Characteristics of the carotid intima-media thickness and atherosclerotic plaques of carotid arteries in elderly people with rheumatoid arthritis at University Medical Center Ho Chi Minh City

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease that has been strongly associated with atherosclerosis. Comprehensive cardiovascular disease (CVD) assessment is advised, which entails screening for asymptomatic atherosclerotic plaques using carotid ultrasound. The objective of this study is to examine the features of carotid ultrasound, including carotid intima-media thickness (cIMT) and carotid plaques (CP), and to compare these characteristics between individuals with RA and control subjects. **Materials and Methods**: A cross-sectional study involved 66 participants, including 40 RA patients and 26 controls. Medical history and physical examination were conducted by a rheumatologist, while cIMT and CP were recorded via carotid ultrasound. **Results**: cIMT was significantly higher in the RA group compared to the control group (0.94 (0.83 - 1.25) mm vs 0.84 (0.80 - 0.92) mm, p = 0.030) and the prevalence of increased cIMT was found significantly higher in RA-patients than non-RA patients (70.00% vs 38.46%, p = 0.011). Compared to non-RA patients, carotid plaques in the RA group were statistically more prevalent on either side of the carotid artery (left 57.50% vs. 26.92%, p = 0.015; right 67.50% vs 26.92%, p = 0.001) and bilateral CP was over three times more common in RA than controls (55.00% vs 15.38%, p = 0.001). cIMT was correlated with age and body mass index. **Conclusion**: The occurrence of subclinical atherosclerosis is higher among patients with RA than in the control participants without RA. Measuring cIMT and CP may be a useful guide to better assess CVD risk in patients with RA and enable clinicians to take interventions promptly.

Keywords: *rheumatoid arthritis, cardiovascular diseases, carotid intima-media thickness, carotid plaques, carotid ultrasound.*

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that significantly accelerates the atherosclerotic process and increases the risk of developing CVD by 1.5 times compared to the general population such as coronary artery disease, stroke, carotid artery disease, and peripheral arterial disease. Moreover, RA has been shown to elevate CVD mortality rates by 50 - 60% [1]. In the elderly with RA, the onset of cardiovascular diseases typically occurs earlier than in their peers without RA. Furthermore, cardiovascular diseases represent the leading cause of mortality within this specific patient group. In addition to the burden of traditional cardiovascular risk factors, the inflammatory process also contributes to adverse cardiovascular outcomes [2]. Characteristics of RA, such as disease activity and duration of disease, increase the cardiovascular risk in this patient group [3]. The cardiovascular disease (CVD) risk in patients with RA, as assessed by traditional CVD risk prediction algorithms, is lower than in reality, and these patients experience more cardiovascular events than estimated by these prediction models. In patients with RA, alongside lifestyle changes and maintaining low inflammatory activity, the European League Against Rheumatism (EULAR) recommends screening for asymptomatic atherosclerotic plaques, which plays a crucial role in assessing cardiovascular disease risk [4]. Atherosclerotic plaques can be detected through cardiovascular imaging at specific organs, such as carotid ultrasound. Carotid ultrasound allows for the detection of subclinical atherosclerotic plaques by measuring carotid intima-media thickness (cIMT) and visualizing carotid atherosclerotic plaque (CP) images. The prevalence of CP in patients with RA was found to be threefold higher than in those without RA, and bilateral plaques increase the risk of cardiovascular events by four times [5]. Due to the non-invasive nature, feasibility, and clinical accessibility of carotid ultrasound, subclinical atherosclerosis surrogates including cIMT and CP via carotid ultrasound have the potential to

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suggest systemic atherosclerotic status and predict cardiovascular events in the elderly with RA.

Therefore, we conducted this study with the aim of investigating the characteristics and comparing the carotid intima-media thickness and atherosclerotic plaques of carotid arteries in elderly patients with RA and those without RA

2. MATERIALS AND METHODS

2.1. Research subjects

Elderly patients (≥ 60 years old) with and without RA who visited the Rheumatology and Geriatrics outpatient clinics at the University Medical Center Ho Chi Minh City from August 2022 to March 2023.

