Inflammatory burden interacts with conventional cardiovascular risk factors for carotid plaque formation in rheumatoid arthritis

Churl Hyun Im¹, Na Ri Kim¹, Jong Wan Kang¹, Ji Hun Kim¹, Jin Young Kang¹, Gi Bum Bae¹, Eon Jeong Nam¹ and Young Mo Kang¹

Abstract

Objective. Patients with RA have an increased risk of atherosclerosis and cardiovascular (CV) diseases compared with the general population. The aim of this study was to evaluate the role of inflammatory burden in the formation of carotid plaques in patients with RA.

Methods. We performed carotid artery US to measure the carotid intima-media thickness (IMT) and plaques in 406 patients with RA and 209 age- and sex-matched healthy controls. To assess the inflammatory burden, the area under the curve (AUC) of ESR over time was calculated.

Results. The carotid plaque frequency and mean IMT were significantly increased in patients with RA relative to controls. After adjustment for age and gender, the presence of carotid plaques in patients with RA was associated with HAQ score, tender joint count (TJC), swollen joint count (SJC), 28-joint DAS, ESR, CRP, LEF use, current corticosteroid dose and the number of conventional CV risk factors. After multivariate regression analysis, the factors significantly associated with plaque formation were TJC (P = 0.002), ESR (P = 0.002) and the number of conventional CV risk factors (P = 0.041). Among 194 RA patients with ESR AUC data, the presence of carotid plaque was independently associated with both the ESR AUC and number of conventional CV risk factors, which showed a synergistic interaction.

Conclusion. Cumulative inflammatory burden contributes to the development of carotid atherosclerosis through a synergistic interaction with conventional CV risk factors in patients with RA.

Key words: rheumatoid arthritis, atherosclerosis, inflammation, risk factors, ultrasound.

Introduction

The incidence of cardiovascular (CV) diseases is significantly increased in patients with RA and CV-related mortality is ~50% higher in patients with RA as compared with the general population [1]. Furthermore, the increase in CV disease risk in patients with RA was reported to be comparable to that of patients with type 2 diabetes in a prospective cohort study [2]. The excess prevalence of CV disease in patients with RA cannot be entirely explained by an excess of conventional CV risk factors [3, 4]. As systemic inflammation is a risk factor for CV disease in the general population [5], the high CV mortality and morbidity of patients with RA has been attributed to their persistent systemic inflammation [6].

Atherosclerosis of the carotid vasculature has a causal relationship with high CV disease rates [7]. Measurement of the intima-media thickness (IMT) of the carotid artery has been established as a useful index for identifying preclinical atherosclerosis and is a non-invasive predictor of coronary artery diseases [8]. In previous studies, RA itself has been identified as an independent risk factor for increased IMT and the presence of focal plaques in the carotid arteries [9–11], which predict incident CV events in RA patients without conventional CV risk factors or events [12]. The inflammatory response is implicated as being predictive of CV disease in patients with RA when...

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combined with the presence of conventional CV risk factors [13, 14]. Furthermore, interactions between conventional CV risk factors and inflammatory biomarkers in RA have been implicated in playing an important role in CV disease development.

As atherosclerosis in patients with RA is essentially a cumulative phenomenon, variables expressed in terms of time-integrated values, such as the area under the curve (AUC) of serial assessments over time, should more accurately predict CV disease development compared with cross-sectional assessments. The ESR AUC has been used as an index of cumulative inflammatory burden to determine radiographic outcomes, which are also the sum of accumulated damage [15, 16].

We hypothesized that cumulative inflammatory burden would be an independent predictive factor for carotid atherosclerosis development in patients with RA. The objectives of the present study were to determine whether cumulative inflammatory burden, expressed as ESR AUC, predicts the presence of carotid atherosclerosis and to assess its interaction with conventional CV risk factors in patients with RA.

**Patients and methods**

**Patients**

Between September 2009 and September 2011 we recruited consecutive patients with RA, defined according to the 1987 ACR criteria, from the rheumatology clinic of a single referral centre, Kyungpook National University Hospital (KNUH), Daegu, South Korea. Patients were enrolled into the KNUH Atherosclerosis Risk of RA (KARRA) cohort. Patients with RA were stratified into 16 categories defined by sex and 10-year age intervals from 11 to 90. Within these categories, one volunteer without significant medical history of disease was recruited per every two patients with RA. Comprehensive data from a formatted questionnaire, physical examination, laboratory tests and medical records review were collected concurrently with carotid US assessment. This study was approved by the KNUH Institutional Review Board and all participants provided written informed consent in accordance with the Declaration of Helsinki.

