Carotid Intimomedial Thickness (CIMT) in Patients with Rheumatoid Arthritis; the Need for More Aggressive Cardiovascular Screening in RA

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ABSTRACT

Objective: To use carotid intimal medial thickness as a marker of early atherosclerosis in patients with rheumatoid arthritis.
Study Design: Cross-sectional descriptive study.
Place and Duration of the Study: Rheumatology Unit of Federal Government Polyclinic Hospital, Islamabad, from 1st June 2019 till 30th January 2022.
Methodology: The study included 190 patients divided equally into cases of rheumatoid arthritis and healthy control groups. Carotid intimal medial thickness was measured using the carotid doppler ultrasound. The mean values of both the study groups were evaluated using the independent sample t-tests. Different statistical tests for correlation were also used where appropriate.
Results: This study included a total of 190 patients, 95 each in case and control groups. There were 15 (15.8%) males and 80 (84.2%) females with mean age of 43.5±12.8 years among cases, while 27 (28.4%) males and 68 (71.6%) females with mean age of 43.1±10.1 years in the control group. A significantly higher number of cases had a carotid intima-media thickness of more than 0.6 mm as compared to controls (43.2% *vs.* 25.3%, p=0.009). Cases with seropositive status were 1.98 times more likely to have higher carotid intima-medial thickness compared with controls.
Conclusion: Carotid intima-media thickness measurement is important as a surrogate marker of atherosclerotic process in patients with rheumatoid arthritis.

Key Words: *Rheumatoid arthritis (RA), Carotid intimal medial thickness (CIMT), Atherosclerosis, Cardiovascular disease (CVD).*

How to cite this article: Khaliq T, Shan S, Shah SA, Saleem S, Adil MH. Carotid Intimomedial Thickness (CIMT) in Patients with Rheumatoid Arthritis; the Need for More Aggressive Cardiovascular Screening in RA. *J Coll Physicians Surg Pak* 2023; **33(04)**:427-432.

INTRODUCTION

Rheumatoid Arthritis (RA) is the most common inflammatory arthritis affecting 0.5 to 1% of the adult Caucasian population.[1] Its incidence in Pakistan is reported as 0.2 to 0.5% in various studies.[2] RA is a debilitating disease that not only affects the quality of life (QOL) but also carries a high cardiovascular disease (CVD) risk.[3] It has been seen that cardiovascular mortality accounts for 30-50% of premature deaths observed in the RA population.[4] The systemic and articular inflammatory load in RA has been linked to accelerated atherogenesis leading to increased cardiovascular mortality.[5] The inflammatory nature of the disease is evidenced by raised markers of inflammation, including CRP and ESR in patients with active arthritis. Interestingly, high-sensitivity CRP has been classified as one of the novel risk factors for atherosclerosis.

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Received: November 08, 2022; Revised: February 27, 2023; Accepted: March 27, 2023
DOI: https://doi.org/10.29271/jcpsp.2023.04.427

Carotid intima-media thickness (CIMT) is an important marker to quantify atherosclerotic burden in the common carotid artery (CCA).[6] Carotid ultrasound provides quantitative measurements of CIMT that can be used to assess cardiovascular disease (CVD) risk and to monitor ongoing disease progression and regression in clinical trials.[7] CIMT has numerous advantages including that it is non-invasive, rapid, reproducible, and carries no risk. Currently, the calculation of CIMT is arguably the most widely used non-invasive measure of atherosclerosis employed by clinicians and clinical investigators, both to quantify the extent of subclinical disease and to monitor change over time and can be used as a surrogate marker for the severity of the disease.[7]

Various studies have shown that CIMT thickness is increased in patients with RA compared to age-matched controls,[8] however, such studies are lacking in Pakistan. Therefore, this study was conducted to calculate CIMT in the RA patients. The rationale of the study was to advocate aggressive screening and primary prevention of cardiovascular mortality, thereby reducing premature deaths in patients with rheumatoid arthritis.

The objective of the study was to use carotid intimal medial thickness as a marker of early atherosclerosis in patients with rheumatoid arthritis.

