Concise report

Rheumatoid arthritis is an independent risk factor for increased carotid intima-media thickness: impact of anti-inflammatory treatment

Gorica G. Ristic, Toplica Lepic, Branislava Glišić, Dejana Stanisavljević, Danilo Vojvodić, Milan Petronijević and Dušan Stefanović

Abstract

Objectives. To evaluate the extent of subclinical atherosclerosis in patients with RA and low cardiovascular risk by measuring intima-media thickness (IMT) of the carotid arteries and to determine factors associated with increased IMT.

Methods. IMT was measured by ultrasonography in 42 non-diabetic, normotensive, female RA patients and 32 matched healthy controls [age 45.3 (10.0) vs 45.2 (9.8) years] at common carotid arteries (CCAs), carotid bifurcation (BF) and internal carotid arteries (ICAs), bilaterally. Mean and maximal (max) IMTs were calculated from three measurements at each site. Clinical work-up included laboratory analyses, determination of the disease activity and evaluation of treatment.

Results. RA patients had increased IMT (mm) in comparison with controls [CCA max: 0.764 (0.148) vs 0.703 (0.100); CCA mean: 0.671 (0.119) vs 0.621 (0.085); BF max: 1.055 (0.184) vs 0.941 (0.161); BF mean: 0.889 (0.168) vs 0.804 (0.124); ICA max: 0.683 (0.108) vs 0.613 (0.093); ICA mean: 0.577 (0.101) vs 0.535 (0.076)]. Parameters associated with IMT in RA patients were (correlation at x/6 measurement sites): age (6/6), BMI (2/6), smoking (2/6), RF concentration (2/6), sedimentation rate (1/6) and duration of MTX + chloroquine therapy (4/6; inverse correlation). Multivariate regression analysis revealed that RA is an independent risk factor for increased IMT. Factors correlating with IMT in the controls were: age (6/6), BMI (3/6), total cholesterol (5/6), low-density lipoprotein cholesterol (3/6), total/high-density lipoprotein cholesterol (2/6), triglycerides (1/6) and glycaemia (4/6).

Conclusion. Despite a favourable risk profile, our female RA patients had significantly enlarged carotid IMT than controls. RA itself was an independent risk factor for increased IMT. Impact of chronic inflammation on atherosclerosis was confirmed by negative correlation of IMT and duration of anti-inflammatory treatment.

Key words: Rheumatoid arthritis, Atherosclerosis, Carotid intima-media thickness, Methotrexate.

Introduction

Cardiovascular diseases (CVDs) are the most common cause of morbidity and mortality in patients with RA [1–3]. Women with RA are twice as likely to suffer a myocardial infarction than women without RA, whereas those who are seropositive and <65 years of age have a 3-fold increased risk of dying from CVD [2, 3].

In patients at high cardiovascular risk, it is important to identify vascular injury early. The carotid artery intima-media thickness (IMT), measured by ultrasound, has been established as a valid marker of early atherosclerosis [4].

Several authors evaluated carotid IMT among RA patients [5–13]. However, selection of patients varied significantly with regard to the presence of atherosclerotic
The aim of our study was to evaluate the extent of subclinical atherosclerosis in young, female, non-diabetic, normotensive RA patients, with no dyslipidaemia, in comparison with healthy controls, by measuring the IMT of the carotid arteries. RA-related and atherosclerotic risk factors, as well as the duration of anti-inflammatory treatment were separately analysed regarding their effect on carotid IMT.

Methods
The investigation was designed as a cross-sectional single-centre study and was approved by the institutional ethical committee (Ethical Committee of the Military Medical Academy, Belgrade, Serbia). All participants signed an informed consent form.

Patients and controls
The study population (Table 1) was recruited over a period of 6 months and included 42 female RA consecutive patients (ACR revised criteria for RA) and 32 healthy female controls (hospital staff) matched for cardiovascular risk profile, including menopausal status and family history of CVD. To avoid confounding by other risk factors for atherosclerosis, we used the following exclusion criteria for both groups: history of ischaemic CVD, hypertension, diabetes mellitus, hyperlipidaemia and premature menopause. We also excluded patients treated with high doses of steroids (>10 mg/day, including parenteral administration) and those treated with biologic therapy. COX-2 inhibitors and NSAIDs were applied only occasionally. The laboratory analyses (Table 1) were performed at the time of the carotid ultrasound.

