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Investigating the relationship between carotid intima-media thickness, flow-mediated dilatation in the brachial artery and nuclear heart scan in patients with rheumatoid arthritis for evaluation of asymptomatic cardiac ischemia and atherosclerotic changes

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Abstract

Background: Cardiovascular disease is the most common cause of death worldwide. In order to prevent and treat heart diseases, we need to estimate the trend of non-cardiac diseases with the cardiovascular system. Arthritis Rheumatoid is a chronic immune/inflammatory process which leads to subclinical atherosclerosis and increases cardiovascular disease. We examined the patients who referred to our nuclear medicine center for MPI and correlated their findings with flow-mediated dilatation (FMD) of the brachial artery and carotid intima-media thickness (CIMT) in arthritis rheumatoid patients.

Material and methods: A total 30 known cases with arthritis rheumatoid were referred to our department for MPI and the single-photon emission computed tomography (SPECT) imaging were visually and quantitatively evaluated by two nuclear medicine physicians and the correlation of the measured FMD and CIMT were evaluated and compared with ultrasonography data. Demographic information such as gender, age and sex and medical history (risk factors, cardiovascular sign and symptoms, lab findings, medication etc…) were recorded in questionnaire sheets and were analyzed by SPSS.20. Chi-square and student t-test were used for further analysis.

Results: The mean CIMT (R = 0.452 ± 0.07, L = 0.447 ± 0.08) and %FMD (R = 7.22 ± 8.66, L = 6.42 ± 11.88) were measured for all subjects. Age was the only parameter correlated with both right and left CIMT (P = 0.033 and P = 0.024, respectively). Among the patients, 26.7% had mild ischemia (SSS < 8) and 3 of them suffered from active arthritis rheumatoid. All **patients** with RA showed **normal** ventricular **ejection fraction** and normal volumes and among them, 93.3% had normal functional performance (normal wall motion…). Moreover, the mean CIMT and %FMD were not significantly different in ischemic and non-ischemic patients. Among ischemic patients, just the course of the disease was associated with CIMT and none of the parameters was correlated with FMD.

Conclusions: There is no significant statistical difference between ischemic and non-ischemic patients and also the functional performance with values of CIMT and FMD. Among all populations, the parameter of age, and in ischemic group, the course of disease were found as the only variable correlated with CIMT.

KEY words: brachial artery, flow-mediated dilatation, intima-media thickness, myocardial perfusion imaging, rheumatoid arthritis, gated SPECT, myocardial ischemia

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Background

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease with a global prevalence of 1–2% [1]. It is reported that RA has increased risk of cardiovascular events that are not fully explained by other classic cardiovascular risk factors. To that end, the relationship between RA, atherosclerosis and cardiovascular events is a controversial topic. RA and atherosclerosis share several pathomechanisms including inflammation [2]. The bold complaint of RA is joints involvement, however; atherosclerotic cardiovascular disease (CVD) is the main cause of morbidity and mortality in these patients. Therefore, an increased risk of CVD occurs even during the initial period of RA, hence; it may be considered as a possible clinical manifestation of the disease. Accordingly, it is necessary to achieve a correct understanding of the pathomechanisms commonly associated with the risks of both diseases to treat RA, reduce atherosclerosis and its subsequent effects on cardiovascular disease in these patients [2]. Patients with RA are more susceptible to myocardial infarction (2 to 3 folds), congestive heart failure (2 folds), sudden death (2 folds) and stroke (1.7 folds) [3].

The presence of chronic inflammatory immune processes leads to subclinical atherosclerosis and increases the incidence of cardiovascular events in these patients. The severity and chronicity of immune responses are directly related to atherosclerotic diseases in patients with RA [4, 5]. Inflammation-induced endothelial dysfunction causes early autogenesis onset and also it is associated with clinical manifestations of vascular disease including the progression of atherosclerotic plaque in late stages [6].

