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Original Article

Internal Medicine Section

Assessment of Subclinical Cardiovascular Disease Risk by Measuring Carotid Intima Media Thickness in Rheumatoid Arthritis Patients: A Cross-sectional Study

TAMANNA SINGH[1], MANASWI CHAUBEY[2], RANJAN BHATTNAGAR[3], NIHARIKA MAYANK[4], ADITYA DEBUKA[5]

ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a chronic inflammatory disease that affects both synovial joints and extra-articular regions. Patients with RA have an increased risk of Cardiovascular Disease (CVD), leading to premature mortality.

Aim: To assess subclinical atherosclerosis in RA patients using Carotid Intima Media Thickness (CIMT) and compare it with age-matched healthy individuals.

Materials and Methods: This cross-sectional study included 50 RA patients and 50 healthy age- and sex-matched controls. Ultrasound was used to measure CIMT, which serves as an indicator of subclinical atherosclerosis. Framingham, Atherosclerotic CVD (ASCVD) risk scores, and QRISK3 scores were used to estimate the 10-year CVD risk. Student's t-test and Chi-square test were used to identify statistically significant differences.

Results: RA patients had significantly higher mean CIMT values compared to controls (p-value <0.001), indicating an increased burden of atherosclerosis. While ASCVD scores were comparable, Framingham scores were significantly lower (p-value=0.028), and QRISK3 scores were significantly higher (p-value=0.007) in RA patients. This suggests an underestimation of CVD risk by Framingham and potentially better prediction by QRISK3.

Conclusion: The study highlights that RA patients have a higher burden of atherosclerotic disease compared to healthy adults of the same age when CIMT is used as a marker of atherosclerosis. These findings indicate the need for early CVD risk assessment and intervention in RA patients using appropriate risk-scoring systems and tools. Further research with larger sample sizes and longitudinal follow-up is warranted to confirm these findings.

Keywords: Atherosclerosis, Carotid ultrasound, Inflammation

INTRODUCTION

The RA is a chronic inflammatory disease that affects not only the synovial joints but also various extra-articular regions, such as the lungs, skin, eyes, kidneys, heart, and other organs [1,2]. The worldwide prevalence rate of RA is approximately 1% [3]. RA patients have a higher risk of premature death, primarily driven by an increased risk of CVD compared to the general population [4]. The CVD risk in RA patients is comparable to that of patients with Diabetes Mellitus (DM) [5-7]. The heightened risk of premature death from CVD in RA patients remains a significant challenge in managing these individuals [8-10].

Atherosclerosis is the main underlying pathogenesis behind CVDs, and inflammation is the common link between atherosclerosis and RA [11]. Recent studies have highlighted the crucial role of inflammation in mediating all stages of atherosclerosis, including initiation, progression, and thrombotic complications [12,13]. Early identification of individuals at risk for cardiovascular events is essential as proactively addressing risk factors can be more successful than treating established atherosclerotic disease. However, traditional risk assessment tools based on conventional factors often fall short in detecting many individuals who will eventually develop CVDs, especially those considered low-risk [14-16].

Subclinical atherosclerosis serves as an early indicator of atherosclerotic burden. CIMT, measured non invasively using ultrasound, is a validated surrogate marker for early subclinical atherosclerosis [17]. A meta-analysis has demonstrated a 10-15% increase in myocardial infarction risk and a 13-18% increase in stroke risk per 0.1 mm increment in CIMT, independent of age and sex. Therefore, CIMT independently predicts coronary heart disease and stroke, even after adjusting for age, sex, race, and conventional risk factors [18].

This study aimed to detect subclinical atherosclerosis by measuring CIMT in patients with RA and compare it with age- and sex-matched healthy individuals.

MATERIALS AND METHODS

This cross-sectional study was conducted among 50 cases of RA and 50 age- and sex-matched healthy controls. The patients were selected from the medicine and rheumatology outpatient department and ward of Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, Uttar Pradesh, India. The study duration was from September 2020 to July 2022. The study was reviewed and approved by the Institutional Ethics Committee (IEC number: ECR/526/Inst/UP/2014/RR-20).