The presence of hypertension, diabetes mellitus and hypercholesterolaemia was ascertained by patient self-report, accompanied by measurement of blood pressure (\(\geq 140\) mmHg for systolic or \(\geq 90\) mmHg for diastolic), fasting blood glucose (\(\geq 126\) mg/dl) and total cholesterol (\(\geq 240\) mg/dl). Current smoking was defined as current active smoking (those who continue to smoke). We calculated the number of CV risk factors, which included diabetes mellitus, hypercholesterolaemia, hypertension and current smoking, as a variable suggested in another study [17]. Obesity was defined as current BMI \(\geq 30\) kg/m\(^2\). Metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III [18]. CV disease included transient ischaemic attack, reversible ischaemic neurological defect, cerebral infarction, angina pectoris, myocardial infarction and other ischaemic heart diseases.

In patients with RA, the following parameters were recorded: scores for the Korean version of the modified HAQ (mKHAQ), tender joint count (TJC), swollen joint count (SJC), ESR, CRP and RF [19]. The 28-joint DAS using ESR (DAS28-ESR) was also calculated [20]. To find out whether ESR elevation above the upper limit of normal (10 and 20 mm/h for men and women, respectively) can determine the presence of carotid plaque in patients with RA, we made a new categorical variable elevated ESR.

**Carotid US**

US of the carotid arteries was performed in all patients and controls according to a standardized vascular protocol developed for the multi-ethnic study of atherosclerosis [21]. We used a Logiq 7 US system with a 10Hz linear probe (General Electric, Milwaukee, WI, USA) and automated IMT measurement software (Intimascope, Media Cross, Tokyo, Japan). Carotid plaque was identified as a discrete projection, with the IMT \(\geq 50\%\) from the adjacent wall into the vessel lumen, of \(> 1.5\) mm, or both [21].

**Calculation of cumulative inflammatory burden using ESR AUC**

ESR AUC was calculated for 194 female patients \(> 40\) years of age with RA with regular measurements of ESR, excluding patients with a total disease duration longer than twice that of the serial clinic follow-up period. Every 2 month ESR value before the baseline was plotted against time and the AUC was calculated using the trapezium rule [22]. Missing data for a given month were estimated by performing linear interpolation from adjacent data.

**Statistics**

Continuous variables were expressed as mean (s.d.). Continuous and categorical variables were evaluated using Student’s t-test and two-sided \(\chi^2\) tests, respectively. Univariate logistic regression analysis was used to estimate the association between the variables and carotid atherosclerosis. Statistically significant variables in the univariate analysis were considered in backward stepwise multiple logistic regression analysis models. To evaluate the combined role of ESR AUC and the number of conventional CV risk factors as predictors of carotid plaque presence, we computed and compared the area under the receiver operating characteristic (ROC) curve for prediction models based on both ESR AUC and CV risk factor number, or each component alone. We also used the likelihood ratio test to determine whether the logistic regression models that included both ESR AUC and the number of CV risk factors provided a significantly better fit than models limited to each component alone. All calculations were performed using the Statistical Package for the Social Sciences (SPSS) version 12.0 (SPSS, Chicago, IL, USA) and MedCalc version 12.7.1.0 (MedCalc Software, Ostend, Belgium).

Statistical
significance was defined as $P < 0.05$. Statistical interactions, measured by the relative excess risk due to interaction (RERI), attributable proportion (AP) and synergy index ($S$) between the variables, were calculated according to Knol et al. [23].

**Results**

The KARRA cohort

A total of 406 patients with RA and 209 age- and sex-matched healthy controls were included in the KARRA cohort. Characteristics of the patients with RA and healthy controls are summarized in Table 1. In this study, patients with RA showed a lower BMI and lower cholesterol level (total and low-density lipoprotein) compared with those of healthy controls, although they had more smoking pack-years. The number of conventional CV risk factors was higher in patients with RA compared with controls.

