Clinical and molecular classification of very early arthritis patients
van de Sande, M.G.H.

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Departments of Vascular Medicine¹ and Clinical Immunology and Rheumatology², Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
NO EVIDENCE OF ACCELERATED ATHEROGENESIS DURING THE EARLIEST STAGES OF RHEUMATOID ARTHRITIS

Sander I. van Leuven\textsuperscript{1}, Marleen G.H. van de Sande\textsuperscript{2}, Maria J. H. de Hair\textsuperscript{2}, Diederik van Wijk\textsuperscript{1}, Roeland Huijgen\textsuperscript{1}, John J.P. Kastelein\textsuperscript{1}, Danielle M. Gerlag\textsuperscript{2}, Erik S. Stroes\textsuperscript{1} and Paul P. Tak\textsuperscript{2}
ABSTRACT

Background: The increased risk for cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) has been largely ascribed to the chronic inflammatory state. Whether the CVD risk is restricted to RA patients with longstanding disease and whether RA-associated autoantibodies also associate with accelerated atherogenesis remains to be elucidated.

Methods: We measured intima media thickness (IMT) in early arthritis patients diagnosed with RA according to the 2010 ACR/EULAR criteria (disease duration < 6 months) (n=20), a group of individuals at risk of developing RA (identified by the presence of arthralgia and elevated serum levels of IgM rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) in the absence of clinical evidence of arthritis) (n=50), and healthy controls (n=70) to study if the CVD risk is increased in the earliest phases of RA. To evaluate the relationship between IMT and RA-associated autoantibodies as well as other parameters, uni- and multivariate regression analyses were performed.

Results: Both in individuals at risk of developing RA and in very early RA patients, the mean IMT was comparable to the mean IMT of healthy controls (0.65 [0.18] and 0.62 [0.21] versus 0.66 [0.17] P=0.44 and P=0.14 respectively). In the early RA group, IMT was associated with age, whereas in the individuals at risk of RA IMT was associated with apoB, total cholesterol, LDL-cholesterol, BMI, systolic blood pressure (SBP), ACPA and ESR levels in univariate analysis. Upon multivariate linear regression analysis only age and SBP remained significantly associated with IMT.

Conclusion: The absence of (a trend towards) increased IMT does not support accelerated atherogenesis during the earliest stages of RA. These findings lend further support to active treatment of inflammation and treatment of CVD risk factors according to national guidelines in RA patients from the onset of clinically manifest arthritis in order to decrease morbidity and mortality from CVD in more advanced RA.
INTRODUCTION

Atherosclerosis is accelerated in patients with rheumatoid arthritis (RA) by a systemic inflammatory state.[1-3] This is illustrated by the observation that carotid intimal media thickness (IMT) is increased and correlates with inflammatory status in RA patients.[4-6] Moreover, increased cardiovascular morbidity and mortality has been observed in these patients[7-9] which could be reduced by potent, anti-inflammatory treatment.[10-13] Mechanistically, cytokines are released from the affected synovial tissue(s), into the systemic circulation which impact distant tissues including skeletal muscle and vascular endothelium, resulting in proatherogenic changes that include insulin resistance, and endothelial dysfunction.[1] Moreover, circulating inflammatory mediators may also stimulate leukocytes and smooth muscle cells within the atherosclerotic plaque thereby promoting plaque growth or rupture.[14]

Although accelerated atherosclerosis has been acknowledged to be promoted by a systemic inflammatory state in patients with established RA it has not been elucidated from which point onwards RA patients are subjected to an increased risk of developing cardiovascular events. It is known that inflammatory mediators are upregulated already in the preclinical phase of RA, before the onset of arthritis. However, no signs of inflammation could be detected in the synovium during the earliest phases, when circulating autoantibodies could already be detected.[15] Also, atherogenic lipid profiles have been demonstrated during the preclinical phase.[16] So far, no data on accelerated atherosclerosis in the preclinical phase are available whereas the data in early RA have been conflicting.[17-19] Furthermore, it remains unclear whether autoantibodies associated with RA, IgM rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), could play a role in promoting atherogenesis in RA patients.[20-25]

To investigate the state of atherogenicity during the very early stages of RA as well as the role of RA-associated autoantibodies, we measured IMT in RA patients who had developed clinical evidence of arthritis within the previous 6 months, and in individuals with elevated RA-specific autoantibodies but without clinically manifest arthritis, who are at risk of developing RA, compared to age- and gender-matched healthy controls.

