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Original Research Article

Factors affecting carotid intimal medial thickness in patients with rheumatoid arthritis, an analytical cross-sectional study

K. M. Prabhuswamy, M. Virgin Joena*

Department of General Medicine, Velammal Medical College and Research Institute, Madurai, Tamil Nadu, India

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***Correspondence:**
Dr. M. Virgin Joena,
E-mail: prabhudoctr@gmail.com

ABSTRACT

Background: IMT assessment as a non-invasive imaging test is quite widely used especially among RA patients, the clinical applications of using such knowledge is scarce, hence study was conducted to compare the carotid artery intima-media thickness (CIMT) in patients with rheumatoid arthritis (RA) with healthy controls also to study the correlation between duration of rheumatoid arthritis, the activity of rheumatoid arthritis and other factors influencing (CIMT).
Methods: In analytical cross-sectional study, of 80 participants of RA and 40 healthy controls, "DAS28" was used to assess disease activity. Carotid intima-media thickness assessed using carotid ultrasonography.
Results: Mean age of the cases and controls was 43.9 and 44.38 years. Subjects with duration of disease <2 years, to 5 years and >5 years were 35%, 45% and 20%. The mean carotid intima-media thickness was 5.61mm in controls, and CIMT was 6.11mm in people below 2 years and 7.08 mm in people between 2 to 5 years and 8.00mm in people above 5 years which was statistically significant. The mean carotid intima-media thickness was 5.61mm controls and 6.86mm in people with low, 7.00mm in people with moderate and 6.95mm in people with high disease activity, which was statistically significant.
Conclusions: Study findings revealed risk of increase in carotid intima-media thickness higher among RA patients in the later stages and can increase the patients' susceptibility to cardiovascular events. The factors showing strong association with intimal medial thickness were the age and symptoms duration.

Keywords: CIMT, DAS28, IMT, RA

INTRODUCTION

Atherosclerosis is one of the leading causes of death across the globe not only in the developed but even in developing countries as well. Growing evidence has been consistently showing that it involves a chronic inflammatory process of the arterial wall set in a backdrop of dyslipidaemia.[1,2] The pathophysiology of atherosclerosis has its roots in early childhood, which usually is asymptomatic until later in life. The major risk factors of atherosclerosis and thereby coronary heart disease (CHD) are unhealthy lifestyles, clinical risk factors, psychological factors and public health transitions. ageing, urbanization and enhanced prosperity seem to be the underlying crucial drivers.[3] The impact of CHD has been huge in Asian countries with a mortality of 103 to 336 per 100, 000 adult populations.[3]

Asymptomatic thickening of the carotid artery is the strongest prognosticator of cardiovascular (CV) morbidity and mortality in general population. Carotid intima-media thickness (cIMT) displays structural

changes in the arterial wall even in initial subclinical phases of atherosclerosis. Mounting evidence suggests cIMT and CHD are directly related and that the former can predict events like myocardial infarction (MI) or stroke in apparently healthy individuals.[4] Blood pressure, altered lipid levels, increased body mass index among others present during childhood have been shown to increase IMT in adulthood by some prospective cohort studies.[5-7]

Such comorbidities cumulatively called metabolic syndrome have been frequently found in patients with rheumatoid arthritis (RA), a systemic autoimmune joint disorder that affects synovial joints with resultant chronic pain, bone erosions and progressive disability.[8,9] Cardiac events like angina, MI or cerebrovascular accidents are significantly higher among patients with RA than the general population and that the heightened CV morbidity and mortality among such groups could not be explained by traditional CV risk factors alone.[10,11]

Growing interest recently has pointed at a relationship between RA and CV risk markers like cIMT and carotid plaque formation, in particular by a couple of case-control studies that showed augmented atherosclerosis in RA patients.[10,11] A meta-analysis by Tyrrell PN et al, and van Sijl et al.[12,13] found those with RA showed a significantly higher IMT in contrast to the controls. However, some studies have debated such an interplay.[14,15] Though, IMT assessment as a non-invasive imaging test is quite widely used especially among RA patients, the clinical applications of using such knowledge is scarce. Hence the present study intends to explore the factors influencing cIMT in RA patients.[16,17] To compare the carotid artery intima-media thickness (CIMT) in patients with rheumatoid arthritis (RA) with healthy controls. To study the correlation between duration of rheumatoid arthritis, the activity of rheumatoid arthritis. Carotid intima media thickness (CIMT) To analyse the factors influencing carotid intima media thickness (CIMT) among rheumatoid arthritis patients.