Carotid US showed more severe atherosclerotic changes in patients with RA. The mean carotid IMT of patients with RA was higher than that of controls [0.792 mm (s.d. 0.169) vs 0.714 (s.d. 0.136), $P < 0.001$]. Carotid plaques were more frequent in patients with RA than in controls (74% vs 26%, $P = 0.004$), while the number of carotid plaques was 0.7 (s.d. 1.3) and 0.4 (s.d. 0.7) [$P < 0.001$; 2.0 (s.d. 1.5) and 1.4 (s.d. 0.8) among those with plaques, $P < 0.001$], respectively. The increased frequency of carotid plaques in patients with RA remained statistically significant after adjustment for age, sex and the number of conventional CV risk factors [odds ratio (OR) 2.109 (95% CI 1.366, 3.256), $P = 0.044$]. These findings indicate that RA is an independent risk factor and has at least a synergistic interaction [RERI 1.25 (95% CI 0.321, 2.192), $P = 0.008$; AP 0.402 (95% CI 0.151, 0.653), $P = 0.002$; S 2.445 (95% CI 0.896, 6.675), $P = 0.081$] with conventional CV risk factors during the development of carotid plaque (Fig. 1).

Factors associated with carotid plaque development in patients with RA

It has been suggested that increased disease activity and the accompanying increase in inflammatory markers contributes to the progression of carotid atherosclerosis and the development of CV disease in patients with RA [4, 6].

![FIG. 1 Proportion of patients with carotid plaque according to RA diagnosis and the number of conventional CV risk factors](https://academic.oup.com/rheumatology/article-abstract/54/5/808/1772885)

**TABLE 1** Demographic data and conventional cardiovascular risk factors of RA patients and age- and sex-matched healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Controls ($n = 209$)</th>
<th>RA ($n = 406$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (s.d.), years</strong></td>
<td>55 (12.1)</td>
<td>55 (12.3)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>169 (80.9)</td>
<td>328 (80.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Obesity, n (%)</strong></td>
<td>5 (2.4)</td>
<td>10 (2.5)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>BMI, mean (s.d.), kg/m²</strong></td>
<td>23.7 (2.8)</td>
<td>22.9 (3.3)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Body muscle percentage, mean (s.d.)</strong></td>
<td>21.9 (4.4)</td>
<td>20.6 (4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>53 (25.5)</td>
<td>163 (40.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>12 (6.0)</td>
<td>34 (8.4)</td>
<td>0.331</td>
</tr>
<tr>
<td><strong>Hyperlipidaemia, n (%)</strong></td>
<td>42 (20.7)</td>
<td>64 (15.8)</td>
<td>0.141</td>
</tr>
<tr>
<td><strong>Total cholesterol, mean (s.d.), mg/dl</strong></td>
<td>201 (35.7)</td>
<td>182 (36.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LDL cholesterol, mean (s.d.), mg/dl</strong></td>
<td>127 (32.4)</td>
<td>108 (32.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HDL cholesterol, mean (s.d.), mg/dl</strong></td>
<td>57 (13.0)</td>
<td>61 (15.6)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Current smoking, n (%)</strong></td>
<td>16 (7.7)</td>
<td>43 (10.6)</td>
<td>0.252</td>
</tr>
<tr>
<td><strong>Smoking, mean (s.d.), pack-years</strong></td>
<td>3.4 (9.9)</td>
<td>5.4 (13.1)</td>
<td>0.039</td>
</tr>
<tr>
<td><strong>Metabolic syndrome, n (%)</strong></td>
<td>44 (21.9)</td>
<td>91 (22.6)</td>
<td>0.918</td>
</tr>
<tr>
<td><strong>CV risk factors, n (%)</strong></td>
<td>0.6 (0.9)</td>
<td>0.9 (1.0)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

$P$-values calculated by $\chi^2$ test for dichotomous variables and $t$-test for continuous variables. CV: cardiovascular; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
TABLE 2 Associations between the presence of carotid plaque and demographic data, conventional CV risk factors and RA-associated markers in 406 RA patients