2.1.1. Inclusion criteria

- *RA group:* Patients aged 60 and older with RA were diagnosed according to the classification criteria established by the American College of Rheumatology and the European League Against Rheumatism in 2010 (ACR/EULAR 2010).

- *Non-RA group:* Individuals aged 60 and older without RA, who agreed to participate in the study, demonstrated gender, age, and cardiovascular risk factors matching with the RA group.

2.1.2. Exclusion criteria

- Diagnosed with other autoimmune arthritis, other connective tissue disorders, myocardial infarction, transient ischemic attack, stroke, angina, or peripheral arterial disease.

- Currently experiencing an acute infection.

- Currently using blood lipid-lowering medication or having lipid-lowering therapy prescribed in the patient's medication regimen.

- Unable to understand Vietnamese or having cognitive issues that prevent the completion of the questionnaire.

2.2. Research methods

Study design: a descriptive cross-sectional study. The study protocol was approved by the ethics committee of the University of Medicine and Pharmacy at Ho Chi Minh City. All participants provided written informed consent before being included in the study.

Participants in the study were documented with detailed information regarding demographic and epidemiological characteristics (gender, age, occupation, height, weight, comorbidities, polypharmacy); features of atherosclerotic risk factors (history of hypertension, type 2 diabetes, chronic kidney disease, family history of early cardiovascular disease, smoking, physical activity); RA patients were assessed for clinical characteristics (number of tender joints, number of swollen joints, morning stiffness duration, disease duration) and disease activity using DAS28-CRP scores (DAS28-CRP = [0.56 x √ t28] + [0.28 x √ sw28] + [0.36 x Ln (CRP+1)] + [0.014 x (PtGA)] + 0.96) [6].

Subsequently, the assessment of intima-media thickness and atherosclerotic plaques in the carotid arteries was performed by a certified cardiovascular radiologist, using a 6 - 12 MHz linear probe with a high-resolution Logiq 7 doppler ultrasonography device (GE Medical Systems, Milwaukee, WI) based on the Mannheim carotid intima-media thickness and plaque consensus [7]. Results of blood tests were also collected including triglycerides, LDL-c, HDL-c, total cholesterol, rheumatoid factor (RF), anti-CCP antibodies, and C-reactive protein (CRP), which were conducted using the same test kits at the University Medical Center, Ho Chi Minh City. The intima-media thickness and atherosclerotic plaques in the carotid arteries of the RA group were then compared with those of the non-RA group.

In the current study, the intima-media thickness was considered increased when cIMT ≥ 0.9 mm. While atherosclerotic plaque was defined as a focal thickening on the arterial wall protruding towards the lumen and measuring > 0.5 mm or more than 50% of the adjacent arterial wall segment, or when the cIMT was > 1.5 mm [8, 9].

2.3. Statistical analysis

Statistical analysis was conducted utilizing Stata 14.0 software. To compare continuous variables, the t-test was employed for those with a normal distribution, while the Mann-Whitney U test was utilized for those lacking a normal distribution. For categorical variables, either the Chi-square test or Fisher's exact test was applied. The correlation between two variables was determined using the Spearman correlation. A p-value of < 0.05 was considered to indicate statistical significance.

3. RESULTS

3.1. Demographic, laboratory, and disease-related data

During the study period, 66 patients were enrolled, including 40 patients with RA and 26 non-RA patients.

RA and non-RA patients demonstrated comparable demographic characteristics, functional status (ADL, IADL, frailty), as well as comorbidities, and polypharmacy. Additionally, they exhibited similar atherosclerotic risk factors, including smoking, physical activity, family history of early-onset cardiovascular disease, hypertension, diabetes, and lipid profiles (Table 1)

Table 1. Demographic and clinical characteristics (n=66)

