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Characteristics of atherosclerotic plaque and the thickness of the carotid artery intima-media complex in patients with rheumatoid arthritis

Karakteristike aterosklerotskog plaka i debljina intima-medija kompleksa karotidnih arterija kod bolesnika sa reumatoidnim artritisom

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Abstract

Background/Aim. Rheumatoid arthritis (RA) represents an independent risk factor for the development of cardiovascular (CV) disease (CVD). Early detection of atherosclerotic changes is of tremendous importance in the prevention of CV events. An increase in the carotid artery intima-media thickness (cIMT) is considered a sensitive marker of early subclinical atherosclerosis. The aim of our investigation was to assess the cIMT, the number and type of carotid plaques (CPs), and the severity of carotid artery stenosis in RA patients. Furthermore, we investigated the correlation between all the above-mentioned parameters and disease duration and activity. **Methods**. The research included 92 participants, of which 58 were patients with RA, and the remaining 34 participants were healthy individuals (control group). In patients with RA, clinical examination and laboratory findings were used for assessing disease activity. All participants underwent a color Doppler ultrasound examination of the carotid arteries with a linear probe in order to assess cIMT, the number and type of CPs, as well as the severity of stenotic lesions. **Results.** The mean cIMT in RA patients was statistically significantly higher compared to the control group (0.8 ± 0.2 mm vs. 0.7 ± 0.2 mm; $p < 0.01$). CPs were found in 34 out of 58 RA patients (58.6%) and 4 out of 34 (11.8%) participants in the control group ($p < 0.001$). The number of CPs per patient was significantly higher in the RA group compared to the control group (1.4 ± 0.9 vs. 0.2 ± 0.4; $p < 0.001$). The cIMT, the presence and number of CPs, and the severity of carotid artery stenosis were not statistically significantly related to disease activity. There was a statistically significant direct correlation between the duration of RA and the percentage of carotid arterial stenosis ($r = 0.320$, $p = 0.034$). **Conclusion.** The cIMT and the presence and number of CPs per patient were significantly higher in RA patients. Moreover, there was a positive correlation between RA disease duration and the severity of carotid artery stenosis. This study showed that RA represents an independent risk factor for an increase in cIMT and the development of subclinical atherosclerosis.

Key words:
arthritis, rheumatoid; atherosclerosis; cardiovascular disease; carotid arteries; plaque, atherosclerotic; risk factors.

Apstrakt

Uvod/Cilj. Reumatoidni artritis (RA) predstavlja nezavisni faktor rizika od nastanka kardiovaskularnih (KV) oboljenja (KVO). Rano otkrivanje aterosklerotskih promena je ključno u prevenciji KV događaja. Povećanje debljine kompleksa intima-medija (DKIM) na karotidnim arterijama smatra se senzitivnim markerom rane, subkliničke ateroskleroze. Cilj našeg ispitivanja bio je da procenimo DKIM, broj i tip karotidnih plakova (KP), težinu stenoze karotidnih arterija kod bolesnika sa RA kao i povezanost navedenih parametara sa dužinom trajanja i aktivnosti bolesti. **Metode**. U studiju je bilo uključeno 92 učesnika, od kojih je njih 58 imalo RA, a preostalih 34 bile su zdrave osobe (kontrolna grupa). Kod bolesnika sa RA procena aktivnosti bolesti vršena je na osnovu kliničkog pregleda i laboratorijskih analiza. Svim ispitanicima urađen je kolor Dopler ultrazvučni pregled karotidnih arterija kojim su procenjivani DKIM, broj i tip KP, kao i težina stenoznih lezija. **Rezultati.** Bolesnici sa RA imali su statistički značajno veće vrednosti DKIM u odnosu na kontrolnu grupu (0,8 ± 0,2 mm vs. 0,7 ± 0,2 mm; $p < 0,01$). KP registrovani su kod 34 od ukupno 58 bolesnika iz RA grupe (58,6%) i kod 4 od ukupno 34 (11,8%) osoba iz kontrolne grupe ($p < 0,001$). Broj KP po ispitaniku bio je statistički značajno veći kod bolesnika sa RA u odnosu na