<table>
<thead>
<tr>
<th></th>
<th>Without plaque (n = 258)</th>
<th>With plaque (n = 148)</th>
<th>Univariate P-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Multivariate P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>51 (11.4)</td>
<td>63 (10.5)</td>
<td>-0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>226 (87.6)</td>
<td>102 (68.9)</td>
<td>0.018</td>
<td>0.007</td>
</tr>
<tr>
<td>CV risk factors, n (%)</td>
<td>0.5 (0.6)</td>
<td>0.9 (0.8)</td>
<td>0.339</td>
<td>0.131</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88 (34.2)</td>
<td>75 (50.7)</td>
<td>0.131</td>
<td>0.016</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (5.1)</td>
<td>21 (14.3)</td>
<td>0.204</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>27 (10.5)</td>
<td>37 (25.0)</td>
<td>0.016</td>
<td>0.568</td>
</tr>
<tr>
<td>Current smoking</td>
<td>18 (7.0)</td>
<td>25 (16.9)</td>
<td>0.204</td>
<td>0.003</td>
</tr>
<tr>
<td>Disease duration, mean (s.d.), years</td>
<td>12.6 (16.1)</td>
<td>13.5 (15.0)</td>
<td>0.713</td>
<td>0.670</td>
</tr>
<tr>
<td>mKHAQ, mean (s.d.)</td>
<td>9 (6.6)</td>
<td>12 (9.8)</td>
<td>0.017</td>
<td>0.001</td>
</tr>
<tr>
<td>TJC68, mean (s.d.)</td>
<td>5 (5.4)</td>
<td>8 (8.3)</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>SJC66, mean (s.d.)</td>
<td>3 (3.5)</td>
<td>4 (5.3)</td>
<td>0.003</td>
<td>0.568</td>
</tr>
<tr>
<td>DAS28, mean (s.d.)</td>
<td>3.10 (1.24)</td>
<td>3.82 (1.45)</td>
<td>-0.001</td>
<td>0.389</td>
</tr>
<tr>
<td>ESR (current level), mean (s.d.), mm/h</td>
<td>20 (17.8)</td>
<td>32 (26.4)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>CRP (current level), mean (s.d.), mg/dl</td>
<td>0.35 (0.64)</td>
<td>0.83 (1.80)</td>
<td>0.012</td>
<td>0.866</td>
</tr>
<tr>
<td>RF, n (%)</td>
<td>231 (89.5%)</td>
<td>124 (83.8%)</td>
<td>0.046</td>
<td>0.012</td>
</tr>
<tr>
<td>MTX, n (%)</td>
<td>236 (91.5)</td>
<td>132 (89.2)</td>
<td>0.262</td>
<td>0.007</td>
</tr>
<tr>
<td>LFF, n (%)</td>
<td>161 (62.6)</td>
<td>101 (68.2)</td>
<td>0.225</td>
<td>0.007</td>
</tr>
<tr>
<td>Corticosteroid dose, mean (s.d.), mg/day</td>
<td>1.8 (2.63)</td>
<td>2.55 (3.00)</td>
<td>0.028</td>
<td>0.526</td>
</tr>
</tbody>
</table>

<sup>a</sup>P-values calculated by logistic regression with age and sex adjustment. Variables with a P-value < 0.05 were considered for inclusion in the multivariate analysis. CV: cardiovascular; DAS28: 28-joint DAS; mKHAQ: modified Korean version of the HAQ; SJC66: 66-joint swollen joint count; TJC68: 68-joint tender joint count.

In the present study, variables reflecting disease activity and systemic inflammation, such as mKHAQ, TJC, SJC, DAS28, ESR and CRP, medications including LEF and current corticosteroid dose and the number of CV risk factors were significantly associated with carotid plaque formation, which remained statistically significant after adjustment for age and sex (Table 2). Multivariate logistic regression analysis revealed that an increased number of conventional CV risk factors, 68-joint TJC and ESR were independent predictive factors for carotid plaque formation in patients with RA. In an analysis of carotid IMT, however, these variables were not significantly different between patients with the highest and the lowest quartiles of carotid IMT. Patients in the highest IMT quartile showed significantly higher BMI, cholesterol and lipoprotein (a) levels than those in the lowest quartile.

Compared with those without CV events, RA patients with CV events differed significantly in the proportion of patients with elevated ESR [OR 5.635 (95% CI 1.230, 25.825), P = 0.026] and CRP level [OR per 1 mg/dl 1.339 (95% CI 1.088, 1.647), P = 0.006] and current corticosteroid dose [OR per 1 mg/day 1.189 (95% CI 1.019, 1.389), P = 0.028], as well as in the conventional CV risk factors [OR per one risk factor 2.010 (95% CI 1.053, 3.838), P = 0.034]. History of CV disease was associated with carotid plaque development [OR 4.063 (95% CI 1.383, 11.932), P = 0.008], which was quantitatively associated with plaque number [OR per one plaque 1.316 (95% CI 1.018, 1.701), P = 0.036], but not with mean carotid IMT. Taken together, RA disease activity and systemic inflammation may influence the CV disease risk via carotid plaque formation rather than by intima-media thickening.