Characteristics		Total (n = 66)	Rheumatoid Arthritis (n = 40)	Controls (n = 26)	p
Age*		68 (64 - 71)	68 (65 - 71)	67 (63 - 71)	0.241[e]
Gender	Female, n (%)	56 (84.85)	35 (87.50)	21 (80.77)	0.456[a]
	Male, n (%)	10 (15.15)	5 (12.15)	5 (19.23)	
Body status	Weight (kg)	54.12 ± 6.84	55.28 ± 7.20	52.38 ± 5.99	0.094[c]
	Height (m)	154.92 ± 5.34	155.64 ± 4.97	153.85 ± 5.79	0.187[c]
	BMI (kg/m^2)	22.53 ± 2.31	22.79 ± 2.30	22.14 ± 2.32	0.269[c]
ADL dependence, n (%)		20 (33.33)	13 (32.50)	7 (26.92)	0.630[a]
IADL dependence, n (%)		52 (78.78)	31 (71.50)	21 (80.77)	0.751[a]
Frailty classification, n (%)	Non Fragile	14 (21.21)	9 (22.50)	5 (19.23)	0.444[b]
	Mild	31 (46.97)	17 (42.50)	14 (53.85)	
	Moderate	20 (30.30)	14 (35.00)	6 (23.08)	
	Severe	1 (1.52)	0 (0.00)	1 (3.85)	
Multimorbidity, n (%)		58 (87.88)	34 (85.00)	24 (92.31)	0.374[b]
Polypharmacy, n (%)		52 (78.79)	29 (72.50)	23 (88.46)	0.217[b]
Smoking, n (%)		0	0	0	-
Physical activity, n (%)		16 (24.04)	10 (25.00)	6 (23.08)	0.859[a]
Family history of early cardiovascular disease, n (%)		8 (12.12)	5 (12.50)	3 (11.54)	0.613[b]
Hypertension, n (%)		35 (53.03)	19 (47.5)	16 (61.54)	0.264[a]
Diabetes, n (%)		16 (24.24)	8 (20.00)	8 (30.77)	0.319[a]
Chronic kidney disease, n (%) (eGFR ≤ 60 ml/min/1.73 m^2)		0	0	0	-
HDL cholesterol (mg/dL)		48.36 ± 11.91	48.45 ± 13.03	48.21 ± 10.04	0.938[c]
LDL cholesterol (mg/dL)		127.17 ± 39.96	121.48 ± 43.96	136.67 ± 30.79	0.142[c]
Total cholesterol (mg/dL)		200.88 ± 54.35	194.53 ± 52.70	211.56 ± 56.54	0.231[c]

BMI, body mass index; ADL, activities of daily living, IADL, instrumental activities of daily living; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] *Chi square test*

[b] *Fisher's exact test*

[c] *Unpaired t-test with equal variances*

[e] *Mann-Whitney test*

** Median - Interquartile range*

Table 2. Features of the rheumatoid arthritis group (n = 40)

Characteristics	N = 40
Duration from RA diagnosis (months)	24 (9 - 48)
RF (UI/ml)	104.65 (20.67 - 185.65)
Anti-CCP (U/ml)	33.15 (1.4 - 195)
CRP (mg/L)	7.10 (3.35 - 23.05)

Characteristics	N = 40
DAS28 - CRP	3.50 (2.98 - 4.88)
Remission, n (%)	3 (7.50)
Low, n (%)	13 (32.5)
Moderate, n (%)	15 (37.5)
Severe, n (%)	9 (22.5)
csDMARDs use, n (%)	36 (90.00)
csDMARDs monotherapy, n (%)	16 (40.00)
csDMARDs combination, n (%)	20 (50.00)
bDMARDs, n (%)	7 (17.50)

RA, rheumatoid arthritis; RF, rheumatoid factor; anti-CCP, anti-citrullinated peptides; CRP, C-reactive protein; DAS28-CRP, 28-joint Disease Activity Score - C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; bDMARD, biological disease-modifying antirheumatic drugs.

Patients diagnosed with RA demonstrated highly elevated positive RF and anti-CCP antibody levels. The median DAS28-CRP score registered at 3.5 and the majority of patients experienced low to moderate disease activity. These patients were primarily treated with conventional DMARDs. Combination therapy involving multiple conventional DMARDs was administered to 50% of the RA patients, whereas a mere 17.5% received biological treatment (Table 2).