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kontrolnu grupu (1,4 ± 0,9 vs. 0,2 ± 0,4; $p < 0.001$). DKIM, prisustvo i broj KP kao i težina stenoza karotidnih arterija nisu se statistički razlikovali u odnosu na aktivnost bolesti. Postojala je statistički značajna korelacija dužine trajanja RA i procenata stenozirajućih promena ($r = 0,320$, $p = 0,034$) **Zaključak.** Kod bolesnika sa RA detektovana je značajno veća vrednost DKIM, kao i veća zastupljenost i broj KP po ispitaniku. Postojala je pozitivna korelacija između dužine trajanja RA i težine stenozirajućih lezija. Ova studija pokazala je da RA predstavlja nezavisni faktor rizika za povećanje DKIM i nastanak subkliničke ateroskleroze.

Ključne reči:
artritis, reumatoidni; ateroskleroza; kardiovaskularne bolesti; aa. carotis; aterosklerotički plak; faktori rizika.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by erosive synovitis, and, despite therapy, it often leads to progressive joint damage [1]. In addition, an increased incidence of cardiovascular (CV) disease (CVD) has been identified, and this cannot be explained by traditional risk factors. It has been proven that RA poses an independent risk for the development of CVD [2].

In RA patients, all stages of the atherogenic process are accelerated. Systemic inflammation underlying RA is an independent risk factor for CVD [3]. The primary inflammation site is the synovial tissue which releases pleiotropic cytokines, such as TNF-α, IL-1, and IL-6 [4]. They perform the role of mediator in numerous metabolic processes – through effects on the liver, skeletal muscles, adipose tissue, and endothelium. That generates proatherogenic changes, prothrombotic effects, and endothelial dysfunction [5]. In patients with a high risk of CVD, early detection of atherosclerotic changes is of tremendous importance in the prevention of CV events that may cause irreversible damage [6]. Today, an increase in the thickness of the carotid artery intima-media complex (cIMT) is considered a sensitive marker of early subclinical atherosclerosis [7].

The aim of our paper was to assess the cIMT, the number and type of carotid plaques (CPs), and the percentage of carotid artery stenosis in RA patients. Furthermore, we investigated the correlation between all the above-mentioned parameters and disease duration and activity.

Methods

Recruitment and patients

The research included 92 participants, of which 58 were RA patients (RA group), and 34 were healthy individuals (control group). All participants in the RA group fulfilled the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for the diagnosis of RA [8]. Likewise, all RA patients were receiving stable treatment with the disease-modifying drug Methotrexate (MTX), 12.5 to 17.5 mg weekly.

All RA patients were diagnosed with RA at least six months before inclusion into the study. Additionally, all RA participants were on stable therapy with MTX for at least three months prior to the beginning of the study.

Patients receiving corticosteroid, biological, or statin therapy were not included in the study. Likewise, patients who received intra-articular corticosteroids in the last three months were not included in the study. Furthermore, patients who had survived a stroke, transient ischaemic attack, or patients suffering from peripheral arterial disease or proven coronary artery disease (patients who survived a heart attack or had any type of myocardial revascularization) were not included in the study. Further exclusion criteria for participation in the study were the existence of systemic autoimmune disease (i.e., systemic lupus erythematosus, Crohn's disease) or malignancy.

The study was approved by the Ethics Committee of the Institute for treatment and rehabilitation Niška Banja, Serbia (No 03-8382/1 from 27 March, 2019).

Study design

All patients underwent a clinical examination (tender joints and/or swelling) and laboratory tests: sedimentation (SE), C-reactive protein (CRP), and rheumatoid factor (RF). In patients with RA, clinical examination and laboratory findings were used for assessing (calculating) disease activity. The disease activity is presented via Disease Activity Score-28 (DAS28) based on erythrocyte sedimentation rate and Clinical Disease Activity Index (CDAI) [9, 10].