METHODS

The study was an analytical cross-sectional study, conducted in the rheumatology outpatient clinic, Velammal Medical College and Research Institute, Madurai, Tamil Nadu, between January to July 2018.The study population was patients attending the study setting who was diagnosed with rheumatoid arthritis (diagnosed according to 2010 American College of rheumatology-European league against rheumatism (ACR-EULAR) criteria) and their age and gender-matched healthy controls.

Exclusion criteria

People who are having the following known risk factors for atherosclerosis were excluded from the study.

- Hypertension (BP >140/90mmHg) or the use of antihypertensive medications, hypercholesterolemia (Total cholesterol>240mg/dl, LDL>160mg/dl, triglycerides >200mg/dl) or use of lipid lowering medication, diabetes mellitus (diagnosed according to WHO criteria) or use of anti-diabetic medication, history of coronary artery disease, history of cerebrovascular accidents (CVA) or any other vascular event, known cases of hepatic or renal impairment.

Considering the mean difference in intimal-medial thickness to be detected as 0.69 with a standard deviation of 0.45 with 5% alpha error and 80% power of the study, the required sample size would be about 36 subjects in each group. To account for about 10%non-participantiopnrahe, it was decided to include 40 subjects in each of the study groups.

The cases who were attending the clinic, who satisfied, inclusion and exclusion criteria were selected consecutively into the study till the sample size is reached; hence no sampling was done. The controls were selected from among the people who were attending a local health-check program at local health-check program at Velammal Medical College Hospital Madurai, by convenient sampling.

The RA patients included in the study as subjects were divided into three groups based on the duration of disease. These were:

All the RA patients included in the study were evaluated for their disease activity using the disease activity score "DAS28". This score is calculated by using the formula: DAS 28 = $0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.70$ (log ESR) + 0.014 GH where, TJC: tender joint count, SJC: swollen joint count, GH: general health status as assessed by the patient on a visual analogue scale (VAS).

All the subjects including the controls were evaluated for carotid intima-media thickness by using carotid ultrasonography. Carotid ultrasonography was carried out by skilled radiologist by using grayscale ultrasonography and then followed by color flow imaging.

Carotid intima-media thickness (CIMT) was measured in common carotid artery bilaterally by examining throughout common carotid artery up to 2cm proximal to the bifurcation. CIMT measurement was taken at the site of greatest thickness, and three readings were taken from each side at different points within the region of interest. All measurements were taken in diastole, measured in phase when the lumen diameter is at its smallest and IMT at its largest. The mean value of 6 readings (3 from each side) was taken as the final CIMT for evaluation. descriptive analysis of all the variables was done using mean and standard deviation for quantitative variables, frequency and percentage or categorical variables. Disease duration and activity were considered as primary

outcome variables. Intimal-medial thickness was considered as the primary outcome variable., the mean intima-medial thickness across the study groups was compared using one-way ANOVA. Mean differences along with their 95% CI were presented. Univariate and multivariate linear regression analysis was done to analyses the factors influencing the intimal-medial thickness in the study population.

Statistical analysis

IBM SPSS was sued for statistical analysis. The results obtained were subjected to one-way ANOVA test for statistical analysis.

Another 40 healthy (age and sex-matched) subjects were taken into group 4 as controls.

RESULTS

A total of 80 participants were included in the study, out of which 40 were cases of rheumatoid arthritis for variable duration, and the remaining 40 were controls.

The mean age of the cases and controls was 43.9 and 44.38 years respectively. Both the study groups were comparable concerning age and gender. The blood sugar values, renal parameters and lipid profile parameters also were comparable among both the study groups. The minor differences between the two groups in the above-mentioned parameters were statistically not significant. The proportion of smokers (12.5% in cases Vs none in controls) and alcoholics (5% in cases Vs none in controls) was slightly higher in cases when compared to controls (Table 1).