**ESR AUC as a predictor of carotid plaque development**

To evaluate the longitudinal effect of the inflammatory response on carotid plaque development, we calculated the ESR AUC as an indicator of cumulative inflammatory burden. In a subgroup analysis of 194 female patients > 40 years of age with available ESR AUC data, patients with carotid plaques showed a significantly higher ESR AUC compared with those without plaques [2719.9 (s.d. 2207.0) vs 1697.4 (s.d. 1581.2), P = 0.003]. The number of conventional CV risk factors and ESR AUC were identified as independent risk factors for carotid plaque development, after adjustment for age, other systemic inflammatory biomarkers (ESR and CRP) and RA disease activity markers (HAQ, TJC, SJC and DAS28), which differed significantly between patients with and without carotid plaques in the univariate analyses. ESR AUC revealed a linear correlation with carotid plaque number (r = 0.258, P < 0.001; Fig. 2), while it did not have a significant correlation with IMT.

To explore the interaction between ESR AUC and conventional CV risk factors during carotid plaque development, we stratified patients into nine groups according to ESR AUC category (<900, 900–2400 and >2400) and number of conventional CV risk factors (Table 3 and Fig. 3). When risks of carotid plaque formation were compared according to ESR AUC category, higher ESR AUC categories were associated with the presence of carotid...
plaque [OR 2.168 (95% CI 1.440, 3.265), P < 0.001], as was the number of CV risk factors [OR 2.214 (95% CI 1.423, 3.444), P < 0.001]. The risk of carotid plaque development was lowest among RA patients with no conventional CV risk factors and the lowest ESR AUC category, whereas it was highest in those with two or more conventional CV risk factors and the highest ESR AUC category. Even among RA patients with no conventional CV risk factors, the risk of plaque formation was significantly higher among those in the highest ESR AUC category compared with those in the lowest ESR AUC category [OR 3.671 (95% CI 1.101, 12.237), P = 0.034]. As a measure of clinical usefulness, we compared the area under the ROC curve based on a combination of number of conventional CV risk factors and ESR AUC category with that based on each component alone. In these analyses, the use of the product term of ESR AUC category and number of conventional CV risk factors significantly increased the AUC of the ROC (0.718) compared with either ESR AUC
category [0.653, difference of 0.064 (95% CI 0.000, 0.128), P = 0.049] or number of CV risk factors [0.636, difference of 0.081 (95% CI 0.022, 0.141), P = 0.007], independently. Moreover, in an analysis with the likelihood ratio test, the model based on both ESR AUC and the number of conventional CV risk factors significantly improved the prediction of carotid plaque development compared with models including either component alone (P < 0.05). To evaluate the synergistic interaction between ESR AUC category and the number of conventional CV risk factors on the presence of carotid plaque, we generated product terms for the number of CV risk factors and calculated the AP, S and RERI as standard measures for synergistic interaction. AP was 0.327 (95% CI 0.109, 0.546, P = 0.003), S was 1.681 (95% CI 1.334, 2.118, P < 0.001) and RERI was 1.704 (95% CI −2.604, 6.013, P = 0.438), thus supporting synergistic interaction between the two variables.

Discussion
The incidence of carotid atherosclerosis and subsequent CV events is higher in patients with RA compared with healthy controls with similar conventional CV risk profiles, which is attributed mainly to systemic inflammation in patients with RA [6]. In the present study we found that the prevalence of carotid atherosclerosis was increased in patients with RA compared with age- and sex-matched healthy controls. In addition to the number of conventional CV risk factors, disease activity parameters including the 68-joint TJC and ESR were found to be independent predictive factors for carotid plaque development in patients with RA. The ESR AUC, which reflects cumulative inflammatory burden, was confirmed to be independently associated with the presence of carotid plaque in patients with RA, after adjustment for conventional CV risk factors. Furthermore, the ESR AUC in patients with RA had a synergistic interaction with conventional CV risk factors for carotid plaque formation.