All participants underwent color Doppler ultrasonography of the carotid arteries with a linear probe, and they had the cIMT, type and number of CPs, and the percentage of carotid artery stenosis estimated.

Color Doppler ultrasonography

Color Doppler ultrasound examination of the carotid arteries was done in all the examinees using the ESAOTE My Lab60 Xvision, with a 4–13 MHz multi-frequency linear probe machine, assessing cIMT, number and type of CPs, and percentage of carotid artery stenosis. Intraluminal lesions were documented using B-mode imaging. cIMT was measured in the posterior wall of the common carotid artery, 2 cm away from the bifurcation apex, in the region without focal changes. On the other hand, for the analysis of stenotic lesions and plaque properties, we used bilateral longitudinal images of the internal, external, and common carotid arteries.

A carotid artery plaque was defined as a localized protrusion of the vessel wall, which extended into the lumen ≥ 1.5 mm or had a thickness exceeding the intima-media thickness of the adjacent portion of the vessel wall by > 50% according to Mannheim Intima-Media Thickness Consensus [11]. The plaque morphology was defined in terms

of its echogenicity as lipid, fibrolipid, fibrous, fibrocalcific, and calcified [12]. The percentage of stenosis was determined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) guidelines [13]. Carotid stenoses were described in accordance with the Consensus Panel Gray-Scale and Doppler Ultrasound Criteria for Diagnosis reported by Grant et al. [14], where the degree of stenosis was classified into the categories of normal (no stenosis), < 50% of stenosis, 50%–69% of stenosis, > 70% of stenosis to near occlusion, near occlusion, and total occlusion, according to Piepoli et al. [15].

Statistical analysis

The data are presented in the form of descriptive measures – arithmetic means, standard deviations, and absolute and relative frequencies. The normality of data was tested by the Kolmogorov-Smirnov test. Due to significant deviation from a normal distribution, measures of central tendencies of the subsamples were compared by the Kruskal-Wallis test, while the Mann-Whitney test was used in a post-hoc analysis. Frequencies of categorical data of the subsamples were compared by the Chi-squared test. In all tests, the level of significance was set to $\alpha = 0.05$. The regression analysis was used to determine the relationship between disease duration and cIMT and plaque characteristics. All statistical procedures were carried out using the R package.

Results

The research was conducted on 58 RA patients (24 men and 34 women) with an average age of 59.8 ± 9.9 years and an average disease duration of 8.3 ± 6.2 years. The control group consisted of 34 healthy participants with an average age of 60.9 ± 0.9 years.

There was no significant difference in the presence of risk factors for the development of atherosclerosis between the groups (Table 1).

The mean cIMT in RA patients was 0.8 ± 0.2 mm, which was statistically significantly higher ($p < 0.01$) compared to the control group, where the cIMT was 0.7 ± 0.2 mm. Atherosclerotic CPs were found in 34 out of 58 RA patients (58.6%) and 4 out of 34 (11.8%) examinees in the control group ($p < 0.001$). The number of CPs per patient in the RA group was 1.4 ± 0.9, which was statistically significantly higher ($p < 0.001$) compared to the control group, where the number of CPs was 0.2 ± 0.4. The percentage of carotid artery stenosis (26.4 ± 14.3% vs. 3.7 ± 8.3%) was also statistically significantly higher in the RA group ($p < 0.001$) (Table 2).

Nineteen patients in the RA group (32.8%) had cIMT ≥ 0.9 mm, which is considered a pathological finding. On the other hand, only one participant (2.9%) in the control group had cIMT ≥ 0.9 mm. Type 4 CP (fibrocalcific) was predominant in 13 out of 34 examinees (38.2%), followed by type 5 CP (calcified) in 11 out of 34 (32.4%) examinees, while type 3 CP (fibrous) was the least represented with 10 out of 34 (29.4%) participants. None of the participants had type 1 CP (lipid) or type 2 CP (fibrolipid).