Atherosclerosis is a systemic process, endothelial dysfunction can be monitored in the peripheral circulation and the coronary system [7, 8]. Ultrasound examination of the flow-mediated dilation (FMD) after brachial artery occlusion is a physiological non-invasive technique for the evaluation of endothelial function [9, 10]. In this method, FMD is an endothelial response to stress caused by reactive hyperemia [10].

Ultrasound-based carotid intima-media thickness test (CIMT) is a non-invasive anatomical method for evaluation of subclinical atherosclerosis (without clinical evidence of atherosclerosis, such as cardiovascular disease, peripheral vascular diseases, etc.) [11]. This method is an excellent indicator of the large arteries atherosclerosis and the most common method for the study of early structural changes in the artery walls. A number of studies showed that CIMT was significantly higher in patients with RA than in the control group [12].

Atherosclerosis affects the arteries which lead to stenosis, obstruction and ultimately ischemic heart disease. Having that said, atherosclerotic indices are normally more severe in patients with ischemic heart disease than those without myocardial ischemia. It is noteworthy that if myocardial ischemia is diagnosed before the incidence of the clinically apparent disease the application of ultrasound (a non-invasive technique) to screen patients at risk of ischemic heart disease, can be replaced with more invasive methods such as angiography.

Therefore, in this study, we assessed the myocardial perfusion and function with gated SPECT, and CIMT and FMD in the brachial artery by using ultrasound in patients with RA. Then, we evaluated the relationship of these findings with myocardial ischemia and dysfunction in these patients.

Material and methods

Study participants

The present study is a descriptive cross-sectional study that was performed on 30 patients (20 to 60 years old) with a definitive diagnosis of RA, based on the clinical and laboratory tests (new 2010 ACR-EULAR criteria). A non-randomized sampling method was used on patients with a proven diagnosis of RA. The study was performed according to the World Medical Association Declaration of Helsinki and approved by local ethics committees.

One of the inclusion criteria is the passage of three years from the onset of the disease and receiving the classic drug for the treatment of RA. Patients were excluded from the study if they had metabolic diseases such as diabetes, hyperlipidemia, and hypertension, history of ischemic heart disease, atherosclerotic lesions, dysplastic vascular diseases, smoking and other rheumatic diseases.

After considering the inclusion and exclusion criteria, a questionnaire was separately completed for each individual including the information on gender, age, duration of disease, disease activity score (DAS), C-reactive protein (CRP), ESR, systolic blood pressure, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C).

Ultrasound

All ultrasonographic tests were performed by a radiologist with 10 years' experience of ultrasound assessment using a 12.5 MHz linear probe device (G50, Affiniti, PHILIPS, USA). To measure CIMT, the patient was placed in the supine position. The neck was stretched out and the face was fixed to the opposite side. Both carotid arteries were examined in both transverse and longitudinal views. CIMT was measured in the wall of the carotid artery common to each side 1–2 cm close to the bulb at three points and in the closest part of the carotid artery of each side, in the vicinity of its origin at three points and the mean of the three points was recorded in each side. This measurement was performed on both sides and the total thickness of the intima carotid artery was measured at four levels.

The brachial artery was studied in the supine position, after a ten minutes rest, from a vein that lacks permanent vascular access. First, the brachial artery size was measured in a 5–10 cm longitudinal scan above the antecubital fossa. The luminal size of the near and far wall IMT was determined. After recording the base size of the artery (D_0), the temporary ischemia was created by a cuff placed around the arm. The cuff was filled up to 200 mm Hg or 50 mm Hg above the systolic blood pressure for 5 minutes and then discharged and the second scan was measured 40 to 60 seconds after emptying the cuff. FMD was calculated as the percentage of change in the post-ischemia luminal size of the artery compared to the base and calculated by the formula $(D_1–D_0 / D_0 \times 100)$.

