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Original Article

Is There Any Relationship between Joint Destruction and Carotid Intima-media Thickness in Patients with Rheumatoid Arthritis?

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Abstract. [Purpose] The purpose of this study was to investigate the possible relationship between joint destruction and carotid intima-media thickness in patients with rheumatoid arthritis. [Subjects and Methods] Thirty-four RA patients and 31 healthy controls were enrolled in this study. The disease activity for 28 joints was recorded for each patient using the erythrocyte sedimentation rate ($DAS28_{ESR}$), a visual analog scale ($VAS_{0–10\ cm}$), and a disability index, the health assessment questionnaire (HAQ). X-ray imagesof the patients were scored according to the modified Sharp/van der Heijde method, and the common carotid intimal medial thickness (CIMT) was automatically measured with software using high-resolution Doppler ultrasound. [Results] Contrary to our hypothesis, the modified total Sharp score (mTSS) and CIMT were not significantly associated. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels of the RA patients and the right CIMT, left CIMT, and mean CIMT scores were significantly elevated. Positive correlation was detected between the mean CIMT score and age, CRP levels, LDL concentration and triglycerides (TG) level. In the regression model, where the mean CIMT was the independent variable and age, CRP, LDL, and TG were dependent variables, age was found to be an independent predictor of CIMT. [Conclusions] Patients suffering from RA require close monitoring for cardiovascular risks, and the comorbidity of age-related cardiovascular disease should not be overlooked.
Key words: Rheumatoid arthritis, Common carotid intima-media thickness, Modified total Sharp score

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory, multisystemic autoimmune disorder that affects (mostly) diarthrodial joints[1)]. It is associated with an increased morbidity and mortality due to cardiovascular disease (CVD); however, the reason for the increased risk of CVD is not explained by traditional risk factors[2, 3)]. In several studies, positive correlations have been shown between the increased disease activity in RA and increased erythrocyte sedimentation rate (ESR)[4)], severe extra-articular manifestations[5)], rheumatoid factor seropositivity[6)], elevated C-reactive protein levels (CRP)[6, 7)], and cardiovascular mortality.

The presence of inflammation leads to endothelial activation and dysfunction, and this is regarded as the primary finding of atherosclerosis[8, 9)]. Subclinical atherosclerosis and vascular structure are measured through a noninvasive method of carotid intima-media thickness (CIMT) measurements in patients with RA[10)]. In addition to predicting the presence of local atheroma, the findings of CIMT can reveal possible damage to the arterial system[11)]. Recent studies have shown increased CIMT scores in RA patients in contrast to healthy controls[12, 13)].

In RA, radiographic assessment of joint damage is the most widely accepted standard for following the course of the disease[14)]. RA is more severe, progressive, and destructive during the early stage[15)], and although inflammation has a negative impact on functional capacity in early RA, increased erosion and joint destruction become more pronounced at the further established stages[16)]. This joint destruction increases the health assessment questionnaire (HAQ) scores of established RA patients[16)]; however, it has been clearly indicated that the real marker of the increment in HAQ score in established RA patients is the Disease Activity Score (DAS)[17)]. In several studies, the joint destruction of RA patients has been measured using the van der Heijde modification of the Sharp method (mTTS)[18, 19)].

Inflammation in RA patients leads to joint destruction

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and subclinical atherosclerosis, and the presence of elevated joint destruction can be a preclinical condition for cardiovascular risk detection. Based on the relationships of inflammation and rheumatoid arthritis with the atherosclerosis and joint destruction mentioned above, no research study has been performed, as of yet, to clarify this issue. We, herein, aimed to investigate the potential relationship between joint destruction and carotid intima-media thickness.

SUBJECTS AND METHODS

Thirty-four RA patients (10M/24F) admitted to the Physical Medicine and Rehabilitation Outpatient Clinic at Harran University School of Medicine, fulfilling the American College of Rheumatology criteria[20] for the diagnosis of RA, were consecutively enrolled in our cross-sectional study. Thirty-one healthy controls matched for age, sex, and BMI were recruited from the staff of the same hospital. The research protocol was approved by the Ethics Committee of the Harran University School of Medicine, and written informed consent was obtained from all subjects. Patients with any other inflammatory diseases, coronary arterial disease, liver disease, neoplastic disease, diabetes mellitus, hypertension, renal failure, history of stroke, or iron deficiency anemia were excluded from the study.