Disease activity in RA patients was determined based on clinical examination and laboratory analyses using DAS28 and CDAI scores. All patients were divided into 3 groups according to the disease activity rate expressed via DAS28. The first group (high disease activity), with DAS28 > 5.1, encompassed 21 out of 58 patients (36.2%); the second group (moderate disease activity), with DAS28 ≥ 3.2 and ≤ 5.1, included 22 out of 58 (37.9%) patients; the third group (low disease activity and remission), with DAS28 < 3.2, consisted of 15 out of 58 patients (25.9%).

Concerning the CDAI disease activity index, high disease activity (CDAI: 22.1–76) was present in 16 out of 58 (27.6%) patients, while the moderate activity group (CDAI: 10.1–22.0) included 28 out of 58 (48.3%) patients, and the low disease activity and remission group (CDAI: 0.0–10.0) encompassed 14 out of 58 (24.1%) patients.

Table 1

Comparison of cardiovascular risk factors between participants with rheumatoid arthritis (RA) and without RA

Risk factors	RA group	Control group	*p*-value
Arterial hypertension, n (%)	33 (56.9)	16 (47.1)	0.473
Hyperlipidemia, n (%)	15 (25.9)	8 (23.5)	0.955
Smoking, n (%)	16 (27.6)	9 (26.5)	0.947
Diabetes mellitus, n (%)	3 (5.2)	0 (0)	0.757
Body mass index, mean ± SD	26.5 ± 4.5	26.4 ± 4.6	0.928

SD – standard deviation.

Table 2

Comparison of carotid artery intima-media thickness (cIMT) and plaque characteristics in participants with rheumatoid arthritis (RA) and without RA

Carotid artery characteristics	RA group	Control group	*p*-value
cIMT (mm), mean ± SD	0.8 ± 0.2	0.7 ± 0.2	< 0.01
CPs, n (%)	34 (58.6)	4 (11.8)	< 0.001
Number of CPs, mean ± SD	1.4 ± 0.9	0.2 ± 0.4	< 0.001
% stenosis, mean ± SD	26.4 ± 14.3	3.7 ± 8.3	< 0.001

SD – standard deviation; CPs – carotid plaques.

Finally, we decided to compare the parameters obtained by Doppler ultrasound of the blood vessels of the neck with the parameters of disease activity in the group of RA patients. The results of our research showed that the cIMT, the presence and number of CPs per patient, and the percentage of carotid artery stenosis were not statistically significantly related to disease activity expressed through DAS28 and CDAI scores (Tables 3 and 4).

The cIMT was significantly higher in patients with a positive RF factor ($p < 0.05$), while the other parameters tested (the percentage of stenosis and the presence and number of CPs) were not associated with RF positivity.

The correlation analysis demonstrated that there is a statistically significant direct correlation between the duration of RA and the percentage of carotid arterial stenosis ($\rho = 0.320$, $p = 0.034$); however, no statistically significant difference was found between the duration of RA and other examined parameters (cIMT and the presence and number of CPs per patient) (Figure 1).

Table 3

Characteristics of carotid arteries in relation to disease activity expressed via Disease Activity Score-28 (DAS28)

Parameter	DAS28			*p*-value
	> 5.1	≥ 3.2–≤ 5.1	< 3.2	
cIMT (mm), mean ± SD	0.8 ± 0.2	0.3 ± 0.2	0.8 ± 0.2	0.815
CPs, n (%)	13 (61.9)	13 (59.1)	8 (53.3)	0.738
Number of CPs, mean ± SD	1.5 ± 1.25	1.4 ± 1.1	1.25 ± 1.4	0.715
% stenosis, mean ± SD	27.3 ± 19.9	26.2 ± 21.9	24.0 ± 22.1	0.165

cIMT – carotid artery intima-media thickness; SD – standard deviation; CPs – carotid plaques.