Image Acquisition and Processing

Patients were referred to the heart hospital for myocardial perfusion imaging (MPI) to investigate the presence or absence of ischemic and the functional performance. All patients were injected the standard dose (555 MBq) of ^{99m}Tc-MIBI after pharmacological stress test (according to the predefined standard Dipyridamole protocol). The same amount of ^{99m}Tc-MIBI was administered to acquire the rest phase data on the following day. All the images were

acquired 45–60 minutes post-injection. The patients were laid in supine position and imaging was performed with a dual-headed SPECT gamma camera (E-cam; SIEMENS) in a 90° orientation with a low energy high resolution (LEHR) collimators in a 180° angle from RAO to LPO. The images were acquired in the tomographic mode (SPECT), thirty-two 30-second projection images with a 64 × 64 matrix size in a step-and-shoot mode and zoom factor of 1.45.

All the images were read by two nuclear medicine physicians. The scans were all evaluated in both visual and quantitative methods using Cedars QGS/QPS (Cedars-Sinai Medical Center). The findings of this study were recorded in a questionnaire designed for this purpose.

Finally, the results were analyzed using SPSS for windows version 20.0 (IMB SPSS Statistics, USA). Descriptive data are expressed as mean and standard deviation, and student's t-test was used for quantitative variables and chi-square test for qualitative variables. The P values of lower than 0.05 were considered significant.

Results

In this study, a total of 30 patients including 29 females (96.7%) and 1 male (3.3%) with RA were recruited within 9 months. Twenty-five patients (83.3%) were housewives and others were employed. Positive and negative CRP results were seen in 8 (26.7%) and 22 patients (73.3%) with RA. According to the DAS, 19 (63.3%) and 11 patients (36.7%) suffered from inactive and active RA disease, respectively. The mean course of the disease was 5.52 ± 4.55 years. A summary of the demographic data and the common risk factors for their cardiovascular diseases are presented in Table 1.

Ultrasound findings

The mean of left and right CIMT were 0.458 ± 0.081 mm and 0.461 ± 0.106 mm, respectively. Also, the thickness of the right and left internal carotid arteries were calculated 0.446 ± 0.086 mm and 0.434 ± 0.07 mm, respectively. The FMD percentage was calculated 7.22 ± 8.66 and 6.42 ± 11.88 in the right and left brachial artery (Tab. 2).

In this study, Pearson and/or Spearman correlations test were used to examine the inter-variable correlation for each parameter (Tab. 3). The findings did not show any correlation between IMT and FMD in patients with RA ($p > 0.05$).

Table 1. Demographic and clinical data regarding common cardiovascular risk factors in all patients with rheumatoid arthritis

Measured parameters	Mean ± SD
Age	45.23 ± 9.09
Systolic blood pressure (mm Hg)	117.33 ± 9.16
Diastolic blood pressure (mm Hg)	79 ± 4.02
Course disease (Year)	6.52 ± 4.55
ESR (mm/h)	20.8 ± 14.25
LDL (mg/dL)	128.1 ± 25.17
HDL (mg/dL)	46.17 ± 9.09

Table 2. Mean intima-media thickness of carotid arteries and flow-mediated dilatation in the brachial artery in all patients with rheumatoid arthritis

Measured parameters			Mean ± SD
Mean Intima-media thickness (mm)		Right CCA	0.458 ± 0.081
		Left CCA	0.461 ± 0.106
		Total CCA	0.46 ± 0.087
		Right ICA	0.446 ± 0.086
		Left ICA	0.434 ± 0.07
		Total ICA	0.440 ± 0.071
Diameter (mm)	Baseline	Right BA	3.513 ± 0.47
		Left BA	3.540 ± 0.41
	After ischemia	Right BA	3.75 ± 0.46
		Left BA	3.75 ± 0.47
Flow-mediated dilatation (%)		Right BA	7.22 ± 8.66
		Left BA	6.42 ± 11.88
		Total BA	6.82 ± 7.38

CCA — common carotid artery, ICA — internal carotid artery, BA — brachial artery

Nuclear medicine scan findings

Myocardial perfusion scan was performed to assess the cardiac functional indexes, the presence or absence of stress induced ischemia, the extent of ischemia and the intended ischemic region. To survey the ischemia and its severity, among 30 patients with RA, 8 of them (26.7%) suffered from mild ischemia while 22 (73.3%) patients possessed normal MPI.