Each patient's disease activity was measured using the disease activity score for 28 joints with the erythrocyte sedimentation rate ($DAS28_{ESR}$)[21], and a visual analog scale ($VAS_{0–10\ cm}$) was used to measure pain. The disability of the RA patients was measured using the Health Assessment Questionnaire (HAQ) index, which ranges from 0 to 3.

The patients' fasting total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, ESR, and CRP concentrations were measured in the morning.

The patients' X-ray images were scored according to the modified Sharp/van der Heijde method by consensus of the readers: one experienced musculoskeletal radiologist and two clinical researchers. The maximum erosion score is 160 for the hand and 120 for the feet; the maximum score for joint space narrowing is 120 for the hands and 48 for the feet, resulting in a maximum total score of 448[22].

The images were obtained using a high-resolution Doppler ultrasound (MyLab Twice; Esaote, Genoa, Italy) with a 12 MHz linear-array transducer, and the CIMT was automatically measured with software. The patients were examined in a supine position at 30–45 degrees opposite the direction of neck extension. The CCA, ICA, and ECA carotid bulbs were morphologically evaluated with all visual segments at the axial level, and the CIMT was measured at the posterior wall when they were clearly visible in the longitudinal plane at 1–1.5 cm proximal to the distal carotid bulbs. Intima-media thickness (IMT) was measured as the distance from the leading edge of the first echogenic line to that of the second echogenic line. The first line represents the lumen-intima interface, and the second line the collagen-containing upper layer of the tunica adventitia. The CIMT scores of all patients were automatically recorded.

Table 1. Demographic and clinical data of patients and healthy controls (mean ±SD)

	Patients n=34	Controls n=31
Age (years)	40.55±8.00	38.83±6.21
Male/female (number)	10/24	8/23
BMI (kg/m^2)	24.84±1.89	24.67±1.86
Disease duration (months)	63.61±69.13	
$Pain_{VAS}$ (0–10 cm)	6.79±2.25	
SJC28	1.14±1.70	
TJC28	7.76±4.43	
$DAS28_{ESR}$	4.89±1.22	
HAQ	1.89±0.77	
ESR (mm)	33.94±22.02	8.93±3.45*
CRP (mg/dl)	1.50±2.56	0.33±0.13**
Rf (IU/ml)	47.76±23.23	
Total cholesterol (mg/dl)	167.49±34.68	152.80±33.28
LDL cholesterol (mg/dl)	109.69±31.70	97.41±23.04
HDL cholesterol (mg/dl)	46.82±9.50	41.77±5.21**
Triglyceride (mg/dl)	120.61±50.75	123.19±43.91
TC/HDL	3.69±1.00	3.68±0.80

* $p<0.001$; ** $p<0.05$. BMI, body mass index; CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HDL, high density lipoprotein; LDL, low-density lipoprotein; Rf, rheumatoid factor; SJC, swollen joints count; TC, total cholesterol; TJC, tender joints count; VAS, visual analog scale; tMSS, total modified Sharp score

All of the sonographic examinations were performed by the same examiner, who was unaware of the subjects' clinical status throughout the study.

Statistical analyses were carried out using SPSS 18.0 for Windows (PASW Statistics for Windows, SPSS Inc., Chicago, IL, USA), and between group comparisons were made using independent sample t-tests. Pearson correlation tests were used to determine the relationships between the variables, and multivariate linear regression analyses were performed to identify independent predictors of CIMT. All demographic and quantitative data are expressed as the mean ± standard deviation (SD). Differences with p values < 0.05 were considered to be statistically significant, and all results are expressed with a 95% confidence interval.

RESULTS

Demographic and clinical data of the patients and healthy controls are shown in Table 1. There was no significant difference in terms of age, gender, and BMI between the patients and the controls. The HDL levels of the patients were significantly higher than in the controls, and the ESR and CRP levels of the RA patients, right CIMT, left CIMT, and mean CIMT scores were significantly elevated. The CIMT of the patients and controls and the mTTS of the patients are shown in Table 2.