Table 1: Comparison of baseline variables among cases and controls in the study population (N=80).

Parameter	Cases (N=40)	Controls (N=40)	P -value
Age (Mean±SD)	43.90±10.52	44.38±9.41	0.832
Male: female	2.3:1	2.3:1	1.0
Blood sugar (Mean±SD)	95.38±20.90	89.20±22.17	0.204
Blood urea (Mean±SD)	26.43±7.40	27.78±9.07	0.468
Serum creatinine (Mean±SD)	0.86±0.13	0.89±0.13	0.275
Total cholesterol (Mean±SD)	166.3±21.84	168.5±16.99	0.625
TGL(Mean±SD)	150.53±16.01	153.48±11.98	0.354
LDL (Mean±SD)	89.63±14.90	92.65±13.21	0.340
VLDL (Mean± SD)	35.73±4.70	35.03±3.59	0.457
HDL	39.15±2.91	39.28±2.59	0.840
Alcohol N (%)	5 (12.5%)	0 (0.0%)	0.021
Smoking N (%)	2 (5.0%)	0 (0.0%)	0.152

All the 40 cases of rheumatoid arthritis have shown EMS (Early Morning Stiffness) positivity.

Table 2: Descriptive analysis of disease related parameters among cases (N=40).

Parameter		Frequency	(%)
EMS		40	100.0
Deformity		37	92.5
C reactive protein		17	42.5
RA factor		31	77.5
Duration of symptoms	<2 years	14	35
	2 to 5 years	18	45
	>5 years	8	20
Disease activity	High	15	37.5
	Low	3	7.5
	Moderate	22	55

Deformity raised CRP level and raised RA factor were seen in 37 (92.5%), 17 (42.5%) and 31 (77.5%) of the patients respectively. The proportion of subjects with a duration of disease <2 years, 2 to 5 years and >5 years were 35%, 45% and 20% (Table 2).

The mean carotid intima-media thickness was 5.61mm in controls, and CIMT was 6.11mm in people below 2 years and 7.08 mm in people between 2 to 5 years (mean difference 1.47, 95% CI 0.79 to 2.16, P value <0.001) and 8.00 mm in people above 5 years (mean difference 2.39, 95% CI 1.45 to 3.33, P value <0.001), which was statistically significant. The mean carotid intima-media thickness was 5.61 mm in controls and 6.86 mm in people with low, 7.00mm (mean difference 1.13, 95% CI 2.07 to 3.06, P value 0.15) in people with moderate and 6.95mm (mean difference 1.13, 95% CI 0.061 to 2.08, P value <0.001) in people with high disease activity, which was statistically significant (Table 3).

Univariate linear regression analysis was carried out to evaluate the factors influencing the intima medial thickness in the study population. The factors which have

shown statistical significance (presence of rheumatoid arthritis, age, duration of symptoms, total count, smoking and disease activity) with p value <0.05 were included in the multivariate regression analysis (Table 4). After controlling for other variables in multivariate analysis, the factors which retained the positive association with intimal medial thickness were presence of rheumatoid arthritis (regression coefficient 1.31, 95% CI 0.86 to 1.76, P Value <0.001), age of the patient (Regression coefficient 0.04, 95% CI 0.021 to 0.058, p value <0.01) and duration of symptoms (Regression coefficient 0.04, 95% CI 0.021 to 0.058, P Value <0.001) (Table 5).

Table 3: Comparison of carotid intimal medial thickness among cases and controls (N=80).

Duration of symptom	Mean	Mean difference	P value	95% CI	
				Lower	Upper
Duration of disease					
Controls	5.61±0.458				
<2 years	6.11±1.00	0.50	0.457	0.25	1.25
2 to 5 years	7.08±1.22	1.47	<0.001	0.79	2.16
>5 years	8.00±1.41	2.39	<0.001	1.45	3.33
Grading of the disease					
Controls	5.61±0.45				
Low	6.86±1.58	1.25	<0.001	0.42	2.10
Moderate	7.00±0.86	1.139	0.157	0.27	3.06
High	6.95±1.29	1.13	<0.001	0.061	2.08

Table 4: Univariate regression analysis showing the factors influencing the intimal-medial thickness among the study population (N=80).