In addition, the comparison of measured parameters in individuals with and without ischemia showed that only the high systolic blood pressure in an asymptomatic cardiac ischemic group was close to the significant level ($p = 0.074$) and there was no significant difference between the two groups in terms of other parameters (Tab. 4).

Among 8 patients with ischemia, 5 (62.5%) of them had inactive RA, the remaining 3 (37.5%) patients had active RA; however, in non-ischemic subjects, these ratios were 14 (63.7%) and 8 (36.3%), respectively. There was no significant difference between the two groups in terms of disease activity score ($p = 0.976$). CRP test was positive for 3 ischemic and 5 non-ischemic patients ($p = 0.418$).

There was no significant relationship between the two groups of ischemic and non-ischemic RA patients in terms of mean CIMT in all four levels and the percentage of FMD in the right and left brachial artery (Tab. 5). Pearson's correlation test was used to investigate the relationship between IMT and risk factors among 8 patients with and without inducible ischemia and the results showed a significant positive correlation between age and IMT in right CCA[1] ($p = 0.057$) and left ICA[2] ($p = 0.038$) and a significant inclination in right ICA ($p = 0.095$). Moreover, a significant positive correlation was observed between the course of the disease and IMT in all four levels in RA ischemic patients ($p < 0.05$) (Tab. 6). Except for two patients (6.7%) with hypokinesia of septal wall, there is a normal

[1]common carotid artery

[2]internal carotid artery

Table 3. Correlation of main clinical parameters with IMT of CCA, RCA and FMD of BA in all patients with rheumatoid arthritis

	CCA - R		CCA- L		ICA - R		ICA- L		FMD - R		FMD - L	
	r	P	r	P	r	P	r	P	r	P	r	P
Age	0.342	0.064	0.304	0.102	0.280	0.125	0.254	0.175	-0.101	0.594	-0.295	0.112
Systolic blood pressure (mm Hg)	0.186	0.326	-0.127	0.503	0.017	0.928	-0.073	0.702	-0.014	0.943	-0.092	0.627
Diastolic blood pressure (mm Hg)	0.080	0.674	-0.254	0.176	0.072	0.704	-0.113	0.550	-0.005	0.981	-0.080	0.674
Course disease (Year)	-0.041	0.829	-0.072	0.706	-0.031	0.870	-0.014	0.942	-0.300	0.107	-0.036	0.851
Activity disease	0.026	0.893	-0.042	0.831	0.084	0.665	-0.057	0.768	0.152	0.431	-0.019	0.922
ESR	0.082	0.666	-0.078	0.680	0.091	0.631	-0.095	0.618	0.068	0.720	-0.088	0.643
CRP	-0.067	0.727	-0.135	0.475	0.112	0.557	-0.219	0.244	-0.120	0.529	-0.043	0.823
LDL	-0.297	0.118	-0.030	0.877	0.046	0.811	-0.170	0.378	0.175	0.363	0.146	0.451
HDL	-0.013	0.947	-0.128	0.509	-0.080	0.680	0.127	0.510	-0.088	0.648	0.152	0.431

CCA — common carotid artery, ICA — internal carotid artery, FMD — flow mediated dilatation, R — right, L — left

Table 4. Comparison of mean demographic and cardiovascular risk factors in patients with and without ischemic heart disease

Measured parameters	Ischemic patients	Non-ischemic patients	P-value
Age (year)	43.62 ± 10.79	45.82 ± 8.6	0.568
Systolic blood pressure (mm Hg)	121.88 ± 6.51	115.68 ± 9.54	0.074
Diastolic blood pressure (mm Hg)	80 ± 0.0	78.64 ± 4.67	0.597
Course disease (Year)	5.75 ± 2.25	6.8 ± 5.15	0.587
ESR	23.62 ± 15.99	19.77 ± 13.82	0.522
LDL	129.71 ± 16.76	127.59 ± 27.63	0.850
HDL	44.71 ± 3.30	46.64 ± 10.30	0.635