METHODOLOGY

The study was carried out at the Rheumatology unit of the Federal Government Polyclinic Hospital, Islamabad. It was a cross-sectional descriptive study, from 1st June 2019 till 30th January 2022. Study participants included cases defined patients with RA based on 2010 ACR/EULAR criteria and a control group of age group matched population not having RA, undifferentiated inflammatory arthritis, crystal arthropathy or arthritis secondary to connective tissue disease (CTD). Patients having diabetes mellitus, hypertension, chronic kidney disease, coronary heart disease, cerebrovascular disease, hyperuricemia, and peripheral vascular disease were excluded from the study. WHO Sample calculator was used to determine sample size. Sample size was calculated using study by Saigal.[9] The level of significance was maintained at 5% and power of test at 99% so a minimum of 70 patients were included in each group.

Patients presenting to the Rheumatology Clinic, fulfilling the inclusion and exclusion criteria were selected. Informed consent was taken and proforma was filled out. Patients were then sent to the radiology department for Carotid Doppler and CIMT measurement. The research was initiated after approval from the ethical review committee. The research was conducted according to the ethical guidelines of Helsinki Declaration and Pakistan Medical Research Council guidelines.

Data were recorded on a pre-designed structured proforma and analysed by using IBM SPSS data management software (version 23.0). The descriptive statistics were reported using frequencies and percentages for categorical data, while mean and standard deviations for continuous variables were reported. The mean values of continuous variables were compared between two study groups using the independent sample t-tests. Categorical variables were compared with study groups using chi-square test. Pearson's correlation test was applied to correlate CIMT with continuous variables including age, cholesterol, triglyceride, HDL and LDL. Regression analysis was applied to assess the relationship between CIMT and independent predictor variables, odds ratio and 95% confidence intervals were reported along with p-values. A p-value of ≤0.05 was considered statistically significant.

RESULTS

This study included a total of 190 participants divided into two groups; cases and controls. There were 95 patients in each group. The cases comprised of diagnosed rheumatoid arthritis patients seeking treatment from the study site, whereas controls comprised of age group matched participants with no history of any inflammatory joint disease. There were 15 (15.8%) males and 80 (84.2%) females with mean age of 43.5±12.8 years among cases, while 27 (28.4%) males and 68 (71.6%) females with mean age of 43.1±10.1 years in the control group. Other baseline characteristics are summarised for cases and controls in Table I.

The majority of the rheumatoid arthritis patients 50 (52.6%) had a disease history dating back to 1-5 years, 21 (22.1%) with a disease duration of 6-10 years; 11 (11.6%) 11-15 years, 5 (5.3%) 16-20 years, 2 (2.1%) >20 years while 6 (6.3%) were diagnosed within the last year. There were 87 (91.6%) RA patients with a seropositive status, with 18 (18.9%) having positive RF factor, 10 (10.5%) positive anti-CCP, and 57 (60%) with both positive RA factor and anti-CCP. There were positive X-ray findings of RA in 67 (70.5%) patients, wherein 10 (10.5%) had periarticular osteopenia, 9 (9.5%) had joint space narrowing, 25 (26.3%) had erosions while 23 (24.2%) had all three X-ray findings together. As per Disease Activity Score-28 (DAS-28 ESR) for Rheumatoid Arthritis, there were 28 (29%) patients in remission, 21 (22.1%) having low disease activity, 36 (37.9%) moderate disease activity, and 10 (10.5%) patients having high disease activity.

The mean CIMT of the RA group was 0.55 ± 0.21mm and that of the control group was 0.45 mm ± 0.19 mm which was statistically significant (p=0.002). Out of the 95 RA patients, 87 (91.1%) had seropositive RA, and in those 87 patients, 37 (42.53%) had a CIMT >0.6 mm, while 50 (57.47%) had CIMT <0.6 mm (p=0.026). The mean ESR of the RA group was 30.65±16.71 mm/ hour as compared to controls which was 16.72±5.42 which was statistically significant (p<0.001). A significantly higher number of cases had a carotid intima--media thickness score of more than 0.6 mm as compared to controls (43.2% *vs.* 25.3%, p=0.009). Correlations test was performed to identify significant correlations between carotid intima media thickness score and other continuous variables as shown in Table II.