Parameter	Linear regression coefficient	95% CI		P-value
		Lower	Upper	
Case vs control	1.31	0.86	1.76	<0.001
Age	0.048	0.023	0.073	<0.001
Gender (baseline=male)	0.107	0.695	0.482	0.719
TC	0.016	0.003	0.030	0.017
LDL	-0.006	0.014	0.025	0.563
HDL	-0.044	0.055	0.143	0.377
Smoking (baseline=present)	-1.103	0.016	2.190	0.047
Alcohol (baseline=present)	-1.265	0.44	0.297	0.144
Duration of symptoms (baseline=controls)	0.768	0.581	0.956	<0.001
Disease activity(baseline=controls)	0.451	0.266	0.637	<0.001

Table 5: Multivariate linear regression analysis of socio-demographic factors affecting intimal medial thickness among the study population (N=80).

Parameter	Linear regression coefficient	95% CI		P-value
		Lower	Upper	
Case vs control	1.31	0.86	1.76	<0.001
Age	0.040	0.021	0.058	<0.001
TC	0.009	0.018	0.001	0.073
Smoking	-0.272	0.471	1.015	0.468
Duration of symptoms	0.736	0.483	0.988	<0.001
Disease activity	0.008	0.224	0.209	0.944

DISCUSSION

The collateral consequence of rheumatoid arthritis is that it affects the CVS, which in turn could be the main cause of death among those affected decreasing their life expectancy by 3 to 10 years.[18,19] The combined effect of CV risk factors and sequelae of RA inflammation is overtly manifested by a significant rise in carotid

atherosclerosis in patients with RA, and each may modify one another's effects.[10]

The mean carotid intima-media thickness (cIMT) significantly increased with increase in the duration of the RA among the cases (6.11mm in cases below 2 years and 8.00mm in those above 5 years of having the disease while it was 5.61mm among controls). The cIMT also varied and was higher among patients with different degrees of severity of RA (6.86mm in those with low RA and 6.95mm in those with high RA). I'm et al, and Kisiel et al, reported similar findings stating that the mean cIMT and carotid plaque thickness was higher among RA patients than in controls.[20,21]

Considerable epidemiological and clinical evidence have been showing that accelerated atherosclerosis may be one of the key aspects of RA.[2,4,22] The clinical significance of such findings can be understood when authors consider that the risk of myocardial infarction increases by up to 43% for every 0.163mm increase in cIMT.[2,12,13]

Recently numerous studies seem to the point that atherosclerosis risk is higher among those with rheumatological disorders, especially RA and systemic lupus erythematosus (SLE) due to accelerated vascular processes.[23,24] It is plausible that the inflammatory cascade and alterations in the immune response inherent to the pathogeneses of autoimmune conditions like RA and SLE may play a critical role in accelerating atherosclerosis due to increased risk of arterial wall damage and endothelial dysfunction.[25,26]

Patients with RA also have elevated C-reactive protein (CRP), a classical marker of inflammation that is often associated with CV risk.[8,20,21] This is in line with present study finding wherein 42.5% of RA patients had elevated CRP. Apart from this elevated ESR levels, which reflect cumulative inflammatory burden be independently associated with carotid plaque thickness, even suggesting a synergistic interaction with traditional CV risk factors.[20,27]

One of the limitations of present study, which is inherent to non-longitudinal studies is that the inflammation markers measured at a single point of time may fail to be associated with cIMT.[28] There are two possible explanations for this. First, the patients included in present study and others of a similar kind have a wide range of disease activity with associated inflammatory markers. Second, it is the cumulative effect of prolonged inflammation that increases the susceptibility to accelerated atherosclerosis.[28] Two studies from Japan, one by Kumeda et al, and another by Nagata-Sakural et al, confirmed that longitudinal studies assess the markers of inflammation more accurately than cross-sectional studies.[29,30] Considering the lower sample size, the role of various potential confounders, which are already proven risk factors for increasing carotid intimal medial thickness could not be evaluated. Long-term prospective studies, with higher sample size, can help us in understanding the attributable factors of carotid intimal medial thickening and related cardiovascular sequelae, after adjusting for the effect of all the proven risk factors.

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