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Original Article

Assessment of Atherosclerosis by Carotid Intima-media Thickness in Patients with Rheumatoid Arthritis

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology marked by a symmetric peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. Atherosclerosis is emerging as an important complication of RA, with coronary artery disease being the major cause of mortality in these patients.

Materials and Methods: Study includes 65 RA patients and 65 normal healthy controls. Ultrasound examinations of the carotids were carried out both in cases and controls by SIEMENS ACUSON X300 diagnostic ultrasound system.

Results: Mean carotid intima-media thickness (CIMT) in RA patient was statistically significant more than controls. In this study, the prevalence of asymptomatic (subclinical) atherosclerosis in RA patients was 32.3%. In RA patients age, duration of RA and serum triglyceride level demonstrated significant univariate correlation with CIMT (<0.05). On multivariate linear regression analysis duration of RA and serum triglyceride level were found to have a significant correlation with CIMT ($P < 0.05$).

Conclusion: Patients with RA had higher mean CIMT. Prevalence of asymptomatic (subclinical) atherosclerosis is more in RA patients as compared to normal healthy people.

Key words: Rheumatoid arthritis, CIMT, IMT, CAD, Atherosclerosis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology marked by a symmetric peripheral polyarthritis.[1] It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. it is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. It affects the synovial tissue and underlying cartilage and bone. The pathological hallmarks of RA are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage. Atherosclerosis is emerging as an important complication of RA,with coronary artery disease being the major cause of mortality in these patients.[2] The inflammatory events in RA patients play an important role in acceleration of atherosclerosis process. Asian Indians as an ethnic group are predisposed to higher incidence of insulin resistance (metabolic syndrome),obesity and premature atherosclerosis.[3,4] Atherosclerotic changes at the carotid bifurcation are a well-known cause of cerebrovascular disease ranging from thromboembolic transient ischemic attacks due to small emboli of fatty debris and platelet aggregates to completed strokes due to carotid thrombosis and secondary embolism.[5] B-mode ultrasound allows for direct visualization of both the vessel wall and the lumen and, subsequently, for detection of early atherosclerosis, indicated by intima-media thickening(IMT). Increases in carotid IMT are directly associated with an increased risk of cardiovascular disease.[6,7] Carotid intimo-medial thickness is a widely accepted surrogate marker of atherosclerosis. It is a reliable, simple and noninvasive marker of subclinical atherosclerosis.[8]

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Aims and Objectives

The aims are to determine the prevalence of subclinical (asymptomatic) atherosclerosis in patients with rheumatoid arthritis (RA).

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To study the determination of disease activity in RA and correlation with CIMT and determination of FLP in RA and correlation with CIMT.

MATERIALS AND METHODS

The study was conducted in the Department of Medicine (Medicine ward and OPD), Netaji Subhash Chandra Bose Medical College, Jabalpur (M.P.), India. Hospital based cross-sectional study was from March 2015 to August 2016. The study includes 65 RA patients and 65 normal healthy controls.

Exclusion Criteria

Patients and control subjects exhibiting traditional risk factors such as hypertension (blood pressure >140/90 mmHg), smoking, diabetes mellitus, and clinically manifest atherosclerosis by way of CAD, peripheral vascular disease, and cerebrovascular disease were excluded from the study. Similarly, patients and controls are known to have dyslipidemia and on treatment for the same were excluded. Patients with disease onset below 18 years, disease duration <5 years, and RA overlap with other rheumatic diseases were excluded from the study. Patients are not willing to be a part of the study.

Methods

All patients were subjected to full history taking including age, sex, duration of RA, presenting complaints, history, treatment history, and addiction history, family history of RA, and presence of associated comorbidities.

Following investigations were included in the study:

- Complete blood count with erythrocyte sedimentation rate.
- Blood urea, serum creatinine, and serum electrolytes.
- Fasting lipid profile- low-density lipoprotein (LDL), high-density lipoprotein (HDL), very LDL (VLDL), triglycerides, and cholesterol.
- Fasting blood sugar and postprandial blood sugar.
- C-reactive protein and RA factor.

