 to 25°C. Patients were positioned supine with their necks extended in the end-of-heading position. Electrocardiogram (ECG) electrodes were applied for heart cycle monitoring. The head was positioned at a 45–50-degree angle to the left or right, and a 10 MHz linear ultrasound transducer with a frequency range of 5 to 15 MHz was used. A minimum refresh rate of 25 Hz was set, with a gain of 30 set at approximately 60 dB. Sequential recording of 3-4 heart cycles was conducted to allow optimal visualization of the double-line pattern of the carotid artery along the near and far walls of the common carotid artery (CCA).

A minimum of three longitudinal-axis images were obtained per patient, to ensure accurate image capture. Vertical dip of ultrasound rays, with a focus on the artery horizontally was considered optimal for capturing end-diastolic images. The internal carotid artery (ICA) and external carotid arteries (ECA) were distinguished using pulse-wave Doppler, documenting the vessel diameter and any plaque formation. The ICA was identified by its larger caliber and absence of extracranial branches, contrasting with the ECA, which may display branches similar to the superior thyroid artery.

Statistical analysis: Study investigators documented the data for all the patients within an MS Excel spreadsheet.

Variables were compared between patients with CIMT <1 mm and ≥ 1 mm. Data analysis was subsequently performed using the Statistical package for Social Sciences (SPSS) software. Descriptive statistics were used for demographic, clinical, and radiographic findings. Categorical variables were presented as frequency and percentage, whereas continuous variables were represented using mean and standard deviations. Statistical tests performed included the chisquare test, Spearman Correlation, Kruskal Wallis Test, Wilcoxon-Mann-Whitney U Test, and student t-test, with a p-value of less than 0.05 considered statistically significant.

RESULTS

Patient demographics and baseline characteristics

A total of 140 participants were enrolled in the present study. Women (n=101) accounted for a significant proportion of the sample compared to men (n=39), highlighting a higher prevalence of RA in females. The mean age of the population was 41.67 ± 10.38. The study population was categorized based on the CIMT into two groups, <1 mm and ≥1 mm. Laboratory findings for these two groups are outlined in [Table 1]. A significant difference between the two groups was observed in several parameters including age, duration of disease, duration of morning stiffness, TJC, SJC, CRP, and DAS-28.

Association between CIMT and other parameters.

[Table 2] for DAS and CIMT describes the association between the various parameters and CIMT. The mean age of patients with CIMT <1 mm was 38.54 years, while for the CIMT >1 mm group, the mean age was 53.17 years [Figure 1]. This demonstrates age as a significant predictor of CIMT in RA patients, with increasing thickness in the elderly population. The number of patients with CIMT ≥1 mm was lowest in the age groups 20-39 (n=0), while it was highest for patients aged 50-59 (n=14) years. The strength of association between the two variables using bias-corrected Cramer's V was 0.56 indicating high association.

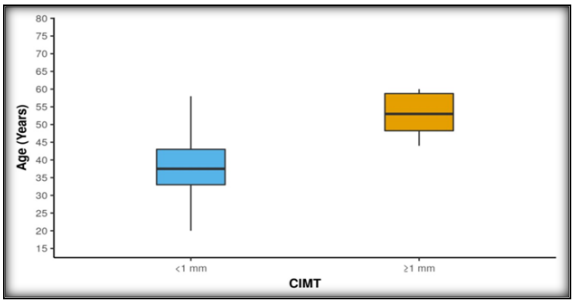

Figure 1: Association between age and CIMT

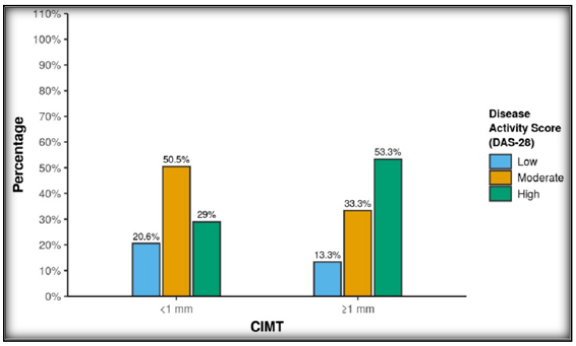

Figure 2: Association between CIMT and Disease Activity Score (DAS-28)

There was no significant difference between the various groups in terms of the distribution of gender (p = 0.279). The strength of association between the two variables using bias-corrected Cramer's V was 0.03 indicating little to no association.

Patients with a CIMT ≥ 1 mm had a significantly longer duration of disease compared to those with a CIMT < 1 mm, 6.43 ± 2.13 and 4.78 ± 2.02 years respectively. Moderate strength of association is observed between CIMT and disease duration (Point-Biserial Correlation = 0.32).

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Participants with a CIMT ≥ 1 mm experienced significantly longer durations of morning stiffness compared to those with a CIMT < 1 mm with a mean duration of 1.78 and 1.48 hours respectively. The strength of association between CIMT and duration of morning stiffness was low (point-biserial correlation = 0.22).

The mean (SD) TJC in the CIMT <1 mm group was 9.53 (5.32), while in the CIMT ≥1 mm group it was 15.00 (5.84). This difference was statistically significant (p<0.001). The strength of the association between CIMT and TJC was moderate (Point-Biserial Correlation = 0.38).