Inclusion criteria: Patients diagnosed with RA who had symptoms for at least six weeks and were aged 18 years or older and willing to provide informed consent were included in the study. Cases were classified as RA according to the 2010 American College of Rheumatology-European League Against Rheumatism classification criteria (ACR-EULAR) if they had symptoms for at least six weeks [19]. An equal number of age- and sex-matched healthy controls were selected after obtaining informed consent.

Exclusion criteria: Patients with established ischaemic heart disease, other inflammatory diseases, smokers, malignancies, stroke, diabetes, chronic liver disease, or diseases known to cause dyslipidaemia (e.g., nephrotic syndrome, hypothyroidism) were excluded from the study. Additionally, patients who received lipid or urate-lowering drugs, treatment with Disease-Modifying

Antirheumatic Drugs (DMARDs), female patients on hormone replacement therapy or oral contraceptive pills, patients with a diagnosis of familial dyslipidaemia, pregnant patients, those with overlap syndrome, and those with other multiple connective tissue disorders besides RA were also excluded from this study.

Sample size: The total sample size was 100, consisting of 50 RA patients and 50 age- and sex-matched healthy controls. The sample size was determined based on a pilot study with 10 cases (RA patients) and 10 healthy controls, considering a confidence level of 95% and a study power of 90%. Detailed clinical history, clinical examinations, and all necessary investigations were conducted for all the patients.

Methods and procedures: The eligible individuals underwent anthropometric, clinical, biochemical, and radiological investigations. Patient details such as age, sex, gender, and place were recorded. A detailed history was obtained regarding the onset, progression, and duration of the disease, including the number of joints involved, morning stiffness, presence of deformity, and activity restriction.

Following the history, all patients underwent a general physical examination and a systemic examination. The disease activity of RA was assessed using Disease Activity Score-28 (DAS-28) scores [20]. Biochemical investigations for all patients included complete blood count, renal function tests, liver function tests, lipid profile, and fasting blood sugar levels. Special serological investigations, including RA factor (using the agglutination technique), anti-Cyclic Citrullinated Peptides (anti-CCP) antibodies (using the ELISA method), and C-Reactive Protein (CRP) levels (using the agglutination technique), were conducted for classification purposes.

Carotid ultrasonography was performed on all cases and controls to measure CIMT values and detect subclinical atherosclerosis. Subclinical atherosclerosis was defined as a CIMT >0.9 mm [21]. The 10-year CVD risk was calculated for all study participants using the Framingham, ASCVD, and QRISK3 online calculators.

STATISTICAL ANALYSIS

For statistical analysis, the Student's t-test was used to assess the significance of observed differences in quantitative data presented as mean±SD. The Chi-square test was employed for data represented as median and Interquartile Range (IQR). A p-value of 0.05 at a two-sided test was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 28.0 software.

RESULTS

In the present study, a total of 100 individuals were evaluated. The study population showed a predominant female representation, with 76 (76%) females. Both study groups were comparable in terms of mean age and sex. The control group consisted of slightly more males, with 15 (30%) compared to 9 (18%) in the cases group, but this difference was statistically insignificant (p-value=0.160). The mean BMI was significantly higher in individuals from the control group (p-value=0.01) [Table/Fig-1].

Variables	Group 1 (cases) (n=50) (mean±SD)	Group 2 (control) (n=50) (mean±SD)	p-value
Age (years)	38.60±12.403	35.56±12.203	0.220
Gender distribution	n (%)	n (%)	
Male	9 (18)	15 (30)	0.160
Female	41 (82)	35 (70)	
BMI (kg/m^2) (mean±SD)	21.77±2.78	23.07±2.16	0.011

[Table/Fig-1]: Clinical characteristics of the study population.

The mean haemoglobin was significantly lower (p-value 0.047), while the mean TLC (p-value <0.001) and platelet counts (p-value 0.001) were significantly higher in cases compared to controls. The mean alkaline phosphatase, serum albumin, and serum creatinine were comparable between the two groups [Table/Fig-2]. Cases (RA patients) had a mean CRP level of 3.218±5.171, mean RA factor of 127.675±149.9, and mean anti CCP2 levels of 220.734±209.333 IU/mL. Disease activity was assessed using the DAS-28 score in cases, which was 5.3968±0.893 [Table/Fig-2]. These parameters (CRP, RA factor, Anti CCP, and disease activity score DAS28) were only measured for cases.