Measurement of CIMT

Ultrasound examination of the carotids was carried out both in cases and controls by SIEMENS ACUSON X300 diagnostic ultrasound system. Ultrasound examination of the carotids carried out for detection of CIMT. The carotid wall is seen as two parallel echogenic lines separated by a hypo-echoic line. The inner hypoechoic line is the lumen-media interface, and the outer line is the media-adventitia interface. The distance between the two lines is the combined intimo-medial thickness. Measurements were made bilaterally at the carotid bulb, 2 cm proximal to the bulb over the common carotid artery (CCA) near its origin.The mean of the six readings was used to calculate the CIMT. The CIMT, defined as the thickness, measured in the far wall of the CCA, from the media-adventitia interface to the intima-lumen interface (with a threshold value for subclinical vascular damage >0.9 mm).

Data Analysis

The data were fed into an excel spreadsheet and then tabulated. Data were statistically analyzed using *t*-test, Chi-square test, Fisher's exact test, and Karl Pearson's correlation using SPSS version 20 and Microsoft excel $P < 0.05$ was considered to be statistically significant.

RESULTS

The present study included a total of 65 RA patients and 65 healthy controls. Majority of cases (41.5%) and controls (43.1%) were in the age group of 40–49 years. Dyslipidemia was defined by high value of National Cholesterol Education Programme-Adult Treatment Panel III (NCEP ATP III) guidelines, that is (total cholesterol >200 mg/dL, LDL cholesterol >100 mg/dL, HDL cholesterol <40 mg/dL, and triglycerides >150 mg/dL).

In this study, 35.38% of patients have high cholesterol level, 67.69% of patients have high triglyceride level, 15.38% of patients have high LDL, and 35.38% of patients have low HDL level [Table 1].

Compared to cases in control group 12.3% of patients high cholesterol level, 38.46% of patients had high triglyceride level, 9.23% of patients had high LDL level, and 15.38% of patients had low HDL level.

In this study total cholesterol, LDL cholesterol, VLDL cholesterol, and serum triglyceride were higher in patients as compared to controls and HDL cholesterol level lower in cases as compared to controls total cholesterol 192.83 ± 41.242 versus 167.22 ± 28.777 mg/dL (<0.05), LDL cholesterol 103.474 ± 23.7529 versus 96.491 ± 20.2395 mg/dL ($P = 0.074$), VLDL cholesterol 33.169 ± 26.2932 versus 28.844 ± 15.0451 mg/dL ($P = 0.252$), serum triglyceride 190.78 ±7 4.269 versus 141.74 ± 28.423 mg/dl ($P < 0.05$), and HDL cholesterol 44.869 ± 9.4617 versus 56.365 ± 16.9516 mg/dL ($P < 0.05$) [Table 2].

In this study, there was the statistically significant difference in the total cholesterol, serum triglyceride, and HDL cholesterol of the patients and controls group. In this study, mean ± SD of CIMT in patients (0.7546 ± 0.193 mm) was significantly ($P = 0.000$) greater than controls (0.6385 ± 0.16672 mm) [Table 3].

Table 1: Profile of dyslipidemia in patients with RA and normal controls

Variable	Cutoff value as per NCEP ATP III GUIDELINES NO.	Patients with RA *n*=65 (%)	Normal controls *n*=65 (%)
High cholesterol (mg/dL)	>200	23 (35.38)	8 (12.3)
High triglyceride (mg/dL)	>150	44 (67.69)	25 (38.46)
High LDL (mg/dL)	>100	10 (15.38)	6 (9.23)
Low LDL (mg/dL)	<40	23 (35.38)	10 (15.38)

Proportion of dyslipidemia is more in cases as compared to controls. RA: Rheumatoid arthritis, LDL: Low-density lipoprotein

- 21 patients (32.3%) with RA had a higher mean CIMT (>0.9 mm).
- 4 normal healthy controls 6.15% are associated with higher mean CIMT (>0.9 mm).
- In this study, the prevalence of subclinical (asymptomatic) atherosclerosis in patients with RA is 32.3%.

The various continuous variables in patients of RA with CIMT >0.9 mm and <0.9 mm were compared using the median values of each continuous variable. The Pearson's Chi-square was applied to these variables [Table 4].

21 RA patients had mean CIMT >0.9 mm.

In RA patients age ($P = 0.007$), duration of RA ($P = 0.000$), and total triglyceride level ($P = 0.046$) were significantly associated with CIMT >0.9 mm.

