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Original Research Article

Carotid Intima-Media Thickness (CIMT): A Marker for Subclinical Atherosclerosis in Rheumatoid Arthritis Patients

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ABSTRACT

Background and Aims: Rheumatoid arthritis (RA) is a systemic inflammatory condition associated with accelerated atherosclerosis. This study aimed to evaluate carotid intima-media thickness (CIMT) as a marker for subclinical atherosclerosis in RA patients compared to healthy controls.

Materials and Methods: This case-control study was conducted at the Department of Rheumatology, Government Rajaji Hospital, Madurai, involving 40 RA patients and 40 healthy controls. RA patients were diagnosed using the 2010 ACR-EULAR criteria. CIMT was measured bilaterally using carotid ultrasonography. Statistical analysis was performed to assess correlations between CIMT and clinical variables such as age, disease duration, and lipid profiles.

Results: Mean CIMT values were significantly higher in RA patients (right: 0.665 ± 0.0634 mm; left: 0.664 ± 0.0698 mm) compared to controls (right: 0.597 ± 0.0602 mm; left: 0.602 ± 0.0627 mm; $P < 0.001$). CIMT positively correlated with age ($r = 0.753$, $P < 0.001$) and disease duration ($r = 0.663$, $P < 0.001$), indicating its utility in assessing atherosclerotic risk.

Conclusion: CIMT is a reliable, non-invasive marker for subclinical atherosclerosis in RA patients, emphasizing the need for early cardiovascular risk assessment in this population.

Keywords: Carotid Intima-Media Thickness, Rheumatoid Arthritis, Subclinical Atherosclerosis, Cardiovascular Risk, Disease Activity Score (DAS28), Ultrasonography.

INTRODUCTION

Rheumatoid arthritis (RA), a chronic systemic autoimmune disease, predominantly targets synovial joints, leading to progressive inflammation, joint destruction, and deformity. Beyond the well-documented musculoskeletal complications, RA significantly contributes to increased morbidity and mortality through its strong association with cardiovascular diseases (CVDs) [1]. Emerging evidence highlights that patients with RA are at a heightened risk of accelerated atherosclerosis, often referred to as “subclinical atherosclerosis,” which remains asymptomatic in its early stages but poses a considerable threat to long-term cardiovascular health [1].

Atherosclerosis, a progressive inflammatory disease of the arterial wall, involves the accumulation of lipids, fibrous elements, and immune cells, culminating in plaque formation and arterial narrowing [2]. In RA, chronic systemic inflammation acts as a key driver of atherosclerosis, amplifying endothelial dysfunction, oxidative stress, and dyslipidemia. This link between RA and atherosclerosis highlights the necessity of early detection and intervention strategies to mitigate cardiovascular risks in RA patients [3].

Carotid intima-media thickness (CIMT), a non-invasive surrogate marker of atherosclerosis, has emerged as a valuable tool for detecting early vascular changes. Measured via high-resolution B-mode ultrasonography, CIMT assesses the thickness of the intima and media layers of the carotid artery wall [4]. It reflects not only structural changes in the vessel but also provides insights into the cumulative effects of risk factors such as

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hypertension, diabetes, dyslipidemia, and chronic inflammation. Importantly, CIMT has demonstrated robust predictive value for future cardiovascular events in both general and high-risk populations, making it a pivotal parameter in cardiovascular risk stratification [5].

In the context of RA, elevated CIMT has been consistently observed in comparison to age- and sex-matched healthy controls. This finding highlights the interplay between chronic systemic inflammation and endothelial damage, which accelerates vascular aging in RA patients. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) not only perpetuate synovial inflammation but also contribute to endothelial dysfunction, arterial stiffness, and lipid metabolism disturbances. The culmination of these processes manifests as increased CIMT, providing a tangible link between RA and subclinical atherosclerosis [6].

The significance of CIMT extends beyond its diagnostic utility. As a marker of cardiovascular risk, it offers an opportunity to monitor disease progression and therapeutic response in RA. For instance, studies have demonstrated that effective disease-modifying antirheumatic drugs (DMARDs) and biologics, such as TNF inhibitors, not only reduce joint inflammation but also attenuate CIMT progression. Thus, CIMT serves as both a biomarker of vascular health and a potential indicator of systemic disease control in RA [7].

Despite its clinical relevance, the routine assessment of CIMT in RA remains underutilized, partly due to the lack of consensus on standardized measurement protocols and cut-off values for risk stratification. Additionally, CIMT measurements can be influenced by age, sex, ethnicity, and traditional cardiovascular risk factors, necessitating careful interpretation within the clinical context of RA [8].