Table 4

Characteristics of carotid arteries in relation to disease activity expressed via clinical disease activity index (CDAI)

Parameter	CDAI			*p*-value
	22.1–76.0	10.1–22.0	0.0–10.0	
cIMT (mm), mean ± SD	0.8 ± 0.2	0.8 ± 0.3	0.8 ± 0.2	0.825
CPs, n (%)	10 (62.5)	16 (57.1)	8 (57.1)	0.846
Number of CPs, mean ± SD	1.50 ± 1.47	1.4 ± 1.2	1.4 ± 1.4	0.738
% stenosis, mean ± SD	27.3 ± 24.8	28.1 ± 26.1	22.6 ± 21.64	0.175

cIMT – carotid artery intima-media thickness; SD – standard deviation; CPs – carotid plaques.

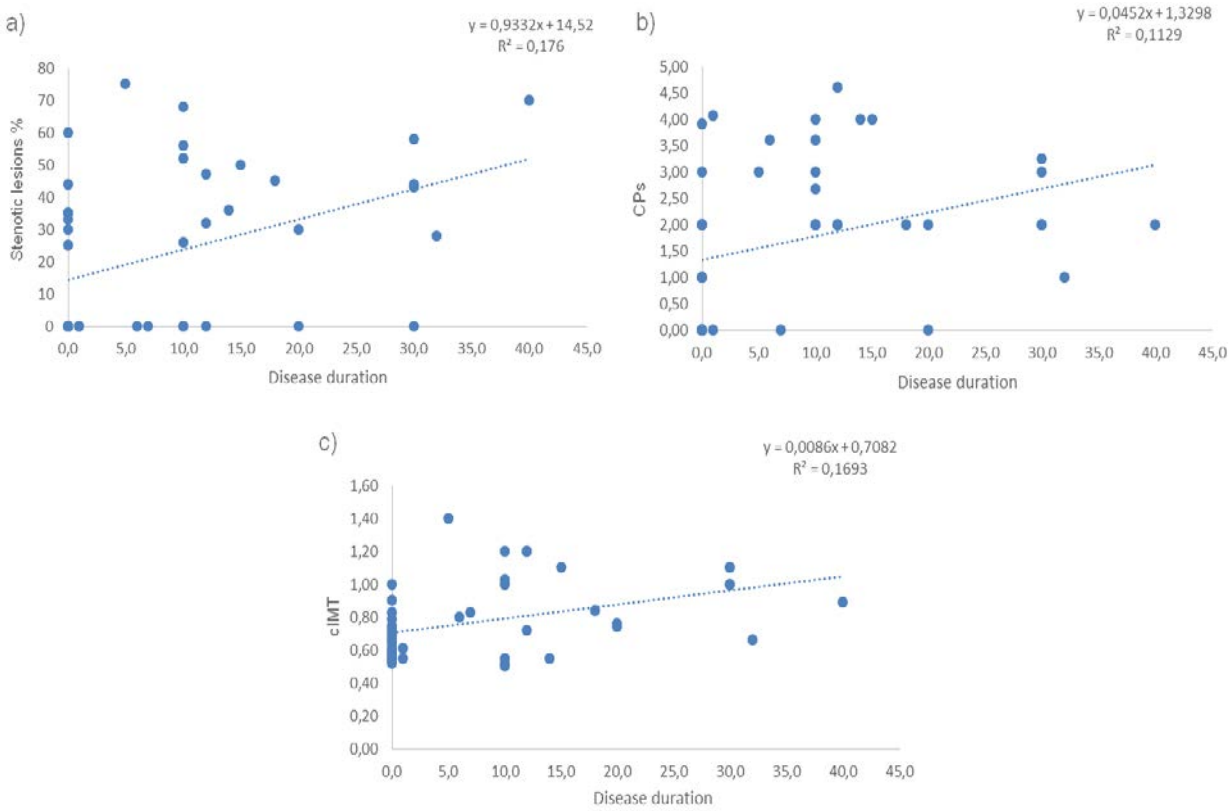

Fig. 1 – Correlation between disease duration and: (a) stenotic lesions %; (b) number of carotid plaques (CPs); (c) the carotid artery intima-media thickness (cIMT).