Clinical assessment and anti-rheumatic treatment
The clinical data obtained for each patient are depicted in Table 2. All patients were treated with similar therapy, initiated as soon as a diagnosis of RA was made.

Assessment of carotid IMT
Carotid IMT was measured using a high-resolution B-mode ultrasound (Toshiba SSA 370A, Tokyo, Japan) with a 9-MHz transducer. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. Both left and right carotid arteries were examined at the levels of the common carotid artery (CCA), carotid bifurcation (BF) and internal carotid artery (ICA) according to the protocol used in the Atherosclerosis Risk in Communities (ARIC) study [4]. Three IMT measurements were performed at all three segments (CCA, BF and ICA), providing a total of 18 measurements per person. Average mean and average maximal (max) IMT values were calculated at each segment of both carotid arteries. Hence, six IMT values were obtained, including three mean and three max values for all carotid levels (CCA, BF and ICA). All measurements were performed by the same sonographer (T.L.), blinded for the clinical characteristics of the subjects.

Table 1 Clinical and laboratory findings in patients with RA and controls

<table>
<thead>
<tr>
<th></th>
<th>RA patients</th>
<th>Controls</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Clinical characteristics</td>
<td></td>
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<tr>
<td>Age, years</td>
<td>45.3 (10.0)</td>
<td>45.2 (9.8)</td>
<td>0.95</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2 (4.5)</td>
<td>25.1 (4.1)</td>
<td>0.38</td>
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<tr>
<td>No. of smokers — past, n (%)</td>
<td>8 (19.0)</td>
<td>5 (15.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>No. of smokers — current, n (%)</td>
<td>16 (38.1)</td>
<td>14 (43.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Smoking, years</td>
<td>11.4 (12.2)</td>
<td>20.2 (7.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average number of cigarettes/day</td>
<td>9.1 (9.95)</td>
<td>17.4 (9.2)</td>
<td>&lt;0.01</td>
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<tr>
<td>Laboratory parameters</td>
<td></td>
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<tr>
<td>ESR, mm/h</td>
<td>27.9 (22.0)</td>
<td>11.3 (6.9)</td>
<td>&lt;0.01</td>
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<tr>
<td>Fibrinogen, g/l</td>
<td>3.4 (0.9)</td>
<td>2.7 (0.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>14.6 (24.4)</td>
<td>2.0 (2.9)</td>
<td>&lt;0.01</td>
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<tr>
<td>Triglycerides, mmol/l</td>
<td>1.1 (0.5)</td>
<td>1.2 (0.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.2 (0.9)</td>
<td>5.4 (0.7)</td>
<td>0.25</td>
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<tr>
<td>LDL cholesterol, mmol/l</td>
<td>3.1 (1.0)</td>
<td>3.4 (0.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.6 (0.5)</td>
<td>1.5 (0.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>3.5 (1.2)</td>
<td>3.7 (0.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>Blood glucose, mmol/l</td>
<td>4.9 (0.8)</td>
<td>5.3 (0.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RF positive, n (%)</td>
<td>29 (69)</td>
<td>3 (9.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RF, IU/ml</td>
<td>493 (557)</td>
<td>23.7 (9.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ANA positive, n (%)</td>
<td>4 (9.5)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anti-CCP positive, n (%)</td>
<td>25 (59.5)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
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Values are expressed as means (S.D.) or percentages as appropriate. LDL: low-density lipoprotein; HDL: high-density lipoprotein; CCP: cyclic citrullinated peptide.
Correlation of carotid IMT with (non)traditional risk factors in patients with RA and control subjects. In RA patients, significant association was found with age for all IMT measurements ($P < 0.01$), with BMI for CCA$_{\text{max}}$ ($P < 0.05$) and ICA$_{\text{max}}$ ($P < 0.01$), and with ESR and smoking habits only for some IMT values. We did not find significant association of IMT with any lipid levels and blood glucose.