RA patient with mean CIMT >0.9 mm had higher mean age (50.14 ± 6.747 years), longer mean disease duration (96.00 ± 14.199 months), and lower mean serum triglyceride level (164.33 ± 61.17 mg/dL).

Pearson's univariate coefficients of age 0.328 (0.004), duration of RA 0.393 ($P = 0.001$), and serum triglyceride level −0.229 ($P = 0.033$) demonstrated significant univariate correlation with CIMT [Table 5].

On applying multivariate linear regression analysis with age, duration of RA and total triglyceride level as the independent variables and CIMT as the dependent variable, only duration of RA and total triglyceride level were found to have a significant correlation with CIMT.

Utilizing the above regression model an equation to predict CIMT was derived =0.396 + 0.004 + (disease duration in months) −0.001 (serum triglyceride level).

The value of R for this model was 0.497, signifying that the correlation between the observed values of CIMT and those predicted by this model was 0.497. The value of R^2 (goodness of fit measure/coefficient of determination) for this model was 0.247 signifying that this model of regression explained 24.7% of the variation in CIMT.

Table 2: Demographic and lipid profile of patients and controls

Variables	RA (*n*=65)	Control (*n*=65)	*P* value
Age (years)	45.829±0.026	43.86±9.033	NS
Total cholesterol (mg/dL)	192.83±41.242	167.22±28.777	0.000
HDL- cholesterol (mg/dL)	44.869±9.4617	56.365±16.9516	0.000
LDL-Cholesterol (mg/dL)	103.4742±3.7529	96.491±20.2395	NS
VLDL-cholesterol (mg/dL)	33.1692±6.2932	28.8441±5.0451	NS
TGs (mg/dL)	190.787±4.269	141.742±8.423	0.000

In this study systolic BP, diastolic BP, total cholesterol, HDL cholesterol, and triglycerides level were found to be statistically significant ($P<0.05$) as compared to cases. RA: Rheumatoid arthritis, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, TGs: Triglycerides

Table 3: Comparison of CIMT among cases and controls

Variables	Mean±SD		
	Case	Control	*P* value
Rt mean CIMT (mm)	0.777±0.173	0.637±0.1746	*P*<0.000
Lt mean CIMT (mm)	0.746±0.2032	0.64±0.173	*P*<0.002
Total mean CIMT (mm)	0.7546±0.193	0.6385±0.166	*P*<0.000

Total mean CIMT value was found to be statistically significant in cases as compared to controls ($P<0.05$), CIMT: Carotid intima-media thickness, SD: Standard deviation

Table 4: Comparison of variables affecting CIMT

Variables	CIMT<0.9 *n*=44 (%)	CIMT>0.9 *n*=21 (%)	*P* value
Age	43.5±9.304	50.14±6.747	0.007*
BMI	22.839±3.10	22.905±3.346	0.938
Disease duration	81.82±13.515	96.00±14.199	0.000*
Systolic BP	120.73±6.264	123.71±6.820	0.086
Diastolic BP	76.61±4.205	77.14±4.498	0.644
Total cholesterol	189.45±34.060	199.90±53.583	0.343
HDL cholesterol	45.00±8.572	44.595±11.32	0.873
LDL cholesterol	103.155±23.111	104.143±25.61	0.877
VLDL cholesterol	35.459±30.955	28.371±10.787	0.313
Total triglyceride	203.409±77.22	164.33±61.17	0.046*

Age, disease duration, and serum triglyceride level ($P<0.05$) significantly associated with CIMT>0.9 cm, CIMT: Carotid intima-media thickness, SD: Standard deviation, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

In this study based on DAS 28. Disease activity scores each group studied as Group A (DAS <2.6, remission),

Table 5: Univariate correlation coefficients of various factors affecting CIMT

Variables	Pearson's univariate correlation coefficient (P)	Multivariate regression analysis (SE)	*P*
Age	0.328 (0.004)*	0.003 (0.002)	0.157
Disease duration	0.393 (0.001)*	0.004 (0.001)	0.007*
Triglycerides	−0.229 (0.033)*	−0.001 (0.000)	0.033*
Total cholesterol	0.064 (0.306)		
HDL cholesterol	0.082 (0.257)		
LDL cholesterol	0.054 (0.334)		
VLDL cholesterol	−0.053 (0.339)		

CIMT: Carotid intima-media thickness, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein

Group B (2.6–3.2, low), Group C (>3.2–5.1, moderate), and Group D (>5.1, high) in these groups the relationship of activity of RA with CIMT was studied.