Discussion

The true frequency of CVD in RA patients is difficult to estimate accurately because they tend to remain asymptomatic [16]. Moreover, if symptoms do occur, they are usually atypical. That is why patients with RA are more likely to experience unrecognized myocardial infarction or death as a result of sudden cardiac failure [17]. On the other hand, it is well-known that patients with RA have a 1.5–2-fold higher incidence of CVD than the general population [16, 18, 19]. Furthermore, life expectancy in RA patients is shortened to six, seven years [20], mainly due to higher CV mortality [21].

The pathogenesis of CVD in RA is rather complex and includes chronic inflammation and immune dysregulation [1]. Both disorders cause endothelial and cardiomyocyte dysfunction [16], which leads to atherosclerosis and/or (ischemic or non-ischemic) heart failure [22]. Atherosclerosis, as a chronic, systemic, and inflammatory disease, can affect any artery in the human body. However, it usually causes the narrowing of coronary and cerebrovascular arteries, which can lead to life-threatening events like acute coronary syndrome (ACS) or stroke. Mainly due to these two disorders, CVDs are the leading cause of death worldwide, with 17.8 million deaths per year [23]. That is why early detection of atherosclerotic changes is of tremendous importance.

The presence of atherosclerotic CP has proved to strictly correlate with atherosclerotic changes in coronary arteries, while an increase in cIMT correlates with manifested coronary artery disease [14, 24]. Namely, a cIMT analysis in a large population study conducted on over 15,000 people in the USA showed that an increase in cIMT by 0.2 mm leads to an increase of the relative risk of myocardial infarction by 33% and cerebral infarction by 28% [25]. Another group of authors showed that the increase in cIMT by 0.2 mm even doubles the risk of CV events [26]. Likewise, an increase in the cIMT is considered a sensitive marker of early subclinical atherosclerosis [27]. Some authors suggest using von Willebrand factor (vWF) activity as an early marker of subclinical atherosclerosis in RA [28]. That being the case, we chose to do a carotid artery examination with high-resolution ultrasound. The ultrasound examination of carotid arteries represents a reliable, accurate, and easily accessible technique that detects atherosclerosis in subclinical stages [27].

In our study, patients with RA had higher values of cIMT and a greater number of CPs compared to the control group. That is not a "breakthrough finding", as patients with RA usually have higher values of IMT and plaques compared to the healthy population [27, 29]. That refers not only to the carotid [30] but also to the femoral arteries [31]. In a meta-analysis by van Sijl et al. [32], which included 22 studies that investigated values of cIMT in RA patients only in one study, cIMT was smaller than in the healthy population. All other studies showed higher cIMT values in RA patients [29]. However, this meta-analysis had some flaws because, in most studies, patients with RA had more CV risk factors compared to the healthy control. In addition, there was a variation in ultrasound protocols among studies used for cIMT estimation [32]. Mohan et al. [33] also showed that RA patients have higher values of cIMT compared to healthy populations, stressing the point that this finding "appears to be a useful surrogate marker for detecting subclinical atherosclerosis in adults". Saigel et al. [34] went even further by suggesting routine screening for silent atherosclerosis in all RA patients by ultrasound examination of cIMT. Ristić et al. [29] showed that RA represents an independent risk factor for atherosclerosis and, what is even more important, long-term anti-inflammatory therapy may decrease cIMT.

CPs are also commonly found in patients with RA [2]. In fact, patients with RA have a 3-fold higher risk for CP development [35]. In a study by Mahajan et al. [36], the difference in the prevalence of CP between RA and healthy subjects was even more pronounced, as 21% of RA patients and only 1% of control group participants had CP. Once again, our study showed that RA patients have significantly higher values of cIMT and a greater number of CPs compared to the healthy population. That is of great importance as both parameters, cIMT and CP, carry high predictive power for the development of CV events [37].