METHODS

Patients

All participants were included at the outpatient clinic of the department of Clinical Immunology and Rheumatology at the Academic Medical Center in Amsterdam, the Netherlands. Patients who had been diagnosed with RA according to the 1987 ACR criteria [26] within the last six months as well as patients who had been diagnosed with undifferentiated arthritis (UA) based on the absence of fulfillment of disease-specific criteria but having elevated serum levels of RA specific autoantibodies (RF and/or ACPA) were invited to participate (study group 1). Retrospectively, fulfillment of the 2010 ACR/EULAR criteria [27;28] was assessed. In addition, individuals with arthralgia and elevated RF and/or ACPA serum levels without clinically manifest arthritis who are at risk of developing RA[15;29] were included (study group 2), referred to as individuals at risk of RA. Healthy controls matched for age and gender were recruited at the department of Vascular Medicine and participated in the analysis of lipid profiles and IMT measurements. Study participants were invited for a visit during which demographics, medication use, and clinical
disease activity parameters were recorded, blood was withdrawn and IMT measurements were performed. Written informed consent was obtained from all participants. The study protocol was approved by the institutional review board at the Academic Medical Center in Amsterdam and written informed consent was obtained.

**Arthritis disease activity parameters**

Arthritis disease activity was assessed by 68 tender and 66 swollen joint count, the patient’s assessment of global disease activity and pain on a visual analog scale (VAS) 0-100 mm, Disease Activity Score in 28 joints (DAS(28)),(30) morning stiffness in minutes, the erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels.

**Laboratory measurements**

Blood was collected in EDTA, citrate, and heparin anticoagulated aliquots, as well as serum tubes, which were kept on ice and centrifuged at 1600g for 15 minutes at 4°C, snap-frozen, and stored at –80°C until analysis. Plasma total cholesterol was measured with an enzymatic colorimetric procedure (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany). HDL cholesterol was determined after precipitation of apolipoprotein (apo)B-containing lipoproteins by MnCl2. Low-density lipoprotein cholesterol was calculated using the Friedewald formula. apoA-I and apoB were measured using Beckman reagents and array nephelometry (Beckman, Brea, CA). Triglycerides were measured using an enzymatic colorimetric method using lipase, glycerol kinase, and glycerol-3-phosphate 3 oxidase. ACPA levels were determined by the cyclic citrullinated peptide (CCP)-2 ELISA kit (Eurodiagnostica, Nijmegen, the Netherlands) (cutoff 25 kAU/L in serum). Rheumatoid factor (RF) IgM was determined with the RF IgM ELISA (Sanquin, Amsterdam, the Netherlands) (cutoff 12.5 kU/L in serum).

**Carotid IMT**

As shown in prospective epidemiological studies, a modest increase of IMT substantially increases the relative risk for myocardial infarction and stroke. IMT is an accepted validated surrogate marker for the status of atherosclerosis and for present and future atherosclerotic disease risk.[31;32] B-mode ultrasound imaging was used to visualize three carotid arterial wall segments comprising common carotid, bulb and internal of the left and right carotid arteries. All scans were performed by the same sonographer. Both the sonographer and the image analyst were blinded to the clinical status of the subjects. Mean IMT was defined as the mean IMT of the right and left common carotid, the carotid bulb and the internal carotid for wall segments. For a given segment, IMT was defined as the average of the right and left IMT measurements. The per-patient average means of the IMT values of segments was used for the primary analysis.