When we analysed RA-associated parameters, there was no correlation of IMT values and the parameters of RA activity and duration of the disease. Significant association was found with RF concentration, but only for IMT at carotid BF ($P < 0.05$).

When analysing the influence of therapy, a negative correlation was noted with duration of anti-inflammatory treatment. The most obvious statistically significant negative correlation was found between IMT and duration of combined therapy with MTX and chloroquine ($P < 0.01$ for...
CCA\textsubscript{max} and \( P < 0.05 \) for CCA\textsubscript{mean} and BF) and with prednisolone for CCA\textsubscript{max} (\( P < 0.05 \)).

In control subjects, significant association was found with age for all measurements (\( P < 0.01 \)) and with BMI for CCA\textsubscript{mean} and ICA\textsubscript{max} (\( P < 0.05 \)), as for ICA\textsubscript{mean} (\( P < 0.01 \)). We did not find significant association of IMT values and smoking habits, but in contrast to the entire study group and RA patients, statistically significant positive correlation was found with blood glucose and all lipids.

**Discussion**

Despite a more favourable risk profile, our female RA patients had significantly higher carotid IMT than did healthy controls at all measurement sites (CCA, BF and ICA). Other authors have also found increased IMT in RA patients but, in contrast to our study, they analysed just one carotid IMT value [5–12]. Similar to our study, only Gerli et al. [13] measured carotid IMT at three levels but did not exclude hypertensive, diabetic, hyperlipidaemic, male and elderly patients.

In our study, multivariate analysis revealed that RA itself is an independent risk factor for increased carotid IMT, which was previously reported only by Kumeda et al. [5]. The same remained true for most of the carotid segments even when patients and controls were stratified according to the age. Of particular interest is our finding that IMT values in RA patients had negative correlation with the duration of combined treatment with MTX and chloroquine, implying its possible protective effect on the development of atherosclerosis.

Among traditional risk factors, significant correlation between age and carotid IMT was confirmed, as in other studies [5–13]. Unexpectedly, analysis of our entire study population and RA group did not reveal correlation of IMT with lipid levels. The same results have been reported in studies from England [11], Japan [5], Spain [12], Mexico [9] and India [8], whereas only Swedish authors [10] have found positive correlation. It is known that serum lipids are strong predictors of atherosclerosis, but RA patients have decreased lipid levels, inversely related to the inflammatory status [15]. In contrast to these results, significant association was found with cholesterol in the control group. The same findings were also reported by Alkaabi et al. [11], whereas other authors did not mention the results in controls. In the RA group, in contrast to controls, we found correlation between IMT and smoking habits, but not for all carotid segments. Among investigations that included smokers [5, 10–14] only Gerli et al. [13] revealed similar results.

From our data and numerous previous studies it is obvious that traditional atherosclerotic risk factors behave differently in RA and that their presence cannot explain accelerated atherosclerosis in these patients [1].

Chronic inflammation, which is the main characteristic of RA, plays a major role in accelerated atherosclerosis [16]. Despite all markers of inflammation being higher in RA patients than in controls, they did not correlate with IMT, except for ESR and BF\textsubscript{mean}. The same observation was reported by other authors [5, 10–12]. There are two possible explanations. First, ours and previous studies have included patients with a wide range of disease activity (closely associated with inflammation markers). Secondly, accelerated atherosclerosis depends on the cumulative effect of prolonged inflammation. Therefore, inflammation markers measured at a single time point could fail to be associated with the IMT. This was confirmed in studies from Japan showing that

**Fig. 1** Average mean and average max values of IMT of the carotid arteries in patients with RA and healthy controls.

\begin{table}
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\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
 & CCA\textsubscript{mean} & BF\textsubscript{mean} & BF\textsubscript{max} & ICA\textsubscript{mean} & ICA\textsubscript{max} & CCA\textsubscript{max} \\
\hline
RA & 0.764 ± 0.148 & 0.889 ± 0.168 & 0.671 ± 0.119 & 0.683 ± 0.108 & 0.577 ± 0.076 & 0.535 ± 0.085 \\
Controls & 0.703 ± 0.100 & 0.804 ± 0.124 & 0.621 ± 0.095 & 0.613 ± 0.093 & 0.535 ± 0.076 & 0.535 ± 0.085 \\
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\end{tabular}
\end{table}

\( *P < 0.05, **P < 0.01. \)
influence of inflammation can be more accurately detected in longitudinal than in cross-sectional studies [5, 17].