A significant association was found between rheumatoid arthritis and mean carotid intimal thickness. Rheumatoid arthritis patients were 2.24 times more likely to have mean carotid intimal thickness of more than 0.6 mm as compared to controls (OR=2.24, 95% CI 1.2-4.1, p=0.01). After controlling for potential confounding factors, including total cholesterol, low density lipoproteins, and triglycerides the odds of having mean carotid intimal thickness of more than 0.6mm slightly reduced to 2.223 (95% CI 1.038-4.760, p=0.04) among rheumatoid arthritis patients as compared to the control groups.

The mean CIMT value was compared for DAS28 ESR groups and the results indicated a significant difference in mean CIMT among various DAS28 ESR groups (p =0.03).

Bivariate regression analysis revealed a significant association between carotid intima media thickness of >0.6mm and age (OR=1.07, 95% CI 1.03-1.11, p<0.001), creatinine (OR=10.6, 95% CI 2.3-48.4, p=0.002), total cholesterol (OR=1.01, 95% CI 1.003-1.02, p=0.024), and triglyceride level (OR=1.01, 95% CI 1.003-1.01, p=0.008) among rheumatoid arthritis patients. Among rheumatoid arthritis cases, significant associations were also found between carotid intima-media thickness of >0.6mm and positive seropositivity (p=0.027), positive X-ray findings (p=0.004), 5-10 years of disease duration (p=0.006), and 1-5 years of symptoms onset (p=0.001).

Table I: Baseline characteristics of cases and controls (n=190).

Characteristics	Rheumatoid arthritis cases group A (n=95)	Age-matched controls group B (n=95)	p
Demographics			
Age in years (mean±SD)	43.5±12.8	43.1±10.1	0.079*
Gender n (%)			0.036**
Male	15 (15.8%)	27 (28.4%)	
Female	80 (84.2%)	68 (71.6%)	
Marital status			0.539**
Married	85 (89.5%)	89 (93.7%)	
Unmarried	9 (9.5%)	5 (5.3%)	
Widowed	1 (1.1%)	1 (1.1%)	
Smoking status			0.090**
Smoker	6 (6.3%)	13 (13.7%)	
Non-smoker	89 (93.7%)	82 (86.3%)	
Laboratory parameters			
ESR (mm/hour)			<0.001**
1-10	4 (4.2%)	0 (0%)	
11-20	29 (30.5%)	77 (81.1%)	
21-30	22 (23.2%)	15 (15.8%)	
31-40	17 (17.9%)	3 (3.2%)	
41-50	13 (13.7%)	0 (0%)	
51-60	8 (8.4%)	0 (0%)	
71-80	1 (1.1%)	0 (0%)	
>90	1 (1.1%)	0 (0%)	
Haemoglobin (g/dL)	11.9±1.5	12.4±1.9	0.050*
Alanine transaminase (U/L)	25.7±11.4	35.5±34.3	0.009*
Creatinine (mg/dL)	0.67±0.15	0.82±0.33	<0.001*
Deranged Lipid profile			0.005**
Yes	48 (50.5%)	29 (30.5%)	
No	47 (49.5%)	66 (69.5%)	
Total cholesterol level (mg/dL)	177.4±37.6	155.1±35.4	<0.001*
High-density lipids level (mg/dL)	41.2±5.3	42.1±6.3	0.332*
Low-density lipids level (mg/dL)	107.7±25.6	101.5±26.1	0.097*
Triglyceride level (mg/dL)	152.6±61.6	158.2±49.1	0.497*

**Independent samples T-test, **Chi-square test.*

Table II: Correlation of carotid intima media thickness (CIMT) with age and laboratory parameters among cases and controls.