**Statistical analysis**

Standard descriptive and comparative analyses were undertaken using SPSS statistical program 16.0 (SPSS Inc., Chicago, IL). Results are expressed as median and interquartile range (IQR)). Median values of continuous variables between patients (study group 1 and 2) and control subjects were compared using Mann Whitney U test for independent samples. The relation between the dependent variable IMT on the one hand and other parameters on the other was first explored univariably using linear regression analysis. In addition,
several multivariate analyses were performed to explore the effect of age and the statistically significant variables on IMT. Throughout these analyses a p-value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Table 1 summarizes traditional risk factors for cardiovascular disease and IMT values of the study participants. In total 20 patients who had recently been diagnosed with RA according to the 1987 ACR criteria of RA or UA with elevated serum levels of RA-specific antibodies were included. All individuals fulfilled 2010 ACR/EULAR criteria for RA at baseline in retrospect. In addition, 50 subjects at risk of RA were included as well as 70 healthy controls matched for age and gender. Seven of the 50 subjects at risk of RA developed clinically manifest arthritis (1 up to 4 year after inclusion). There were no statistically significant differences between the study groups with regard to age, sex, BMI, systolic and diastolic blood pressure and lipid profile. One patient who had recently been diagnosed with RA and one subject at risk of RA also suffered from diabetes mellitus. Two subjects at risk of RA had recently suffered a transient ischemic attack and one had a history of myocardial infarction. Eight subjects at risk of RA and 2 early RA patients had high blood pressure for which they were treated. Six healthy controls had high blood pressure for which they were treated.

Table 1. Baseline Characteristics of the Study Subjects.

<table>
<thead>
<tr>
<th></th>
<th>Patients with recent onset RA or UA n=20 (Group 1)</th>
<th>Subjects with RA specific antibodies (preclinical arthritis patients) n=50 (Group 2)</th>
<th>Group 1 &amp; 2 combined n=70</th>
<th>Healthy controls n=70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49 (20)</td>
<td>48 (15)</td>
<td>49 (18)</td>
<td>48 (12)</td>
</tr>
<tr>
<td>Male/female</td>
<td>5/15</td>
<td>14/36</td>
<td>19/51</td>
<td>19/51</td>
</tr>
<tr>
<td>BMI</td>
<td>25.7 (2.6)</td>
<td>25.0 (5.4)</td>
<td>25.4 (5.1)</td>
<td>24.8 (4.8)</td>
</tr>
<tr>
<td>SBP</td>
<td>121 (27)</td>
<td>127 (17)</td>
<td>126 (21)</td>
<td>127 (16)</td>
</tr>
<tr>
<td>DBP</td>
<td>77 (12)</td>
<td>78 (15)</td>
<td>78 (14)</td>
<td>79 (12)</td>
</tr>
<tr>
<td>DM, n</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Prior CVD, n</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.03 (1.30)</td>
<td>5.33 (1.31)</td>
<td>5.27 (1.30)</td>
<td>5.34 (1.23)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>2.85 (1.37)</td>
<td>3.07 (1.20)</td>
<td>3.06 (1.31)</td>
<td>3.13 (1.25)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.34 (0.43)</td>
<td>1.43 (0.53)</td>
<td>1.40 (0.51)</td>
<td>1.50 (0.46)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.05 (1.00)</td>
<td>1.01 (1.00)</td>
<td>1.01 (0.61)</td>
<td>0.85 (0.63)</td>
</tr>
<tr>
<td>IMT</td>
<td>0.62 (0.21)</td>
<td>0.65 (0.18)</td>
<td>0.63 (0.17)</td>
<td>0.66 (0.17)</td>
</tr>
</tbody>
</table>

Values are given as median (IQR). BMI=Body Mass Index, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, DM=Diabetes Mellitus, LDL=Low Density Lipoprotein, HDL=High Density Lipoprotein, CRP=C-Reactive Protein. Blood pressure values are in mmHg, lipid values in mmol/L, CRP in mg/L, carotid IMT in mm.
Characteristics related to inflammation and RA