Table 5. Comparison of mean CIMT and BA FMD in patients with and without ischemic heart disease

Measured parameters			Ischemic patients	Non-ischemic patients	P-value
Mean Intima-media thickness (mm)		Right CCA	0.483 ± 0.10	0.450 ± 0.07	0.333
		Left CCA	0.462 ±0.10	0.458 ± 0.12	0.933
		Total CCA	0.483 ±0.10	0.450 ± 0.07	0.333
		Right ICA	0.448 ±0.08	0.441 ± 0.09	0.853
		Left ICA	0.433 ± 0.10	0.434 ± 0.05	0.961
		Total ICA	0.470 ± 0.11	0.456 ± 0.07	0.689
Diameter (mm)	Baseline	Right BA	0.441 ± 0.06	0.437 ± 0.09	0.891
		Left BA	3.70 ± 0.40	3.48 ± 0.41	0.210
	After ischemia	Right BA	3.67 ± 0.53	3.77 ± 0.44	0.601
		Left BA	3.88 ± 0.49	3.70 ± 0.46	0.342
Flow-mediated dilatation (%)		Right BA	5.91 ± 7.40	7.69 ± 9.18	0.626
		Left BA	5.14 ± 7.4	6.88 ± 13.26	0.730
		Total BA	86.48 ± 10.8	6.21 ± 5.90	0.913

CCA — common carotid artery, ICA — internal carotid artery, BA — brachial artery

systolic and diastolic function and volumes in the rest of these patients.

Discussion

The ultrasound-based measurement of the FMD of peripheral arteries and IMT of the carotid artery is a non-invasive technique for the diagnosis of atherosclerosis in patients with RA [13]. Our study showed, RA patients possess higher carotid arteries IMT and lower brachial artery FMD in comparison with in control subjects.

So far, there are several reports from different countries about the prevalence of subclinical atherosclerosis in patients with RA. Most of these studies focused on long-standing and a few of them [13, 14] concentrated on early stages (less than 12 months old) of RA in the subjects. Some studies investigated both IMT and FMD markers while others studied only IMTs to predict subclinical

Table 6. Correlation of main clinical parameters with IMT of CCA, RCA and FMD of BA in rheumatoid arthritis patients with ischemic heart disease

	CCA - R		CCA- L		ICA - R		ICA- L		FMD – R		FMD - L	
	r	P	r	P	r	P	r	P	r	P	r	P
Age	0.693	0.057	0.594	0.121	0.628	0.095	0.735	0.038	-0.110	0.795	-0.543	0.164
Systolic blood pressure (mm Hg)	0.682	0.062	0.614	0.105	0.374	0.361	0.333	0.420	-0.086	0.839	0.199	0.839
Course disease (Year)	0.905	0.002*	0.858	0.006*	0.877	0.004*	0.809	0.015*	0.094	0.825	-0.128	0.763
Activity disease	-0.126	0.767	-0.231	0.582	-0.076	0.857	-0.335	0.417	-0.019	0.964	0.367	0.330
ESR	0.150	0.722	-0.009	0.984	0.042	0.921	-0.195	0.643	0.158	0.709	0.337	0.415
CRP	-0.126	0.767	-0.231	0.582	-0.076	0.857	-0.335	0.417	-0.019	0.966	0.397	0.330
LDL	0.002	0.996	-0.186	0.690	-0.134	0.775	-0.420	0.348	0.277	0.548	0.677	0.095
HDL	-0.332	0.467	-0.257	0.578	-0.318	0.487	-0.490	0.264	0.477	0.278	0.703	0.078

CCA — common carotid artery, ICA — internal carotid artery, FMD — flow mediated dilatation, R — right, L — left

atherosclerosis. However, these studies pointed out the importance of IMT and FMD determination as a useful tool to assess the risk of cardiovascular disease as the most common cause of mortality in RA patients.