Correlations	RA cases group A (n=95)` Coefficient "r"	p	Controls group B (n=95) Coefficient "r"	p
CIMT and age	0.508	<0.001	0.422	<0.001
CIMT and total cholesterol	0.274	0.007	0.532	<0.001
CIMT and HDL level	-0.278	0.006	-0.386	<0.001
CIMT and LDL level	0.161	0.120	0.624	<0.001
CIMT and triglyceride level	0.365	<0.001	0.615	<0.001
CIMT and ESR	-0.082	0.431	0.100	0.336
CIMT and DAS 28 ESR	-0.089	0.389	-	-
CIMT and haemoglobin level	0.036	0.729	-0.253	0.013
CIMT and creatinine	0.335	0.001	0.472	<0.001
CIMT and ALT	0.033	0.750	0.422	<0.001

Table III: Bivariate regression analysis of carotid intima media thickness of >0.6 mm with various risk factors among cases and controls.

Risk factors	RA cases group A (n=95) OR (95% CI)	p	Controls group B (n=95) OR (95% CI)	P
Age	1.07 (1.03-1.11)	<0.001	1.12 (1.05-1.19)	<0.001
Gender, Male	1.62 (0.53-4.9)	0.389	0.79 (0.27-2.28)	0.668
Smokers	1.34 (0.25-7.02)	0.727	3.04 (0.90-10.21)	0.071
Haemoglobin (mg/dL)	0.98 (0.75-1.27)	0.892	0.74 (0.57-0.97)	0.033
Creatinine (mg/dL)	10.6 (2.3-48.4)	0.002	30.8 (1.6-576.3)	0.022
Alanine transaminase (U/L)	1.01 (0.98-1.05)	0.357	1.03 (1.08-1.06)	0.011
Total cholesterol level (mg/dL)	1.01 (1.003-1.02)	0.024	1.04 (1.02-1.06)	<0.001
Triglyceride level (mg/dL)	1.01 (1.003-1.01)	0.008	1.04 (1.02-1.05)	<0.001
Positive seropositive status	1.98 (1.08-3.63)	0.027	-	-
Positive X-ray findings	2.5 (1.33-4.65)	0.004	-	-
Duration of disease (5-10 years)	3.9 (1.48-10.5)	0.006	-	-
Onset of symptoms (1-5 years)	3.5 (1.68-7.27)	0.001	-	-

Cases with seropositive status were 1.98 times more likely to have higher CIMT, cases with positive X-ray findings were 2.5 times more likely to have higher CIMT, similarly, cases with 5-10 years of disease and 1-5 years of symptoms onset were 3.9 and 3.5 times more likely to have carotid intima media thickness of >0.6mm respectively. The associations among different variables in the control groups are also given in Table III.

DISCUSSION

Rheumatoid arthritis is a disease characterised by chronic inflammation and leads to increased cardiovascular morbidity and mortality in both the genders because of premature atherosclerosis secondary to inflammation.[10] The common inflammatory mediators TNF alpha and the interleukins 1 and 6 have been linked with increased risk of development of atherosclerosis in rheumatoid arthritis, and therefore, the utilisation of these as the treatment target helps in decreasing the cardiovascular morbidity and mortality associated with the atherosclerotic process in RA patients.[11,12]

Carotid intimal medial thickness, measured by using a high--resolution b mode of ultrasound, has been studied as an independent marker of increased cardiovascular mortality in general as well as in patients having rheumatoid arthritis. It is a non-invasive method to see the atherosclerotic burden of the disease and also predicts the cardiovascular events in rheumatoid arthritis patients.[13] A meta-analysis showed that the carotid intimal medial thickness was more in the RA group as compared to the control groups.[14] It evaluated more than 47 papers each before reaching this conclusion.