There was a trend towards an increased acute phase response in patients recently diagnosed with RA compared to subjects at risk of developing RA, which did not reach statistical significance (Table 2). Of note, previous work has shown that acute phase reactants may be somewhat elevated during the preclinical stage. [33] DAS28 was significantly higher in the early RA patients compared to subjects at risk of RA (Table 2). Whereas the percentage of patients with elevated level of RF did not significantly differ (75% vs 60% P=0.24) the percentage of patients with elevated ACPA levels was significantly higher in the early RA group (85% vs 66% P=0.05). Similarly, the absolute ACPA levels were significantly higher in the early RA patients (1780 (3298) vs 145 (1196) P=0.02; data not shown).

IMT measurements

Mean IMT was similar in patients recently diagnosed with RA and subjects at risk of RA (0.62 [0.21] vs. 0.65 [0.18]; P=0.39), and moreover, in both groups there was no difference with healthy controls (0.66 [0.17] vs 0.62 [0.21] P=0.24 and 0.65 [0.18] P=0.46 respectively). In addition, mean IMT of the combined patient groups was comparable to mean IMT levels of healthy controls 0.63 [0.19] vs 0.66 [0.17] P=0.21).

Determinants of IMT

Mean IMT was only determined by age in patients recently diagnosed with RA. In the subjects at risk of RA mean IMT was determined by age, SBP, BMI, ESR, ACPA levels, apoB, total cholesterol and LDL cholesterol levels in univariate analysis (see table 3). Upon multivariate linear regression analysis age and SBP remained significantly associated with IMT. When evaluating the two patient groups combined IMT was significantly associated with age, SBP, LDL cholesterol, total cholesterol, apoB, and ESR. Only age remained significantly associated with IMT in multivariate analysis.

Table 2. Characteristics related to inflammation and RA.

<table>
<thead>
<tr>
<th></th>
<th>Patients with recent onset RA or UA n=20 (Group 1)</th>
<th>Subjects with RA specific antibodies n=50 (Group 2)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>3.4 (8.0)</td>
<td>2.0 (3.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>18 (27)</td>
<td>11 (16)</td>
<td>0.06</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>9 (11)</td>
<td>4 (10)</td>
<td>0.05</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DAS28</td>
<td>3.6 (1.9)</td>
<td>3.0 (2.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>RF</td>
<td>34 (50)</td>
<td>18 (34)</td>
<td>0.08</td>
</tr>
<tr>
<td>ACPA</td>
<td>1780 (3298)</td>
<td>145 (1196)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are given as median (IQR). CRP= C-Reactive Protein, ESR= erythrocyte sedimentation rate, VAS=visual analog scale, DAS= Disease Activity Score, RF=rheumatoid factor, ACPA= anti-citrullinated antibodies.
Table 3. Determinants of IMT in subjects with RA associated antibodies as well as in patients with recent onset RA or UA combined with patients with RA associated antibodies (preclinical arthritis patients).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 and 2 combined</th>
<th>Preclinical arthritis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P$-value in univariate analysis</td>
<td>$P$-value in multivariate analysis</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.11</td>
<td>0.158</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.11</td>
<td>0.03</td>
</tr>
<tr>
<td>SBP</td>
<td>0.002</td>
<td>0.005</td>
</tr>
<tr>
<td>ApoA1</td>
<td>0.96</td>
<td>0.83</td>
</tr>
<tr>
<td>Apo B</td>
<td>0.017</td>
<td>0.03</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.012</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>IgMRF</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>ACPA</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

BMI=Body Mass Index, SBP=Systolic Blood Pressure, LDL= Low Density Lipoprotein, HDL= High Density Lipoprotein, CRP= high sensitivity C-Reactive Protein, ESR= erythrocyte sedimentation rate, RF= rheumatoid factor, ACPA= anti citrullinated antibodies.