3.2. Characteristics of carotid intima-media thickness and carotid plaques in patients with rheumatoid arthritis and subjects without rheumatoid arthritis

Table 3. Carotid ultrasound characteristics (n = 66)

Characteristics		Total (n = 66)	Rheumatoid Arthritis (n = 40)	Controls (n = 26)	p
Catoid plaque characteristics	cIMT* (mm)	0.89 (0.81 - 1.18)	0.94 (0.83 - 1.25)	0.84 (0.80 - 0.92)	0.030[e]
	cIMT ≥ 0.9 mm, n (%)	38 (57.58)	28 (70.00)	10 (38.46)	0.011[a]
Right carotid plaque, n (%)		34 (51,51)	27 (67.50)	7 (26.92)	0.001[a]
Left carotid plaque, n (%)		30 (45.45)	23 (57.50)	7 (26.92)	0.015[a]
Bilateral carotid plaque, n (%)		26 (39.39)	22(55.00)	4 (15.38)	0.001[a]

cIMT, carotid intima-media thickness

[a]*Chi square test*

[e]*Mann-Whitney test*

**Median - Interquartile range*

The group with RA exhibited a statistically significant greater carotid intima-media thickness of 0.94 mm (0.83 - 1.25) compared to the non-RA group, which had a cIMT of 0.84 mm (0.80 - 0.92), p = 0.03. The prevalence of elevated carotid intima-media thickness was higher among the RA patients, with 70% presenting a cIMT ≥ 0.9 mm. Furthermore, the occurrence of carotid artery plaques on either the right or left side was significantly higher in the RA group relative to the control group. Specifically, 55% of the RA patients had plaques on both sides, a notably higher percentage than the 15.38% observed in the non-RA group (p = 0.001) (Table 3).

3.3. Correlation between carotid intima-media thickness (cIMT) and selected clinical features and laboratory values in the rheumatoid arthritis group

Table 4. Correlation between carotid intima-media thickness (cIMT) and selected clinical features and laboratory values in the rheumatoid arthritis group (n = 40)

	Carotid Intima-Media Thickness		
	r	**β coefficient (95% CI)**	**p**
Age (years)	0.40	0.024 (0.006 - 0.042)	0.011
BMI (kg/m^2)	0.36	0.051 (0.008 - 0.094)	0.020
RF (IU/ml)	0.15	0.0002 (-0.0004 - 0.001)	0.423
Anti-CCP (IU/ml)	-0.065	-0.008 (-0.016 - 0.016)	0.973
CRP (mg/l)	-0.24	-0.001 (-0.003 - 0.0005)	0.141
DAS28-CRP	-0.22	-0.051 (-0.126 - 0.025)	0.182

BMI, body mass index; RF, rheumatoid factor; anti-CCP, anti-citrullinated peptides; CRP, C-reactive protein; DAS28-CRP, 28-joint Disease Activity Score - C-reactive protein

In patients with RA, carotid intima-media thickness (cIMT) demonstrated a moderate positive correlation with age and BMI. However, we did not observe any correlation between cIMT and RF, anti-CCP, CRP, or disease activity as measured by the DAS28-CRP.

4. DISCUSSION

In the current study, the majority of patients in the RA group were female, comprising 80.77% of the cohort. This finding aligns with existing literature, which indicates that women have a 3 times higher prevalence of RA compared to men [10]. Similarly, Suad et al. (2020) reported an 84% female prevalence in their investigation of subclinical carotid artery atherosclerosis among patients with RA [11]. No significant differences were detected between the patient and control groups in terms of atherosclerotic risk factors, such as age, gender, physical activity, smoking, family history of early-onset cardiovascular disease, hypertension, diabetes, chronic kidney disease, and LDL-c. This congruence aided in mitigating confounding variables when comparing cIMT and the status of carotid artery atherosclerosis between these two groups.