The mean age in a study done in India by Patel *et al.* was 48.4 years,[15] while in this study group it was 43.5±12.8 years among cases and 43.1±10.1 years in the control group. The mean CIMT of the RA group was 0.55mm ± 0.21mm, and that of the control group was 0.45mm ± 0.19mm which was statistically significant (p=0.002); similar findings were observed by Patel *et al.* where the cases had a mean carotid intimal thickness of 0.862 ± 0.18 mm (p <0.001). Observations from this study are also supported by results from studies done by others where the CIMT in cases was higher than the control subjects (0.598 ± 0.131 *vs.* 0.501 ± 0.081 mm; p = 0.001).[5,16]

In this study, it was found that among rheumatoid arthritis cases, those having positive X-ray findings had a higher value of CIMT (p=0.004). Similarly, subjects who had positive anti-CCP antibodies or rheumatoid factor also had a higher value of carotid intimal medial thickness compared to those who were seronegative (p=0.027), a finding also supported in a study done by Merza *et al.* which showed higher mean CIMT values in seropositive than the seronegative patients (0.72 ± 0.10 mm *vs*. 0.57 ± 0.08 mm; p <0.001).[17]

The disease duration has found to be a very important factor in the development of atherosclerosis in patients with RA. This study showed that the CIMT was higher among those having a longer disease duration that is more than 5 years (p = 0.006) as shown by Arif where similar findings were observed that is disease duration 5-10 years CIMT was 1.23 ± 0.59 (p = 0.007).[18]

Literature review showed that a few studies have been done to see the association of carotid intimal thickness and its correlation with the radiographic damage in rheumatoid arthritis patients. One such study done by Tutoglu *et al.* in Turkey did not show any correlation between the modified sharp score and the CIMT.[19] The present authors did not use the Sharp score, however, it was noticed that cases with positive x-ray findings related to RA were 2.5 times more likely to have higher CIMT that is >0.6mm.

Another feature that was revealed by the results of this study was the positive correlation of mean carotid intimal thickness with the disease activity status. Arif's study carried out on an Indian population also showed that with higher disease activity, the CIMT values were significant at a p-value <0.001 as compared to the presently reported p=0.03.[18] However, another study done by van Breukelen[20] in the Netherlands showed that there was no significant difference in the CIMT among the different RA groups. The reason for this disparity could be that this particular study was carried out on a cohort of RA patients having remission or low disease activity as calculated by DAS28 ESR score, whereas in the present study, only 49 (51.5%) patients belonged to the remission and low disease activity group while 46 (48.5%) had moderate to high disease activity. Another study done by Prabhakaran *et al.* using CDAI as a disease activity index showed that those having high disease activity had a higher CIMT value and a greater risk of cardiovascular events.[21] In a study done by Arieda *et al.* it was noticed that those patients of RA who had better control of the inflammatory disease and were in remission or low disease activity were more likely to have reversal of the harmful effects of RA on atherosclerosis.[22] This could not be validated in this study, however, it can be considered as a subject for future research and can provide valuable insight.

The traditional risk factors like smoking, high LDL, total cholesterol, and high triglycerides levels were found significantly associated with the increased carotid intimal thickness in both the cases and the control groups, but even after removing these confounding factors, the CIMT >0.6mm was found to be 2.225 times higher in the RA group as compared to the control group in this study (95% CI 1.038-4.760, p=0.04). Several other studies have shown that these traditional modifiable risk factors are associated with increased cardiovascular risk.[23]

There are a few limitations in this study that the sample size was small, so it cannot be generalised to all the patients.

Both the disease activity score and the carotid intimal thickness were measured at one point in time and then patients were not followed up for a longer duration to assess if treatment and stringent control of RA using a treat-to-target approach, reduced the CIMT.

CONCLUSION

Rheumatoid arthritis carries a high risk of atherosclerosis because of the chronic inflammation in the vessel walls. This study highlights the importance of picking up the disease process earlier by measuring the carotid intimal thickness in patients with RA.

ETHICAL APPROVAL:

Ethical approval was obtained from the institutional ethical review board *via* registration No. 1/2017-E/C-76 on August 19th 2019.

PATIENTS' CONSENT:

A well-informed written consent was taken from the participants of the study.

COMPETING INTEREST:

The authors have nothing to declare and conflicts of interest.

AUTHORS' CONTRIBUTION:

TK: Conceptualisation of the topic, data collection, drafting, and proofreading with critical analysis.
SS: Data collection and performing the carotid doppler of the cases and controls.
SAS: Data collection, drafting, data analysis, and referencing.
SS, MHA: Data collection.
All authors have approved the final version of the manuscript to be published.

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