To the Editor:  

We thank Dr. Makrilakis and colleagues for their interest in our study of 236 patients with rheumatoid arthritis (RA) that documented a potential role of the adipokine chemerin in atherogenesis and cardiovascular disease (CVD) risk stratification.

Dr. Makrilakis, et al reported on their own recent findings that interleukin 6 (IL-6) inhibition with tocilizumab (TCZ) in RA resulted in reduced chemerin concentrations, as well as decreased plasminogen activator inhibitor 1 levels (PAI-1) and arterial stiffness as estimated by the carotid-femoral pulse wave velocity (PWV); reductions in chemerin concentrations were associated with those of PAI-1 levels and decreases in carotid-femoral PWV. In our investigation, we had shown that not only excess was adiposity, but also disease activity and inflammatory markers were strongly related to chemerin concentrations. Taken together, our findings and those in the Makrilakis, et al study support the notion that chemerin may contribute to the reported link between inflammation and enhanced CVD risk in RA. Further, whereas greater disease activity suppression during TCZ treatment is associated with reduced major adverse cardiovascular events, the Makrilakis, et al study provides a potential mechanism whereby IL-6 inhibition can modulate CVD risk in RA.

The fact that we found chemerin concentrations to be independently associated with carotid plaque on ultrasound, particularly in our participants who did not experience obesity (n = 161, 68.2%), raises the possibility that the respective cardiovascular risk biomarker could be useful in CVD risk stratification in RA. In this regard, current recommendations were reported in 2017 on primary cardiovascular risk management with lipid-lowering agents in patients with RA without established CVD and high-risk comorbidities, including chronic kidney disease and diabetes. These entailed the use of multiple major traditional risk factor assessment equations such as the Framingham score and the systematic coronary risk evaluation score (SCORE), with the additional application of a multiplier of 1.5 in patients with RA who met 2 of 3 criteria consisting of (1) a disease duration > 10 years, (2) rheumatoid factor or anticyclic citrullinated peptide positivity, and (3) the presence of extraarticular manifestation, thereby creating the modified Framingham (mFramingham) and mSCORE. However, a large proportion of patients with RA without an estimated high CVD risk according to the mSCORE were recently found to have carotid artery plaque, which represents very high risk, and therefore an indication for lipid-lowering intervention. These findings call for the use of additional risk assessment tools including vascular imaging, as well as cardiovascular risk biomarkers in RA. In view of these considerations, we examined the potential usefulness of chemerin concentrations in CVD risk stratification amongst nonobese patients with RA. Among the 161 patients without obesity in our initial study, 61 had established CVD, chronic kidney disease, diabetes, or were taking lipid-lowering therapy, or experienced a combination of these. As shown in Figure 1, in the remaining 100 patients, to estimate the accuracy of chemerin levels in the independent prediction of plaque presence in nonobese patients with RA, we performed receiver-operator-characteristic (ROC) curve analysis with the inclusion of the mFramingham score as a covariate. The mean (SD) chemerin and mFramingham scores were 105.3 (31.4) pg/ml and 4.6 (5.9), respectively. The area under the curve (AUC) of the ROC curve was associated with plaque presence for both the chemerin concentrations and mFramingham, with the respective AUC being of similar size.

To determine the optimal cutoff values for chemerin concentrations and the mFramingham score in determining plaque presence, we calculated the Youden index. The obtained values and their corresponding sensitivity, specificity, and positive and negative predictive values as determined by applying Bayes theorem are given in Table 1. The optimal cutoff value for the mFramingham score was small at 2.5, which is in keeping with the reported observation that applying multiple major traditional risk factor

Figure 1. Receiver operator-characteristic curves showing the accuracy of chemerin concentrations (AUC shown as dotted line) and mFramingham (AUC shown as dashed line). The p values are given for the AUC-plaque associations. mFramingham: modified Framingham; AUC: area under the curve.

assessment equation as recommended in the population at large results in a gross underestimation of plaque presence in RA. Both the corresponding specificity and negative predictive values for the mFramingham score, as well as chemerin concentrations, were relatively large at 71.2% and 75.1%, and 72.9% and 68.2%, respectively, suggesting that patients with nonelevation of these measures are unlikely to experience high-risk atherosclerosis. Chemerin concentrations and mFramingham scores above these cutoff levels were strongly associated with plaque presence independent of one another. Our current data analysis suggests that in nonobese patients with RA with an mFramingham score above a value of 2.5 or/and chemerin concentrations above 107.6 pg/ml, carotid ultrasound is indicated to more accurately determine the actual CVD risk and delineate its optimal management or, when the latter investigation is unavailable, the use of lipid-lowering therapy may need to be considered.

REFERENCES


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Table 1. Optimal cutoff chemerin concentration and mFramingham score values in ROC curves with corresponding characteristics and associations with plaque.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cutoff Value</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>OR (95% CI)*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemerin, pg/ml</td>
<td>107.6</td>
<td>51.2</td>
<td>72.9</td>
<td>32.7</td>
<td>68.2</td>
<td>2.92 (1.18–7.25)</td>
<td>0.02</td>
</tr>
<tr>
<td>mFramingham</td>
<td>2.5</td>
<td>65.9</td>
<td>71.2</td>
<td>39.3</td>
<td>75.1</td>
<td>4.88 (2.01–11.86)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

* Associations were identified in a logistic regression model in which both chemerin concentrations and mFramingham scores larger than the optimal cutoff values were entered as independent variables. The Youden index was calculated to determine the optimal cutoff values. The PPV and NPV were determined by applying Bayes theorem. mFramingham: modified Framingham; ROC: receiver-operator characteristic; PPV: positive predictive value; NPV: negative predictive value.