Within the RA group, the median DAS28-CRP score registered at 3.5, with the majority of patients presenting low to moderate disease activity. The current study observed elevated concentrations of RF and anti-CCP, exceeding three times the upper limit, measuring 104.65 (20.67 - 185.65) ng/ml and 33.15 (1.4 - 195) ng/ml, respectively. These findings are consistent with the research of Ozisler et al. (2018) [12]. Such factors indicate a severe prognosis for RA and play a role in initiating biological treatment. Nevertheless, the current study reported that a mere 17.5% of patients were administered biological DMARDs. This could be attributed to limited access to biological therapies, especially due to financial constraints in developing countries. Furthermore, 90% of patients received conventional DMARDs, similar to the results of Ozisler et al. (2018) [12] and Marta et al. (2022) [9]. This suggests that conventional DMARDs remain the predominant first-line treatment option for patients with RA according to international guidelines.

The median cIMT was significantly higher in the RA group 0.94 (0.83 - 1.25) mm compared to the control group 0.84 (0.80 - 0.92) mm (p = 0.030), similar to the studies by Suad et al. (2020) [11] and Marta et al. (2022) [9]. However, the cIMT in our study was higher than that in the studies of these two authors. This difference may be due to variations in the study populations. Our study population was older (the median age for the RA and non-RA groups being 67 and 68, respectively) compared to the study population of Suad [11] (with median ages of 47 and 49 for the RA and non-RA groups, respectively) and that of Marta [9] (55 ± 13.1 for RA and 46.87 ± 12 for non-RA). Furthermore, a higher proportion of individuals in the RA group had a cIMT ≥ 0.9 mm (70.00%) than in the control group (38.46%), p = 0.011. These findings align with prior research by Martin et al. (2018) [8], indicating a higher risk of atherosclerosis and cardiovascular events in these patients.

Regarding the presence of carotid plaques, the RA group demonstrated a significantly higher prevalence

of right carotid plaques (67.50%) compared to the control group (26.92%), p = 0.001. Likewise, left carotid plaques were more prevalent in the RA group (57.50%) than in the control group (26.92%), p = 0.015. Moreover, the occurrence of bilateral carotid plaques was notably higher in the RA group (55.00%) than in the control group (15.38%), p = 0.001. These findings concur with those from the study by Martin et al. (2018), which also reported an increased prevalence of carotid plaques in individuals with RA. The presence of bilateral plaques has been shown to elevate the risk of cardiovascular events fourfold compared to the general population [5]. Consequently, the existence of carotid plaques, in conjunction with increased cIMT, emphasizes the amplified risk of atherosclerosis and cardiovascular events in patients with RA. The elevated risk of CVD outcomes might be attributed to the systemic inflammation process of RA apart from traditional risk factors [1]. This underlines the significance of monitoring and managing cardiovascular risk factors in this patient group, alongside controlling the underlying RA disease activity [1, 4].

In the patient group with RA, our study observed a moderate correlation between cIMT and age (r = 0.40, p = 0.011) and BMI (r = 0.36, p = 0.020). However, no correlation was found between cIMT and RF, anti-CCP, CRP concentrations, and disease activity as per the DAS28-CRP. Similarly, Ozisler et al. (2018) reported a correlation between cIMT and age but not with RF, anti-CCP, and CRP concentrations [12]. Marta et al. (2022) also showed that cIMT had no correlation with RF, anti-CCP, CRP concentrations, and DAS28-CRP, but was correlated with the mean CRP concentration from the previous five years [9]. From these results, it can be concluded that cIMT is positively correlated with age and body mass index, which corresponds with the literature, as these factors are known risk factors for cardiovascular disease. However, the absence of a correlation between cIMT and disease activity could be attributed to the fact that assessing disease activity at a single time point may not accurately represent long-term disease activity. Since the progression of atherosclerotic plaque formation occurs over time, a correlation between cIMT and disease activity at a single time point may not be evident.

5. CONCLUSION

Elderly patients with RA have a higher burden of atherosclerosis compared to their non-RA counterparts, as reflected in the increased carotid intima-media thickness and carotid artery plaques. Assessing the carotid artery using ultrasound can help provide better cardiovascular risk predictions, allowing clinicians to intervene promptly.

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