In this, we measured IMT in two levels (common and internal carotid artery) at four points (on both sides of the body) which is the advantage of this study in comparison with others. Some studies failed to prove increased IMT in patients with RA in comparison controls; having that said, this design aimed to provide a more accurate comparison while reducing the effect of the error. Besides, the present study was the comparison of these two markers in two subgroups of RA patients with and without silent cardiac ischemia confirmed by a cardiac perfusion scan.

According to our findings, the mean IMT on both sides of the CCA and ICA were 0.460 ± 0.67 mm and 0.440 ± 0.071 mm, respectively. To that end, Ristic et al. performed a study to compare women with long-term RA and the same age-matched healthy control group. They reported a higher value for carotid IMT in patients with RA than the control group in all measured positions [15]. The mean CCA of both sides in patients with RA was 0.671 ± 0.119 mm, which was significantly greater, compared to the control subjects (0.621 ± 0.085) and the mean ICA in the RA group was 0.577 ± 0.10 mm and 0.535 ± 0.076 mm in the control group.

Ristic et al. performed a study which the mean of age was close to ours (45.3 ± 0.10 compared to 45.23 ± 9.09 years), even though their reported average course of the disease was slightly higher than ours (7.1 ± 5.4 compared to 5.52 ± 4.55 years). Therefore, it can be stated that the lower values of IMT in our study may be due to the high number of participants in the early stages of the disease and the lower course of the disease (less than 5 years).

Articles that have reviewed patients with long-standing RA, reported higher IMT values than the present study [16–18]. However, Adhikari et al. study which was performed on a group of people with early stages of rheumatoid arthritis (less than 12 months old), reported IMT values very close to our study [13].

There are many discussions about the risk of developing CVD and the course of the disease. For example, in the study on the health of nurses, scientists have posed the possibility of an increased risk of cardiovascular disease only in patients with a disease course for more than 10 years. Del Ricon et al. stated that the effect of the disease course was only significant after the age of 60 [4], whereas people under the age of 60 participated in our study. Some also mentioned more invasive rheumatoid arthritis treatments as a reason for no relationship between IMT values and the course of the disease.

Adhikari et al. reported mean values for FMD are very close to our study (6.82 ± 7.38%). In this study, the FMD value in patients with RA (5.26%) was significantly lower than that of the control group (10.34%) ($p = 0.004$) [13]. Fan et al. also found that the percentage of FMD of the brachial artery in patients (5.45% ± 2.65%) is significantly lower than that of the control group (8.47% ± 2.85%) ($p < 0.001$) [17].

Overall, the scientists showed a higher IMT of carotid arteries and lower FMD of the brachial artery in patients with RA than the control group, indicating subclinical atherosclerosis in these patients [19, 20]. These results are very important in evaluating the cardiovascular outcomes and suggest alternative subclinical atherosclerosis markers that can predict the risk of cardiovascular diseases, especially the incidence of this disease in these patients. However, these studies did not investigate the predictive power of these markers in certain cases of cardiovascular diseases, especially silent myocardial ischemia, which is highly prevalent in these patients.

In our study, when patients were compared to investigate the presence of inducible ischemia using nuclear medicine imaging, 8 patients (26.7%) had mild ischemia. Although the mean IMT of the common and internal carotid artery in the ischemic group (0.470 ± 0.11 mm and 0.441 ± 0.06 mm, respectively) was higher than that of the non-ischemic group (0.456 ± 0.07 mm, 0.437 ± 0.09 mm, respectively), but this difference was not statistically significant.

Carlos Gonzalez-Juanatey et al. studied the effect of carotid IMT in predicting cardiovascular diseases, including silent myocardial ischemia, and found that only 9% of patients had stress induced ischemia [16]. Among the studied clinical factors, there was a significant difference only in the cardiovascular disease group with old patients. Among the ultrasound markers, the higher carotid IMT and the number of patients with carotid plaque were more significant. In their study, only the IMT value of the right common carotid artery

was measured which was 1.01 ± 0.16 and 0.74 ± 0.12 mm Hg in patients with and without cardiovascular diseases, respectively [16]. However, in our study, the mean IMT of the right carotid artery was 0.483 ± 0.10 mm and 0.450 ± 0.07 mm in patients with and without ischemia, respectively. in contrast to Gonzales-Juanatey et al., we found no statistically significant relationship.