The present study aims to address this critical gap by investigating the correlation between CIMT and the progression of atherosclerosis in patients with RA. By elucidating the relationship between chronic systemic inflammation and vascular health, this study seeks to enhance the understanding of cardiovascular risk in RA and pave the way for early detection and intervention. The growing recognition of cardiovascular disease as a major cause of mortality in RA highlights the importance of adopting a multidisciplinary approach to patient care. Identifying reliable markers such as CIMT to detect subclinical atherosclerosis early can facilitate timely interventions, improving long-term outcomes and quality of life for patients with RA.

MATERIALS AND METHODS

Study Setting: This case-control study was conducted over six months in the Department of Rheumatology at Government Rajaji Hospital (GRH), Madurai, Tamil Nadu. The hospital serves as a tertiary care center, catering to a diverse patient population and providing an ideal setting for investigating the relationship between rheumatoid arthritis (RA) and subclinical atherosclerosis.

Study Participants: The study population included patients attending the Rheumatology Department for treatment and diagnosis, alongside healthy individuals participating in a master health check-up program.The study comprised 40 RA patients and 40 age- and sex-matched healthy controls. The RA patients were diagnosed based on the 2010 American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) criteria. Healthy controls were recruited from the hospital's master health check-up program and met the same exclusion criteria as the RA group to eliminate potential cardiovascular confounders.

The inclusion and exclusion criteria for the study ensured a homogenous population to minimize confounding variables. Inclusion criteria were RA patients diagnosed per the ACR-EULAR 2010 criteria, age range of 18 to 45 years, disease duration of more than five years, and participants without ischemic heart disease (IHD), diabetes mellitus, hypertension, or a history of cerebrovascular events. Participants were excluded if they had hypertension (blood pressure >140/90 mmHg), hypercholesterolemia (total cholesterol >240 mg/dL, LDL >160 mg/dL, triglycerides >200 mg/dL) or were on lipid-lowering therapy, diabetes mellitus, history of coronary artery disease or cerebrovascular accidents, features suggestive of non-RA diseases, history of smoking or alcohol consumption, and evidence of hepatic or renal impairment.

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Sample Size and Sampling Technique: A total of 80 participants (40 RA patients and 40 controls) were included in the study. A purposive sampling method was employed to ensure balanced representation across both groups. This approach facilitated age and sex matching while maintaining the homogeneity of the control population.

Study Tools: RA patients were assessed for disease activity using the Disease Activity Score-28 (DAS28). Carotid intima-media thickness (CIMT) was measured using gray-scale ultrasonography followed by color flow imaging. The ultrasonography was conducted by a skilled radiologist using a high-resolution ultrasound device. Patient and control data, including demographic details, clinical parameters, and radiological findings, were documented in pre-designed proforma.

Study Methodology: RA patients underwent comprehensive clinical evaluation to assess disease activity and general health. DAS28 scores were calculated to quantify RA disease severity. Both cases and controls were subjected to carotid ultrasonography for CIMT measurement.

CIMT Measurement Protocol: Bilateral common carotid arteries were examined up to 2 cm proximal to their bifurcation. The site of greatest intima-media thickness was identified, and three measurements were taken from each side at different points within the region of interest. Measurements were performed during diastole, ensuring consistency as the lumen diameter was at its smallest and IMT at its largest. The mean of six measurements (three per side) was calculated for final CIMT evaluation. This standardized approach minimized inter-observer variability and ensured reliable results. The meticulous methodology facilitated a robust comparison between the RA and control groups.

Ethical Issues: The study was conducted after getting approval from the Institutional Ethics Committee of Government Rajaji Hospital, Madurai, Tamil Nadu. Informed consent was obtained from all participants after explaining the study's purpose, procedures, and potential risks. Confidentiality of participants' data was strictly maintained throughout the study.

Statistical Analysis: The collected data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 25. Descriptive statistics such as mean and standard deviation were used to summarize demographic and clinical characteristics. The primary outcome variable, CIMT, was analyzed using unpaired Student’s t test to compare differences between the RA and control groups. Correlations between DAS28 scores and CIMT were examined using Pearson correlation coefficients. A p-value <0.05 was considered statistically significant.

RESULTS

The study evaluated the baseline characteristics of 40 rheumatoid arthritis (RA) patients (cases) and 40 healthy controls (Table 1). There were no significant differences between the two groups in terms of age, BMI, blood pressure, total cholesterol, LDL, or HDL levels. The mean age of cases was 36.03 years (SD ± 5.96) compared to 36.93 years (SD ± 5.61) in controls ($p = 0.489$). Similarly, BMI was nearly identical, with cases averaging 20.88 kg/m² (SD ± 1.81) and controls 20.93 kg/m² (SD ± 1.86; $p = 0.908$). Systolic and diastolic blood pressures were also comparable, with means of 113 mmHg (SD ± 10.67) and 71.25 mmHg in cases versus 112.75 mmHg (SD ± 10.62) and 72.00 mmHg in controls ($p = 0.917$ and 0.454, respectively).