DISCUSSION

In the present study we show that mean IMT of subjects at risk of developing RA and very early RA patients is comparable to the mean IMT of healthy controls, which contrasts with the significant increase of IMT in long-standing RA.[25] Since the atherosclerotic process is not accelerated during the preclinical phases of RA yet, preventive measurements for cardiovascular disease should be instituted at the onset of clinically manifest RA.
In univariate regression analyses, IMT of subjects at risk of RA was determined by age, SBP, BMI, apoB, total cholesterol, LDL cholesterol levels, ESR, and ACPA levels, whereas after multivariate analysis only age and SBP remained statistically significant.

It is well documented that the pathophysiological mechanisms of RA initiate long before symptoms occur or the actual diagnosis of RA is established,[15;34] similar to what has been shown in other autoimmune disorders.[35;36] In fact, several studies have shown that autoantibodies can be present more than 10 years before the clinical onset of RA.[37;38] Interestingly, immunohistological studies may show signs of inflammation in synovial tissue from clinically uninvolved joints in established RA[39;40] but not during the earliest preclinical stages when RA-associated autoantibodies can already be detected,[15] indicating that a systemic inflammatory response precedes the onset of subclinical synovitis. In line with these findings, serum levels of CRP,[33] sPLA2 [41 and MCP-1 [42] were shown to be increased in the preclinical phase of RA compared to healthy controls. Thus, increased serum levels of CRP, sPLA2, and MCP-1, which are known to predict future coronary artery disease in apparently healthy individuals,[43-45] during preclinical RA indicate that an acute phase response can develop years before symptoms of RA occur. Accordingly, it has been suggested that ten years before onset of their symptoms, patients who after follow up develop RA already have a significantly more atherogenic lipid profile.[16] In the years prior to the clinical onset of RA, patients are thereby exposed to risk factors which could accelerate the atherosclerotic process significantly.

However, we show normal IMT in the earliest stages of RA, both in the preclinical phase of RA and in recent onset RA, suggesting that atherosclerosis is not accelerated in the preclinical phases of RA. Our results are in agreement with a recent study in early arthritis where no differences in IMT at baseline were observed between recent onset RA (n=79) and healthy controls [19]. However, an increase in IMT after 18 months follow up was observed as well as elevated biomarkers of endothelial activation at baseline, suggesting that the endothelium gets activated from the first signs of arthritis.[19]

Two other studies did show a clear difference in IMT between healthy controls and early RA patients. This might be explained by the increased disease activity seen in these patients reflected by DAS28 compared to the early arthritis patients in our study (mean DAS28 of 4.39 (SD 1.6) [18] and mean 5.8 (SD 1.0) [17] versus 3.6 (1.7) in our study). In addition, in these studies the patients were somewhat of older age (mean 53 years (min 22-max 78) [18] and mean 53 (SD 13) [17] versus median 49 (IOR 20) in our study) and limits for disease duration were < 1 year. A limitation of our study is that only 20 early RA patients were included, which made it only possible to detect relatively large differences in IMT. However, even no trends were observed that would suggest increased atherosclerosis during very early RA. Although in the preclinical phase individuals are subjected to risk factors that promote the atherosclerotic process, it is not known if a specific (cumulative) burden of inflammation is needed or a specific period of time during which individuals are subjected to these risk factors before the enhanced atherosclerosis becomes apparent.

Contradictory results with regard to the role of autoantibodies in RA-mediated acceleration of the atherosclerotic process have been reported. Indeed, increased IMT in 82 RA patients was associated with elevated levels of IgG anticardiolipin (IgG aCL) antibodies.[22] Moreover, RF positivity was associated with an increased likelihood of ischemic heart disease in a cross-sectional study in 567 apparently healthy men in a general population.[20] In contrast, IMT was
not associated with various autoantibodies (e.g. ACPA, IgG aCL, IgM aCL) in a recent study in 71 RA patients. It should be noted however that IMT in RA patients was not increased compared to healthy controls.[20] In the current study we found a positive correlation between serum ACPA levels and IMT in subjects at risk of RA reflected by elevated levels of RA specific autoantibodies. This is in line with recent studies demonstrating an association with serum ACPA and increased IMT [46] as well as premature death due to cardiovascular disease.[47] Further studies are needed to evaluate the potential effects of autoantibodies on atherogenesis. In a recent study, IgG antibodies to β2 GP-I were obtained from a patient with antiphospholipid syndrome.[48] Administration of these antibodies to apoE−/− mice significantly enhanced atherogenesis compared to apoE−/− mice receiving IgG from a healthy control. Comparable studies to determine the atherogenicity of RA associated autoantibodies have not been reported.