Given that the higher incidence of CVD in RA patients is explained by systemic inflammation, a positive correlation between RA activity and the severity of atherosclerotic carotid lesions is expected. However, the results obtained in larger studies are contradictory. Patel et al. [38] have demonstrated the existence of a correlation between the cIMT and disease activity in RA patients, who were divided into low, moderate, and high disease activity groups. Likewise, in 2019, Abd El-Monem et al. [39] showed a positive correlation between cIMT and disease activity expressed in DAS28. Furthermore, compared to RA patients in remission, RA patients with active disease seem to have less stable and more vulnerable plaques, which increases the probability of an acute CV event [40]. RA activity represents an independent risk factor for impaired glucose metabolism, known to be an independent risk factor for CVD [41]. In contrast, Jonsson et al. [42], Roman et al. [35], and Cuomo et al. [43] have shown in their research that there is no correlation between cIMT and disease activity, while Semb et al. [40] stated that there is a positive correlation between CP vulnerability and RA disease activity assessed with CDAI but not with DAS28. In our research, disease activity was expressed through DAS28 and CDAI indices. cIMT, the number of CPs per patient, and the percentage of carotid arterial stenosis were the lowest in the group of patients who were in remission or had low disease activity. On the other hand, our study didn't find a significant correlation in the severity of atherosclerotic lesions with the group of moderate and high disease activity. Similar findings were observed in an Italian study with young RA patients [44]. In fact, even patients with continued low RA disease activity appear to suffer from atherosclerotic lesions [44, 45]. However, this does not diminish the need for aggressive control of RA activity because chronic inflammation is probably the driving force for premature atherosclerosis.

In our study, there was a positive correlation between the duration of RA and the percentage of stenotic lesions; however, there was no correlation between the duration of RA and other parameters tested (cIMT, number of CPs per

patient, and type of plaque). These findings are in contrast with previous studies [35, 46, 47]. There are two possible explanations for why such results were obtained. First is the duration of RA. Namely, in most conducted studies, RA lasted for more than 10 years [39], and in our study, the average duration of the disease was about 8 years. However, in the Del Rincon et al. [46] study, the borderline for higher values of cIMT was lower – seven years [46]. Many studies support the assumption that disease duration has more impact on the development of atherosclerosis than the disease activity [48, 49]. However, our study failed to confirm this hypothesis. That highlights the need for more prospective studies on a larger number of patients, which will confirm or reject this allegation. The second explanation is that the obtained results are influenced by the therapeutic approach. For instance, the positive correlation between the cIMT and disease duration in the study by Kumeda et al. [31] can be explained by the small number of patients receiving MTX (12%). In studies where RA patients were intensively treated with MTX (54%–98%), the correlation between the cIMT and disease duration was not significant [30, 50]. In our study, there was no correlation between disease duration and cIMT, probably due to the early aggressive treatment and the fact that all patients were on MTX therapy.

Finally, many authors [49, 51] suggest that the existence of the RF factor (RF positivity) is a risk factor for the development of atherosclerosis [52]. Moreover, RA patients with RF seropositivity have a higher incidence of ACS and a worse prognosis after acute myocardial infarction [53]. That is why the European Association of Rheumatologists defines seropositivity (alongside high disease activity and RA duration over 10 years) as the main CV risk factor [54]. In our study, cIMT was significantly greater in patients with a positive RF factor, while other parameters of the carotid arteries tested were not associated with RF positivity.

Conclusion

The results of our study showed that the cIMT, the presence and number of CPs per patient, and the percentage of carotid artery stenosis were statistically significantly higher in RA patients. Moreover, there was a positive correlation between disease duration and the severity of carotid stenotic lesions. Our study showed that RA represents an independent risk factor for an increase in cIMT and the development of subclinical atherosclerosis.

Conflict of interest

The authors declare no conflict of interest regarding the present paper.

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