In Group C (>3.2–5.1) the value of CIMT was found to be maximum mean ± SD 0.8361 ± 0.16323 mm [Table 6]. Patients with RA duration <7 years mean ± SD of CIMT was (0.7188 ± 0.1496).

Patients with RA duration 7–8 years mean ± SD of CIMT was (0.8429± 0.186 mm). Patients with RA duration >8 years mean ± SD of CIMT was (0.8591 ± 0.157 mm).

Patients with RA duration >8 years had more mean CIMT value [Table 7].

Table 6: Correlation of DAS 28 with mean CIMT

DAS	Number	Mean CIMT±SD (mm)
<2.6	19	0.7342±0.160
2.6–3.2	21	0.7476±0.168
>3.2–5.1	18	0.8361±0.163
>5.1	7	0.7571±0.200.

RA patients with DAS28>3.2–5.1 had maximum value of mean CIMT 0.8361±0.0163, CIMT: Carotid intima-media thickness, SD: Standard deviation

Table 7: Comparison of duration of RA with mean CIMT

Duration of RA	Number of RA patients	CIMT (mean±SD) (mm)
<7 years	40	0.7188±0.1496
7–8 years	14	0.8429±0.186
>8 years	11	0.8591±0.157
Total	65	0.7692±0.16972

Mean CIMT value higher in RA patients with duration>8 years, CIMT: Carotid intima-media thickness, SD: Standard deviation, RA: Rheumatoid arthritis

DISCUSSION

The patients with RA have a 2 to 5 times increased the risk of developing a premature cardiovascular disease that shortens life expectancy by 5–10 years. Thus, in patients with active RA, the majority of cardiovascular deaths result from accelerated atherosclerosis.[9]

The inflammatory events in RA patients play an important role in the acceleration of atherosclerosis process. Atherosclerosis, previously thought to be a passive disease of lipid accumulation, is now widely acknowledged as a dynamic inflammatory process beginning with endothelial activation, leukocyte recruitment, lipid oxidation, and culminating with plaque destabilization, and thrombosis. In RA although the primary site of inflammation is the synovial tissue, cytokines such as tumor necrosis factor α, interleukin (IL1β), and IL 6 are released into systemic circulation. These circulating cytokines alter the function of distant tissues, including adipose tissue, skeletal muscle, and liver which leads to dyslipidemia.[10]

Atherosclerotic changes at the carotid bifurcation are a well-known cause of cerebrovascular disease ranging from thromboembolic transient ischemic attacks due to small emboli of fatty debris and platelet aggregates to completed strokes due to carotid thrombosis and secondary embolism. In this study, the prevalence of asymptomatic (subclinical) atherosclerosis in RA patients was 32.3%. In RA patients age, duration of RA and serum triglyceride level demonstrated significant univariate correlation with CIMT (<0.05). On multivariate linear regression analysis duration of RA and serum triglyceride level were found to have a significant correlation with CIMT ($P < 0.05$).

CONCLUSION

Patients with RA had higher mean CIMT.

Prevalence of asymptomatic (subclinical) atherosclerosis is more in RA patients as compared to normal healthy people.

Duration of RA and total triglyceride level were found to have a significant correlation with CIMT.

Increased duration of RA was associated with the higher value of CIMT.

Limitations of Study

Some patients with RA were taking corticosteroids and methotrexate, and since both of these drugs are known to

be having atherogenic effects, this can be a confounding factor in our study.

Since our sample size was small due to a lesser number of patients attending OPD, this was insufficient to estimate the exact prevalence of atherosclerosis in patients with RA.

ABBREVIATIONS

- FLP – fasting lipid profile
- CAD – coronary artery disease
- IL 1β - interleukin 1β
- IL 6 - interleukin 6
- OPD – outpatient department
- CIMT – carotid intimo-medial thickness
- IMT - intimo-medial thickness
- RA – rheumatoid arthritis

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