One of the reasons for this difference is the higher age of the Gonzales_Juanatey et al. patients, considering the fact that atherosclerosis is a chronic process strongly associated with age, this difference is reasonable. Longer disease course can be accounted for as another factor in their study. The course of RA disease for Gonzales_Juanatey et al. patients was 20.5 ± 5.9 (patients with CVD) and 21.2 ± 8.8 (patients without CVD) years; however, in our study, the course of the disease was 5.75 ± 2.25 (patients with myocardial ischemia) and 6.8 ± 5.15 (patients without myocardial ischemia) years.

Interestingly, Gonzales-Juanatey et al. observed that none of the subjects with IMT less than 0.77 mm suffer from cardiovascular disease, and 6 out of 10 patients with carotid IMT greater than 0.91 mm cardiovascular disease was part of the group with CVD [16]. In the present study, the diagnosis of ischemia, despite the mean IMT of less than 0.77 mm in people with inducible ischemia, may be indicative of a higher detection power and a higher sensitivity of the nuclear medicine imaging in the diagnosis of myocardial ischemia; science, Gonzales-Juanatey et al. diagnosed ischemia using electrocardiography [16].

In the present study, when the relationship between the common risk factors of atherosclerogenesis with IMT and FMD were examined, a correlation between age and IMT was observed only in the right CCA position. In different studies, Fan et al. [17], Amin et al. [19] and Adhikari et al. [13] found a positive correlation between the age and magnitude of IMT of the common carotid artery.

When the correlation between common risk factors of cardiovascular disease, IMT and FMD in the subgroup of silent ischemia was studied, a significant positive correlation between age and IMT was found in the right CCA and left ICA and the tendency of a significant correlation in the right ICA. In a study conducted by Gonzales et al., after examining the models that measure the effect of various risk factors on the progression of carotid IMT and incidence of cardiovascular disease, it was found that age has an independent larger or similar effect with other risk factors for cardiovascular disease such as hypertension or dyslipidemia [9]. Also, there was a significant positive correlation between the course of the disease and IMT in all four levels of ischemia in patients with RA. The course of RA is considered as a risk factor for the early onset of atherosclerosis, but similar studies have shown contradictory findings.

Contrary to the fact that serum lipids are a strong predictor of atherosclerogenesis, our study did not show any correlation between IMT and lipid levels, which is in agreement with Ristic et al. reported results [15]. Chronic inflammation, which is the main characteristic of rheumatoid arthritis, plays a major role in exacerbating atherosclerosis [15]. In our study, there was no correlation between IMT and inflammatory markers of ESR and CRP. Likewise, Ristic et al. [15] and Gonzalez-Gay et al. [5], failed to demonstrate this correlation, while Fan et al. [17] and Amin et al. [19] found a significant correlation between IMT and CRP. The possible explanation for this result is that the exacerbation of atherosclerosis depends on the cumulative effect of prolonged inflammation. Therefore, measuring inflammatory markers at a single time point may not be related to IMT [15]. This finding was confirmed by studies conducted in Japan which showed that the effect of inflammation was more accurately detected in longitudinal than in cross-sectional studies [21, 22].

Some limitations of the present study include the inadequate number of participants and the absence of a control group due to the need to perform a myocardial perfusion scan for all patients.

Conclusions

In the present study, although there was no significant difference between the group with inducible ischemia and without inducible ischemia and no relationship between functional indexes and various values of subclinical atherosclerosis indices (IMT and FMD). it is noteworthy that the higher IMT values in patients with inducible ischemia and its relation with age and course of the disease showed the need for larger and wider studies to suggest ultrasound as a tool for screening people with rheumatoid arthritis at risk of ischemia.

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