Positive correlation was detected between the mean CIMT score and age, and the CRP levels, LDL concentra-

Table 2. Common carotid artery IMTs and total Modified Sharp score (mean ±SD)

	Patients n=34	Controls n=31
Right CIMT	0.59±0.13	0.50±0.06**
Left CIMT	0.61±0.15	0.49±0.06*
Mean CIMT	0.60±0.14	0.49±0.06*
tMSS	66.17±30.79	

* p<0.001; ** p<0.05. CIMT, Common carotid artery intima-media thickness; tMSS, total Modified Sharp Score

Table 3. The relationship between patients' mean CIMT score and demographic, clinical, and laboratory characteristics

	Pearson's coefficient	B Regression coefficient[a]
Age (years)	0.628*	0.499**
Disease duration (months)	1.000	
$Pain_{VAS}$	0.201	
SJC28	0.307	
TJC28	0.021	
$DAS28_{ESR}$	0.249	
HAQ	0.246	
ESR	0.261	
CRP	0.429**	0.277
Rf	0.115	
Total cholesterol	0.083	
LDL cholesterol	0.387**	0.102
HDL cholesterol	−0.265	
Triglyceride	0.410	0.061
TC/HDL	0.252	
tMSS	0.164	

* p<0.001; ** p<0.05. [a]From multiple lineer regression analysis; BMI, body mass index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Rf, rheumatoid factor; SJC, swollen joints count; TC, total cholesterol; TJC, tender joints count; VAS, visual analog scale; tMSS, total modified Sharp

tion and triglycerides level were positively correlated. In the regression model in which the mean CIMT was the independent variable and age, CRP, LDL, and TG were the dependent variables, age was found to be an independent predictor of CIMT.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the relationship of CIMT and joint destruction with rheumatoid arthritis, and the main findings of the present study were that: (i) that contrary to our hypothesis, mTSS and CIMT were not significantly associated and (ii) that the CIMT scores were positively correlated with age, CRP levels, LDL concentration, and triglycerides level.

Radiographic follow-up is one of the most widely accepted methods of monitoring disease progression in RA patients. Additionally, mTSS as a radiographic measure evidently shows the effectiveness of medical options[18, 19]. It has also been proven that mTSS is associated with impaired hand function and elevated HAQ scores in RA patients[23]. These findings presumably differ from the CVD risk in the radiographic progression. In our study, the RA patients' CIMT scores were significantly elevated. Similarly, Veselinovic et al. determined that their RA patients' CIMT scores were significantly higher than in the controls, and the brachial artery flow-mediated vasodilatation values were lower, which was attributed to the development of endothelial dysfunction and accelerated atherosclerosis[13]. Adhikari et al. also studied early RA patients, and they reported the same findings as previous researchers[12].

According to the EULAR guidelines for cardiovascular risk management, low HDL levels with increased LDL and TG levels are a predictor of CVD in the general population[24]. Furthermore, if the SCORE model is used, increased TC/HDL levels could be an additional prognostic indicator in terms of CV risks[25]. In our study, the HDL levels of the patients were significantly higher than in the controls; however, the LDL, TG, and TC/HDL levels were not significantly different between the groups. These findings show that endothelial dysfunction and atherosclerosis in RA patients are seen at the early stages of RA and that existing data about the general population are not sufficient to evaluate RA patients.

Previously, the relationships between CIMT scores and cardiac events (myocardial infarction, angina pectoris, and coronary revascularization), cerebrovascular events (stroke or transient ischemic attacks), and hypertension were evidently shown[26, 27]. Moreover, the CIMT findings were worse, despite treatment with disease modifying drugs and biological agents like anti-TNF inhibitors[28, 29].

In order to determine the potential factors affecting CIMT in patients with RA, subjects with any comorbidity associated with CIMT progression were excluded from the study. For that reason, age was found to be the only independent predictor of CIMT in multivariate regression analysis. In parallel with our findings, one study has revealed increased CIMT scores with older ages[30]. Additionally, we detected a positive correlation between CRP and CIMT among the controls, but the regression analysis excluded CRP as an independent predictor. Unlike our results, Gonzalez-Gay et al. evidently proved that there is a positive association between the maximum CRP and CIMT scores[31] (Table 3).

The limitations of our study include a cross-sectional design and a small sample size. Despite the fact that our patients were not classified in terms of disease duration, we have tried to minimize the potential negative factors that may affect CIMT measurements.

In conclusion, patients suffering from RA require close monitoring for cardiovascular risks, and the comorbidity of age-related cardiovascular disease should not be overlooked. Although we could not detect a positive relationship

between CIMT and mTSS, further large-scale, multicenter, prospective studies are needed to clarify this issue.

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