Notably, RA cases had significantly higher erythrocyte sedimentation rate (ESR), averaging 30.55 mm in the first hour (SD ± 12.81), compared to 19.35 mm (SD ± 2.26) in controls ($p < 0.001$). Additionally, carotid intima-media thickness (CIMT) was significantly elevated in cases. The mean right CIMT was 0.665 mm (SD ± 0.0634) in cases versus 0.597 mm (SD ± 0.0602) in controls ($p < 0.001$). Left CIMT followed a similar pattern, with means of 0.664 mm (SD ± 0.0698) and 0.602 mm (SD ± 0.0627) for cases and controls, respectively ($p < 0.001$). Triglyceride levels were significantly lower in cases, with a mean of 110.9 mg/dL (SD ± 10.998) compared to 124.83 mg/dL (SD ± 7.39) in controls ($p < 0.001$). Total cholesterol, LDL, and HDL levels did not differ significantly, with means of 171.05 mg/dL, 101.13 mg/dL, and 43.63 mg/dL in cases versus 173 mg/dL, 104.75 mg/dL, and 42.9 mg/dL in controls, respectively ($p > 0.05$).

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Table 1: Baseline characteristics of the study participants

Variables	Cases Mean (SD)	Controls Mean (SD)	P value
Age (Years)	36.03 (5.96)	36.93 (5.61)	0.489
BMI (kg/m²)	20.88 (1.81)	20.93 (1.86)	0.908
Systolic Blood Pressure (mm Hg)	113 (10.67)	112.75 (10.62)	0.917
Diastolic Blood Pressure (mm Hg)	71.25	72.00	0.454
ESR (mm 1st hr)	30.55 (12.81)	19.35 (2.26)	< 0.001
CIMT (Right) (mm)	0.665 (0.0634)	0.597 (0.0602)	< 0.001
CIMT (Left) (mm)	0.664 (0.0698)	0.602 (0.0627)	< 0.001
Triglycerides (mg/dl)	110.9 (10.998)	124.83 (7.39)	< 0.001
Total Cholesterol (mg/dl)	171.05 (9.69)	173 (9.37)	0.363
LDL (mg/dl)	101.13 (9.4)	104.75 (7.62)	0.062
HDL (Mg/dl)	43.63 (3.96)	42.9 (3.36)	0.380

Correlation analysis revealed significant relationships between mean CIMT, and several RA-related variables as illustrated in Table 2. Age showed a strong positive correlation with CIMT ($r = 0.753$, $p < 0.001$). Disease duration also correlated strongly ($r = 0.663$, $p < 0.001$), indicating that prolonged disease may contribute to vascular changes. DAS28, a measure of RA activity, exhibited a moderate correlation with CIMT ($r = 0.468$, $p = 0.001$), while HDL levels showed a moderate inverse relationship ($r = 0.420$, $p = 0.001$). Other variables, such as BMI, systolic and diastolic blood pressure, ESR, triglycerides, total cholesterol, and LDL, did not exhibit significant correlations with CIMT ($p > 0.05$).

Table 2: Correlation of CIMT mean with various variables of RA cases

Correlation of CIMT mean with other variables	Correlation coefficient (r)	P value
Age (Years)	0.753	<0.001
Disease Duration (Years)	0.663	<0.001
DAS 28	0.468	0.001
BMI (kg/m²)	0.175	0.852
Systolic Blood Pressure (mm Hg)	0.262	0.660
Diastolic Blood Pressure (mm Hg)	0.171	0.902
ESR (mm 1st hr)	0.265	0.595
Triglycerides (mg/dl)	0.165	0.525
Total Cholesterol (mg/dl)	0.136	0.450
LDL (mg/dl)	0.275	0.722
HDL (Mg/dl)	0.420	0.001

DISCUSSION

The study investigated the association between rheumatoid arthritis (RA) and subclinical atherosclerosis, utilizing carotid intima-media thickness (CIMT) as a surrogate marker of cardiovascular risk. The mean CIMT, both right and left, was significantly higher in RA patients than in healthy controls, confirming the association between RA and subclinical atherosclerosis. The right CIMT was 0.665 mm (SD ± 0.0634) in RA cases compared to 0.597 mm (SD ± 0.0602) in controls, while the left CIMT was 0.664 mm (SD ± 0.0698) in cases versus 0.602 mm (SD ± 0.0627) in controls ($p < 0.001$ for both). Pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, play pivotal roles in promoting atherogenesis by enhancing lipid oxidation, vascular inflammation, and plaque formation [9].