In this study, plaque frequency was increased in patients with RA compared with age- and sex-matched healthy controls. Several studies have shown that carotid IMT and plaque are independent risk factors for CV disease, although the predictive value of IMT remains controversial [24, 25]. Numerous studies reporting the diagnostic performance of carotid IMT incorporate carotid plaque into IMT measurement [26]. However, the carotid IMT measured precisely without focal plaques in the common carotid artery was not an independent predictor of subsequent coronary heart disease in a prospective study [27]. In the general population, carotid plaque rather than mean carotid IMT contributed to the predictive power of the risk factors used in calculating the Framingham risk score and improved risk classification on the basis of this score [25]. US assessment of carotid plaque, compared with that of carotid IMT, had greater diagnostic accuracy for the prediction of future coronary heart disease in a meta-analysis of population-based studies [26]. In RA cohorts, both carotid plaque and IMT predicted future CV events [12, 28]. However, few reports have quantified the role of atherosclerosis as a contributor to CV events in RA. Further clinical and pathological evidence is needed to confirm the predictive value of carotid plaque formation for future CV events compared with carotid IMT in patients with RA.

Among the systemic inflammatory biomarkers, ESR rather than CRP was more significantly associated with carotid plaque in patients with RA in the present study. The clinical importance of inflammation in CV disease has been supported by the evidence that even a subtle increase in inflammatory biomarkers can predict future CV events in apparently healthy people [29–32]. Furthermore, CRP levels have been incorporated into CV risk-predicting algorithms, such as the Framingham risk score, to improve CV event risk assessment [33]. Carotid atherosclerosis, a surrogate marker of CV disease, is also influenced by systemic inflammation [34]. Independent associations between CRP and the extent and progression of carotid plaque have been established in the general population and asymptomatic individuals [35, 36]. In patients with RA, however, both ESR and CRP have been investigated as risk factors for carotid atherosclerosis [4, 10, 11, 13, 37]. Distinct mechanisms for ESR and CRP alteration may result in differential associations of these biomarkers in atherosclerosis and CV disease prediction in patients with RA and healthy individuals.

We showed that the ESR AUC was an independent predictor of carotid plaque but not of carotid IMT in patients with RA. IMT and plaque may reflect different stages and aspects of atherosclerosis with distinct pathological processes [38, 39]. Carotid IMT mainly represents the thickening of smooth muscle in the media, whereas plaque formation is largely a result of intimal eccentric thickening [38, 39]. A carotid plaque represents a later stage of the atherosclerotic process, ranging from an initial fatty streak to an advanced atheromatous plaque with necrotic core, and ultimately leading to the clinical thrombotic complications of atherosclerotic disease [40]. Therefore cumulative inflammatory burden may correlate with plaque formation in the atherosclerotic lesions of patients with RA and may increase the occurrence of CV events [14].

We found that the ESR AUC had a synergistic interaction with conventional CV risk factors during carotid plaque formation. In a previous study of carotid IMT and plaque in patients with RA, cross-sectional ESR provided a positive modulation of established CV risk factors for carotid IMT, and it has been suggested that these two variables modify the effect of one another [13]. Compared with that study, we demonstrated statistical significance of synergistic interactions between conventional CV risk factors and cumulative inflammatory burden on plaque formation by AP and S. While the RERI showed a trend of synergistic interaction, all of these calculations represent the same direction towards the synergistic interaction. The present results support the pathogenic hypothesis that inflammation may potentiate localized atherogenesis, thus provoking plaque formation in cooperation with conventional CV risk factors [39, 40].
whereas conventional CV risk factors mainly influence IMT progression. Furthermore, the synergistic interaction between inflammatory burden and conventional CV risk factors may accelerate the atherosclerotic process, which eventually increases the incidence of CV disease in patients with RA. This is the first report to show statistical synergy between inflammatory burden and conventional CV risk factors for the atherosclerotic process in patients with RA.

The major limitation of the present study was its cross-sectional nature, which makes it difficult to elucidate causal relationships in the atherosclerotic process. Although we determined time-integrated inflammatory effects on carotid atherosclerosis, the ESR AUC was retrospectively calculated from female patients with RA using available longitudinal data with imputation of missing data performed by linear interpolation. This may be another limitation in generalizing ESR AUC results for male patients with RA. To overcome these limitations we are conducting a prospective cohort study based on the same study population.

In conclusion, the cumulative inflammatory burden has a synergistic interaction with conventional CV risk factors for carotid plaque formation in patients with RA. These data suggest the importance of tight control of disease activity accompanied by management of conventional CV risk factors for the prevention of carotid atherosclerosis and CV morbidity in patients with RA.

**Rheumatology key messages**

- The presence of carotid plaque is increased in patients with RA compared with healthy controls.
- Carotid plaque formation is associated with cumulative inflammatory burden in patients with RA.
- Cumulative inflammatory burden interacts with conventional cardiovascular risk factors in patients with RA.

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