Atherosclerotic vascular disease is a major source of morbidity and mortality among RA patients. The notion that RA patients are subjected to an increased CVD risk from early RA onwards would have major consequences with regard to the timing of preventive strategies in these patients. Despite the fact that RA is associated with CVD, atheroprotection is not routinely incorporated in treatment strategies of RA patients. However with the recent EULAR recommendations for cardiovascular risk management in RA,[49] treatment in RA is not only focused on diminishing inflammation, but increasingly also on CVD risk assessment and preventive strategies. Anti-atherosclerotic therapy should be considered during the early stages of clinically manifest RA in the presence of other risk factors to lower the risk of accelerated atherosclerosis from arthritis onset onwards. Two recent studies demonstrated endothelial dysfunction in patients with recent onset RA (duration of symptoms <18 months [49] and <12 months [50]) by plethysmography. Endothelial function was 34%[50] and 59% [51] lower in patients diagnosed with RA within the previous 18 or 12 months, respectively, compared to healthy controls. Interestingly, anti-inflammatory and/or disease-modifying antirheumatic drugs (DMARD) therapy for a period of six months[50] as well as a single treatment of TNF blockade[51] were shown to reverse endothelial dysfunction. The fact that endothelial dysfunction was readily and fully reversible in newly diagnosed RA patients supports early and aggressive prevention of CVD in all RA patients. Pending the outcome of ongoing statin intervention clinical trials in RA patients (e.g. trial of atorvastatin for the prevention of cardiovascular events in rheumatoid arthritis (TRACE RA; https://cz-qt13ade86pxdun.sec.amc.nl/tracera/ estimated report date 2016), the use of CV-preventive compounds in RA patients with persistent inflammatory activity deserves closer attention in the near future.

Several aspects need to be taken into account when interpreting the results of the present study. A potential limitation of the current cross-sectional study is a diminished capacity to identify additional risk factors due to the fact that atherosclerosis is a continuous process. In addition, only a limited number of patients who were recently diagnosed with RA was included complicating analyses of IMT. Furthermore, we included individuals who have an increased risk of developing RA. So far, of these individuals only 7 have progressed towards clinically manifest arthritis. It might be that we underestimated the risk of accelerated atherosclerosis in the preclinical phase because of the low number of individuals who truly developed RA. No significant difference between IMT between the autoantibody positive individuals who did developed arthritis and those who didn’t was observed in our study. We do not have serial data on IMT in subjects at risk of RA, both at the preclinical stage and during early RA. However, as
there were no differences in IMT between the early RA patient group and the subjects at risk of RA, we do not expect that IMT increases over time during the transition of the preclinical phase to early RA (disease duration < 6 months). Another methodological issue is related to the effects of treatment. Although 11 of the 20 early RA patients were already treated with DMARDs (10 MTX and one hydroxychloroquine) at inclusion, it appears unlikely that IMT values were lower because of the treatment effect since all patients were treated for less than 6 months. However, this might help to explain that CRP, ESR, morning stiffness, and VAS global disease activity were not significantly different between the preclinical and the very early RA patient groups. Furthermore, in another study in early RA patients, increases in IMT were seen over time even after active treatment.[19]

CONCLUSION

The known increased CVD risk combined with evidence of endothelial dysfunction in recent onset RA versus the absence of enhanced atherogenesis in preclinical and very early RA observed in this study underlines the EULAR recommendations [49] to actively treat inflammation and treat CVD risk factors according to national guidelines in RA patients from the onset of clinically manifest arthritis in order to decrease morbidity and mortality from CVD in more advanced RA.

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