Variables	Group 1 (cases) (mean±SD)	Group 2 (control) (mean±SD)	p-value
Haemoglobin (g/dL)	11.632±1.5809	12.228±1.3676	0.047
Total leukocyte count (cells/microlitre)	8639.60±2809.546	6894.60±1350.303	<0.001
Platelet count (lacs/mm^3)	2.4536±1.09292	1.9108±0.33242	0.001
SGPT (U/L)	22.734±10.3386	27.776±6.8457	0.005
SGOT (U/L)	22.188±6.7500	26.660±7.6361	0.003
Serum total protein (g/dL)	7.642±0.7783	7.158±0.6085	0.001
Serum albumin (g/dL)	3.933±0.4032	3.798±0.3992	0.095
Serum alkaline phosphatase (U/L)	198.460±64.5961	190.734±44.3405	0.487
Serum creatinine (mg/dL)	0.708±0.1338	0.728±0.1400	0.467
Cholesterol (mg/dL)	176.920±36.050	193.628±29.152	0.012
Triglycerides (mg/dL)	132.68±46.362	133.52±35.240	0.919
HDL (mg/dL)	51.776±11.4329	49.570±8.3885	0.274
LDL (mg/dL)	103.028±34.104	103.780±29.199	0.906
VLDL (mg/dL)	29.340±10.601	30.560±9.348	0.543
Fasting sugar (mg/dL)	90.20±13.290	86.24±7.291	0.068
C-reactive protein (mg/L)	3.218±5.171	-	-
RA factor (IU/mL)	127.675±149.995	-	-
Anti-CCP (IU/mL)	220.734±209.333	-	-
DAS-28	5.3968±0.893	-	-

[Table/Fig-2]: Laboratory characteristics of the study population.
SGPT: Serum glutamic pyruvic transaminase; SGOT: Serum glutamic oxaloacetic transaminase; HDL: High density lipoprotein; LAD: Low density lipoprotein; VLDL: Very low density lipoprotein; DAS: Disease activity score

Bilateral mean CIMT was significantly higher (p-value <0.001) in RA patients compared to healthy controls [Table/Fig-3]. Among the 50 cases, only two RA patients had CIMT >0.9 mm, while all controls had CIMT below 0.9 mm, but this difference was statistically insignificant (p-value 0.49).

Variables	Group 1 (cases) (n=50)	Group 2 (control) (n=50)	p-value
Left CIMT (mm)	0.604±0.1340	0.388±0.0895	<0.001
Right CIMT (mm)	0.6010±0.13795	0.3890±0.0790	<0.001

[Table/Fig-3]: Carotid Intima Media Thickness (CIMT in mm) in study populations.

When comparing the median Framingham score, ASCVD, and QRISK3 score between group 1 (cases) and group 2 (controls), the median Framingham score was significantly lower (p-value=0.028) in group 1, while the median QRISK3 score was significantly higher (p-value=0.007) in group 1 compared to group 2. The median ASCVD score was comparable between the two groups [Table/Fig-4].

Variables	Group 1 (cases) {median (IQR)}	Group 2 (control) {median (IQR)}	p-value
Framingham	0.800 (0.300-1.400)	1.400 (1.000-1.850)	0.028
ASCVD	1.200 (0.500-2.300)	1.300 (1.000-1.800)	0.929
QRISK3	3.600 (0.850-6.100)	1.800 (1.200-2.100)	0.007

[Table/Fig-4]: Comparison of median 10-year CVD risk estimate by Framingham Score, ASCVD, and QRISK3 Score between two study groups.

DISCUSSION

The findings of this study indicate that the mean CIMT, which is a surrogate marker of carotid atherosclerosis, was significantly

higher (p-value <0.001) in RA patients compared to healthy age-sex matched controls. This suggests a higher atherosclerotic burden in RA patients relative to their age-sex matched controls. A meta-analysis revealed that even a mere 0.1 mm increase in CIMT translates to a striking 10%-15% increase in myocardial infarction risk and a 13%-18% increase in stroke risk, even after adjusting for age and sex [18]. This indicates that a higher CIMT predicts a higher risk of future CVD in RA patients compared to age-sex matched controls.