Patients with mild to moderate DAS-28 demonstrated a higher percentage of patients with CIMT less than 1mm. Conversely, those with moderate to high DAS-28 showed CIMT higher than 1mm (Figure 2). This difference was statistically significant (p=0.046). However, the strength of association between the two variables was low (Cramer's V = 0.21).

Table 1: Association of CIMT with Age, Gender, Duration of Disease and ESR, CRP.

Parameters		**CIMT**	
	<1 mm (n = 110)	**≥1 mm (n = 30)**	**p-value**
Age (Years)***	38.54 ± 9.14	53.17 ± 5.31	<0.00111
Age***			<0.0012
20-29 Years	17 (15.5%)	0 (0.0%)	
30-39 Years	47 (42.7%)	0 (0.0%)	
40-49 Years	32 (29.1%)	11 (36.7%)	
50-59 Years	9 (8.2%)	14 (46.7%)	
60-69 Years	5 (4.5%)	5 (16.7%)	
Gender			0.27933
Male	33 (30.0%)	6 (20.0%)	
Female	77 (70.0%)	24 (80.0%)	
Duration Of Disease (Years)***	4.78 ± 2.02	6.43 ± 2.13	<0.00113
Duration of Morning Stiffness (Hours)***	1.48 ± 0.58	1.78 ± 0.54	0.00311
TJC***	9.53 ± 5.32	15.00 ± 5.84	<0.00111
SJC***	6.22 ± 4.18	9.00 ± 4.98	0.00211
ESR (mm/Hr)	41.05 ± 12.48	40.43 ± 11.36	0.94911
CRP (mg/L)***	1.11 ± 0.64	1.44 ± 0.50	<0.00111
Anti-CCP (Positive)	110 (100.0%)	30 (100.0%)	1.00033
RF (Positive)	110 (100.0%)	30 (100.0%)	1.00033
Mean CIMT (mm)***	0.65 ± 0.11	1.18 ± 0.06	<0.00111

***Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: Fisher's Exact Test, 3: ChiSquared Test

Table 2: Statistically significant association between CIMT and DAS

	Disease Activity Score (DAS-28)			**Chi-Squared Test (χ^2)**	**P Value**
Low	22 (20.6%)	4 (13.3%)	26 (19.0%)	6.171	0.046
Moderate	54 (50.5%)	10 (33.3%)	64 (46.7%)		
High	31 (29.0%)	16 (53.3%)	47 (34.3%)		
	SJC			Wilcoxon-Mann-Whitney U Test (W)	P Value
Duration Of Disease (Years)				Wilcoxon-Mann-Whitney U Test (W)	P Value
Mean (SD)	4.78 (2.02)	6.43 (2.13)		923.500	<0.001
Median (IQR)	5 (3-6)	6.5 (5-8)			
Min-Max	0-10	1-10			
Duration of Morning Stiffness (Hours)				Wilcoxon-Mann-Whitney U Test (W)	P Value
Mean (SD)	1.48 (0.58)	1.78 (0.54)		1095.000	0.002
Median (IQR)	1.5 (1-2)	2 (1.5-2)			
Min-Max	0.5-3	1-3			
TJC				Wilcoxon-Mann-Whitney U Test (W)	P Value
Mean (SD)	9.53 (5.32)	15.00 (5.84)		806.000	<0.001
Median (IQR)	8 (6-12)	16 (8.5-20)			
Min-Max	2-26	4-26			

DISCUSSION

The study investigated subclinical atherosclerosis in RA patients by determining the association between CIMT and various clinical parameters. The results revealed that older age, longer disease duration, and higher disease activity were significantly associated with increased CIMT. Furthermore, a positive correlation was found between CIMT and symptoms of RA, such as TJC and SJC. These findings suggest that the severity of the disease and advanced age in RA patients can be predictors of atherosclerosis and cardiovascular risks. Therefore, it is crucial to monitor cardiac health and implement preventive strategies in RA patients who are at risk, to mitigate future cardiovascular complications.

The present study observed a significantly higher proportion of females with RA compared to males, indicating a higher risk of developing RA in women. This finding is in accordance with previous studies.

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According to data from epidemiological studies, RA affects approximately 12% of individuals worldwide, with women exhibiting a two to three times higher risk of developing RA compared to men.[6] Furthermore, genome-wide association studies (GWAS) have identified multiple genetic variants associated with increased RA risk, with certain variants showing gender-specific activity.[7]

Several biological factors have been proposed to explain the higher prevalence of RA in females, which include hormonal and genetic influences. Estrogen, a hormone present in higher quantity in females, has been indicated in the regulation of immune activity and inflammatory pathways that contribute to RA pathogenesis.[8] The gender disproportionate in RA prevalence has significant implications for clinical and research domains. Clinicians are recommended to recognize the increased RA burden in female patients and provide customized treatments, taking into account potential differences in disease expression, progression, and response to treatment between genders.[9] While the present study does not observe a significant impact of gender in increasing CIMT, RA-associated CVD risk is higher in females as they contribute majorly to the RA patient population.