Interestingly, our study also demonstrated a significant positive correlation between CIMT and age ($r = 0.753$, $p < 0.001$), indicating that age-related vascular changes are exacerbated in RA patients. Disease duration similarly showed a strong correlation with CIMT ($r = 0.663$, $p < 0.001$), emphasizing the cumulative impact of prolonged inflammation on vascular health. These findings highlight the importance of early diagnosis and aggressive disease management in RA to mitigate long-term cardiovascular risks [10].

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The correlation between disease activity, as measured by DAS28, and CIMT ($r = 0.468$, $p = 0.001$) highlights the role of active inflammation in driving atherosclerosis. Patients with higher DAS28 scores had greater CIMT, reflecting the systemic inflammatory burden's impact on vascular health. Anti-inflammatory therapies, such as methotrexate and biologic agents targeting cytokines, may provide dual benefits by controlling joint inflammation and reducing cardiovascular risk [11].

While the lipid profile did not differ significantly between RA cases and controls in terms of total cholesterol, LDL, and HDL levels, triglycerides were notably lower in RA patients (110.9 mg/dL vs. 124.83 mg/dL; $p < 0.001$). In our study, HDL levels showed a significant inverse correlation with CIMT ($r = 0.420$, $p = 0.001$). This finding highlights the anti-atherogenic role of HDL, which includes cholesterol efflux, anti-inflammatory effects, and endothelial protection. However, inflammation in RA may impair HDL functionality, limiting its protective effects [12].

The erythrocyte sedimentation rate (ESR) was significantly elevated in RA patients (30.55 mm in the first hour vs. 19.35 mm in controls; $p < 0.001$), reflecting systemic inflammation. While ESR did not show a significant correlation with CIMT in our study, its role as a cardiovascular risk marker in RA has been well documented. Persistently elevated ESR and C-reactive protein (CRP) levels have been associated with increased cardiovascular events in RA, emphasizing the need for routine monitoring of inflammatory markers [13].

Systolic and diastolic blood pressures were comparable between cases and controls, with no significant differences observed. However, the correlation analysis revealed no significant associations between blood pressure and CIMT. This finding may be attributed to the relatively young cohort and the exclusion of patients with overt cardiovascular disease. Despite this, hypertension remains a critical modifiable risk factor for cardiovascular disease in RA, warranting regular monitoring and management [14].

The findings of this study have several implications for clinical practice. First, the significant increase in CIMT among RA patients highlights the need for cardiovascular risk stratification in this population. Routine CIMT measurements, along with other non-invasive imaging modalities such as coronary artery calcium scoring, could aid in early detection of subclinical atherosclerosis. Second, the strong correlations between CIMT and disease activity, age, and disease duration highlight the importance of aggressive disease management. Achieving tight control of inflammation through conventional and biologic DMARDs should be prioritized to reduce both joint and cardiovascular complications [15].

The inverse correlation between HDL levels and CIMT highlights the importance of addressing lipid dysfunction in RA. Although conventional lipid-lowering therapies, such as statins, are effective in the general population, their role in RA-specific dyslipidemia requires further investigation. Emerging therapies targeting HDL functionality and inflammatory lipid pathways may offer novel avenues for reducing cardiovascular risk in RA patients[16].

The strengths of this study include the use of a well-defined cohort of RA patients and controls, as well as the comprehensive evaluation of CIMT and cardiovascular risk factors. The correlation analysis provided valuable insights into the relationships between CIMT and various disease and metabolic parameters. However, the relatively small sample size may limit the generalizability of the findings. Future research should focus on longitudinal studies to evaluate the impact of RA disease progression and treatment on cardiovascular outcomes. Investigating the role of novel biomarkers, such as myeloperoxidase and advanced glycation end-products, may provide additional insights into atherogenesis in RA.

CONCLUSION

This study highlights the significant association between RA and subclinical atherosclerosis, as evidenced by increased CIMT in RA patients compared to healthy controls. The correlations between CIMT and age, disease duration, and disease activity highlight the multifactorial nature of cardiovascular risk in RA. While traditional risk factors such as lipid profiles and blood pressure did not differ significantly between groups, the

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inflammatory milieu of RA appears to be the primary driver of atherogenesis. These findings emphasize the need for integrated cardiovascular risk management in RA, combining aggressive control of inflammation with monitoring and treatment of traditional risk factors.

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