Achieving optimal cardiovascular health outcomes in RA patients, with the aim of preventing premature deaths from CVD, remains a significant challenge in the management of RA [8-10]. Therefore, early correction of emerging risk factors offers a more efficient approach in preventing cardiovascular events than therapy for advanced atherosclerotic disease. Early identification of at-risk individuals is crucial. Subclinical atherosclerosis, an early warning sign of increased atherosclerotic burden, can be identified through non invasive measurement of CIMT, which is a well-established marker of the early stages of this subclinical condition [17]. Early recognition of subclinical atherosclerosis through CIMT opens the door for timely intervention and the potential to slow or even prevent the progression of cardiovascular risk. The present study assessed naïve RA patients for CIMT and compared them with their healthy age and sex matched controls.

On demographic analysis of study participants, 76% were females and 24% were males. The mean age of both groups was comparable, with cases having a mean age of 38.60±12.403 years and controls having a mean age of 35.56±12.203 years. A similar study conducted by Muhammed H et al., included 332 Indian patients, among whom 85% were females and 15% were males [21].

RA patients were diagnosed based on clinical history and laboratory tests. In this study, RA patients had a mean CRP level of 3.218±5.171 mg/L, mean RA factor of 127.675±149.9 IU/mL, and mean anti-CCP2 levels of 220.734±209.333 IU/mL. Disease severity was assessed using the DAS-28 score in cases, and it was 5.3968±0.893.

In the present study, the mean CIMT was higher among RA patients compared to the healthy controls. A meta-analysis conducted by Wang P et al., concluded that CIMT in RA patients is thicker than in healthy controls [22]. Mazario R et al., also found that RA patients had thicker CIMT than healthy individuals, and this was positively associated with longer disease duration and higher disease activity (DAS28 score) [23]. Another study by Grover S et al., revealed that CIMT increased in RA patients, and the tender joint count was an independent predictor of abnorma CIMT [24]. Therefore, the higher CIMT thickening observed in RA patients compared to healthy controls in this study was consistent with previous research [22-24]. These findings suggest a greater burden of subclinical atherosclerosis in patients with RA compared to the general healthy population.

In this study, the Framingham, ASCVD, and QRISK3 cardiovascular risk scores were calculated for both groups. The median values of the 10-year CVD risk QRISK3 (p-value 0.007) were significantly higher among cases compared to controls. However, the ASCVD scores were comparable between both groups, while the Framingham scores were significantly lower (p-value 0.028) among RA patients. This suggests that the Framingham and ASCVD scores may underestimate the CVD risk in RA patients, and the QRISK3 risk calculator may be more effective in predicting CVD risk in RA patients. A similar study by Muhammed H et al., concluded that ASCVD and QRISK3 3 scores exhibited the highest utility in predicting subclinical atherosclerosis (defined by CIMT >0.9 mm) in the Indian RA population [21].

Limitation(s)

One limitation of the present study was its small sample size. Due to the relatively small number of participants, the findings may not be generalisable to larger populations. Secondly, it was a cross-sectional study, which means that it cannot determine the cause of the increased burden of carotid atherosclerosis in RA patients. Since the present study was a cross-sectional study with a small sample size, these findings should be confirmed through a longer follow-up study with a larger sample size.

CONCLUSION(S)

Despite these limitations, the present study provides important evidence that RA patients have an increased burden of carotid atherosclerosis, as measured by CIMT. Additionally, RA patients had higher QRISK3 scores than healthy controls, suggesting that QRISK3 scores may better predict CVD risk in RA patients compared to ASCVD scores. Therefore, RA patients may benefit from early and aggressive preventive interventions, such as lifestyle modification and pharmacotherapy, to reduce their risk of CVD.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
2. Associate Professor, Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
3. Associate Professor, Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
4. Junior Resident, Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
5. Junior Resident, Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Ranjan Bhattnagar,
Associate Professor, Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, Uttar Pradesh, India.
E-mail: dr.rbngaya@gmail.com

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