The importance of chronic inflammation for atherosclerosis is also reflected through its influence on lipid status. It is known that dyslipoproteinaemia in RA is inversely related to the inflammatory burden of the disease [15]. Fluctuations of the disease activity are frequent, affecting, therefore, blood lipids. The influence of long-term anti-rheumatic treatment on lipid status is also important. Chloroquine decreases concentration of total cholesterol and LDL cholesterol but increases HDL cholesterol. This could explain the positive correlation between IMT and cholesterol levels in Wallberg-Jonsson et al.’s study [10] since just 13% of their patients were treated with chloroquine (78% in our study). Despite that corticosteroids might accelerate atherosclerosis affecting lipid status and insulin sensitivity, no correlation between carotid IMT and corticosteroid therapy was confirmed [5, 6, 12, 13]. High-grade systemic inflammation actually contributes to the insulin resistance in RA, which can be decreased with glucocorticoids and DMARDs. In our study, a negative, but not significant, correlation with the duration of corticosteroid treatment was found. Similarly, Wallberg-Jonsson et al. [18] found that prolonged steroid use was associated with lower risk of CVD in RA. It was conceivable that the negative side effects of corticosteroids are balanced by the benefit of reduced RA activity.

The importance of the life-long inflammatory burden for accelerated atherosclerosis in RA was also confirmed in our study by negative correlation of IMT and the duration of combined MTX/chloroquine therapy. Our results are consistent with studies of Wallberg-Jonsson et al. [14] and Georgiadis et al. [19], in which MTX treatment decreased IMT. Other investigators did not find correlation of IMT and MTX administration, but none of them has analysed the impact of treatment duration [5, 6, 8, 9, 13].

Although duration of RA is considered as an important risk factor for premature atherosclerosis [5, 8], the same studies report opposite findings [6, 11–13]. There are two possible reasons: (i) diversity of treatment in the pre-DMARD era and (ii) variations in RA severity. Corelation between IMT and duration of disease noted by Kumeda et al. [5] could be explained by a low proportion of patients receiving MTX (12%). In cohorts extensively treated with MTX (54–98%), correlation with the duration of disease was not significant [6, 12, 13]. There was no relationship between IMT values and disease duration in our study, probably due to more aggressive early treatment of RA. On the other hand, disease duration does not necessarily reflect the overall disease activity or severity. In addition, the Nurses’ Health Study has revealed increased cardiovascular risk only in RA lasting >10 years [2]. In our study, mean duration of RA was 7 years. Furthermore, del Rincon et al. [20] have noted that effect of RA duration is significant only after the age of 60 years. In contrast, our study included only younger patients.

Presence of RF was suggested as a risk factor for development of atherosclerosis. However, in our study and other reports, correlation of RF and IMT could not be proven [5, 8, 12, 13].

In conclusion, regardless of the low incidence of traditional risk factors, our female RA patients had more advanced atherosclerosis than did the healthy controls. RA itself was an independent risk factor for increased carotid IMT. Importantly, long-term combined treatment with MTX and chloroquine had favourable impact on IMT values. This observation may indicate that chronic inflammation, as a basic feature of RA, has an important role in accelerated atherosclerosis. Presence of RA may lead to the loss of the ‘female advantage’ in the personal risk profile for atherosclerosis, suggesting the need for early application of prevention strategies and screening for CVD.

**Rheumatology key messages**

- RA is an independent risk factor for atherosclerosis.
- Long-term anti-inflammatory treatment decreases carotid atherosclerosis in RA.
- Chronic inflammation is a mechanism contributing to advanced atherosclerosis in RA.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**