In this study, age emerged as a significant factor influencing CIMT. This is consistent with existing literature. Smith et al. (2020) identified a significant association between age and CIMT, with elderly patients reporting a higher CIMT value than the younger group.[10] Similarly, Garcia et al. (2020) conducted a longitudinal study, which found that advanced age at baseline was predictive of greater CIMT progression over time, further supporting the association between age and CIMT progression.[11] Various studies have documented contrasting findings. Chen et al. (2019), performed a large-scale population-based study. Their study did not observe a significant age-related difference in CIMT, indicating that other factors influence CIMT outcomes including genetic susceptibility or ethnicity.[12] Additionally, Johnson et al. (2017) reported contradictory findings on the relationship between age and CIMT, underscoring the need to further investigate the complex interplay between age and cardiovascular risk.

This study highlights the role of advanced age in increasing cardiovascular risk factors, suggesting age as a predictor of high CIMT in elderly patients. It strongly indicates that elderly patients with RA are at a higher risk for increased CIMT, which can eventually contribute to CVD. However, contrasting data from previous investigations necessitate the need for highquality studies to understand the underlying biological mechanisms linking age, inflammation in RA, and CIMT. In clinical practice, recognizing the association between age and CIMT could enhance cardiovascular risk stratification in RA patients. RA healthcare providers are advised to assess the heightened risk for atherosclerotic changes in older RA patients and consider incorporating CIMT evaluations into their risk assessment strategies.

A moderate positive correlation between SJC and CIMT was observed. This result is in alignment with the longitudinal study performed by Jones et al. (2020), which identified a similar positive correlation between joint inflammatory markers and CIMT, highlighting the role of inflammation in the progression of CVD.[13] Conversely, findings from a cross-sectional study reported no significant association between joint inflammation markers and CIMT.[14] Overall, there does not exist a strong correlation between pro-inflammatory markers and CVD risk. Additionally, research must focus on determining the extent of association taking into account possible confounding variables such as medication usage and disease severity.

A significant association was documented between the duration of morning stiffness and CIMT. In alignment with these findings, a longitudinal study by Lee et al. (2018) reported a significant correlation between morning stiffness duration and subclinical atherosclerosis, highlighting the relevance of rheumatologic symptoms in cardiovascular risk assessment.[15] Contradictory results were reported by Johnson et al. (2020), who found no significant correlation between morning stiffness and CIMT in a population-based study.[16] The contrasting findings of the present study and existing literature warrant further investigation into the underlying pathways guiding CIMT increase with the increase in rheumatologic symptoms.

A medium effect size was observed between the number of SJC and CIMT. Yang et al. (2019) reported similar results, finding a significant correlation between SJC and CIMT in a crosssectional study.[17] Their study emphasized the role of joint inflammation in cardiovascular risk assessment in rheumatologic conditions. Conversely, Park et al. (2020) found no significant correlation between SJC and CIMT. Unambiguous results pertaining to the impact of SJC and CIMT require further research.[18] Nonetheless, high SJC has potential predictive value for subclinical atherosclerosis risk. A deeper understanding of the role of SJC and the pathogenesis of CIMT can improve risk stratification and ensure timely management and prevention strategies.

TJC, SJC, and morning stiffness, all showed a positive correlation with the development of atherosclerosis. These parameters can be considered as indirect indicators of RA. Higher values of these parameters represent an advanced disease stage. Therefore, the association of these parameters with CIMT is a novel finding providing evidence for the increase in subclinical atherosclerosis with the progression of RA and inflammation. Therefore, clinicians are advised to consider these markers alongside traditional cardiovascular risk factors when evaluating cardiovascular health in RA patients.

DAS-28 was positively correlated with the CIMT with a moderate association. A higher score was

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associated with a higher proportion of patients with CIMT greater than 1mm. A crosssectional observational study reported no correlation between DAS-28 and the values of CIMT.[19] Similarly, two independent studies by Kolarz et al. (2003) and Ozisler et al. (2019) reported no significant difference in the CIMT in patients with varying levels of RA severity as assessed by DAS-28.[20,21]

Limitations

limitations of the study must be considered. First, the observational design of this study potentially impacts the results due to confounding variables. Second, as a single-center study, the sample population is majorly enrolled from a similar geographical area, which limits the generalizability of the results and introduces selection bias. Third, the present study did not account for the potential influences of medication use or lifestyle factors, such as diet, physical activity, and smoking, which are recognized as significant contributors to cardiovascular risk.

CONCLUSION

The study suggests a potential association between CIMT(carotid intima media thickness) and RA(Rheumatoid arthritis) disease severity as assessed by DAS-28(Disease activity score), with patients reporting less than 1 mm CIMT had mild to moderate RA disease while greater than 1 mm CIMT had moderate to high RA disease. Hence it is prudent to mention that a positive correlation exists between RA severity and CIMT. A strong correlation between SJC, TJC, and duration of morning stiffness, do exist with RA disease activity that hints towards the role of RA associated inflammation in the progression of CIMT. So every patient of RA should be evaluated for development of sub clinical atherosclerosis as a predictor of cardiovascular disease.

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