Coronary and Abdominal Aorta Calcification in Rheumatoid Arthritis: Relationships with Traditional Cardiovascular Risk Factors, Disease Characteristics, and Concomitant Treatments

Julien Paccou, Cédric Renard, Sophie Liabeuf, Said Kamel, Patrice Fardellone, Ziad A. Massy, Michel Brazier, and Romuald Mentaverri

ABSTRACT. ***Objective.*** To assess the influence of traditional cardiovascular (CV) risk factors, disease characteristics, and concomitant treatments in patients with rheumatoid arthritis (RA) on coronary artery calcification (CAC) and abdominal aorta calcification (AAC).

Methods. In our cross-sectional study, 75 patients with RA were compared with 75 age-matched and sex-matched control participants. The CAC and AAC scores were measured by computed tomography in patients with no clinical evidence of coronary artery disease. The relationships between the presence or absence of CAC and AAC and traditional CV risk factors, disease characteristics, and concomitant treatments in patients with RA were assessed in a multiple logistic regression analysis.

Results. The RA and control groups did not differ significantly in terms of age, sex composition, or the prevalence of traditional CV risk factors. AAC and CAC were more prevalent and severe in patients with RA than in controls. Older age (OR = 1.15, $p < 0.01$) and hypertension (OR = 3.77, $p = 0.04$) were found to be independently associated with CAC, whereas current use of methotrexate (MTX; OR = 0.12, $p = 0.01$) was found to be associated with the absence of CAC. Older age (OR per yr = 1.17, $p < 0.001$) and erosive arthritis (OR = 3.78, $p = 0.03$) were found to be independently associated with AAC.

Conclusion. Our study demonstrates that in patients with RA, (1) CAC and AAC are more prevalent and more severe compared with age-matched and sex-matched control participants, (2) current use of MTX is a major determinant of the absence of CAC, and (3) erosive arthritis is a major determinant of AAC. (First Release Oct 1 2014; J Rheumatol 2014;41:2137–44; doi:10.3899/jrheum.140239)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
CORONARY ARTERY CALCIFICATION
ABDOMINAL AORTA CALCIFICATION
METHOTREXATE
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TRADITIONAL CARDIOVASCULAR RISK FACTOR

Patients with rheumatoid arthritis (RA) are exposed to accelerated atherosclerosis and a substantially elevated risk of cardiovascular (CV) events (especially coronary heart disease) and death[1,2,3,4,5]. However, this morbidity and mortality cannot be fully explained by traditional CV risk factors[1,2]. Indeed, stratification tools that are widely used in primary prevention in the general population (such as the Framingham risk score[6]) may be less suitable in patients with RA[7,8].

However, a growing body of evidence suggests that nontraditional CV risk factors (such as chronic inflammation, disease characteristics, and concomitant treatments[9,10,11]) have a pivotal role in accelerated atherosclerosis and the increased CV disease risk in patients with RA[12,13,14,15]. Data from the COnsortium of Rheumatology Researchers Of North America (CORRONA) registry showed that the presence of subcutaneous rheumatoid nodules was independently associated with the occurrence of CV events[13]. Concomitant treatments, such as glucocorticoids (GC), are also associated with an increased risk of

From the Department of Rheumatology; INSERM U1088 (Pathophysiological mechanisms and consequences of cardiovascular calcification: role of cardiovascular and bone remodelling); Clinical Research Center, Division of Clinical Pharmacology; Department of Endocrine and Bone Biology, Amiens University Hospital, Amiens; Department of Nephrology, Amboise Paré University Hospital, Boulogne Billancourt, France.

J. Paccou, MD, PhD; P. Fardellone, MD, PhD, Department of Rheumatology, INSERM U1088; C. Renard, MD; S. Kamel, PhD, INSERM U1088; S. Liabeuf, PharmD, PhD, INSERM U1088, Clinical Research Center, Division of Clinical Pharmacology, Amiens University Hospital; Z.A. Massy, MD, PhD, INSERM U1088, Amiens University Hospital, Department of Nephrology, Amboise Paré University Hospital; M. Brazier, MD, PharmD, PhD; R. Mentaverri, PharmD, PhD, INSERM U1088; Department of Endocrine and Bone Biology, Amiens University Hospital.

Address correspondence to Dr. J. Paccou, Department of Rheumatology, Amiens University Hospital, FR-80054 Amiens, France.
E-mail: julienpaccou@yahoo.fr

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myocardial infarction (MI) in patients with RA[14]. Vascular calcification is commonly used as a subclinical marker of atherosclerosis and has been linked to increased all-cause mortality, CV mortality, and coronary events[16]. Moreover, patients with RA are known to develop early-onset CAC[9].

We therefore hypothesized that (1) coronary artery calcification (CAC) and abdominal aorta calcification (AAC) are more prevalent and more severe in patients with RA than in age-matched and sex-matched control subjects, and (2) the presence of vascular calcification in RA is related to disease characteristics and concomitant treatments as well as traditional CV risk factors.

MATERIALS AND METHODS

Study design. In our cross-sectional study, 75 patients with RA (enrolled by the rheumatology outpatient department at Amiens University Hospital, France) were compared with 75 age-matched and sex-matched non-RA control subjects (enrolled from within a pool of volunteers set up by the hospital's Clinical Research Center). All patients and control subjects gave their written informed consent to participate. Our study's objective and protocol were approved by the local independent ethics committee (Comité de Protection des Personnes Nord-Ouest 2, Amiens, France; reference: 2012-A00323-40) and the national health regulatory authority (Agence Française de Sécurité Sanitaire des Produits de Santé).

Study population. The main inclusion criteria for patients with RA were as follows: presence of the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA, age between 45 years and 80 years, and ability to understand the study's objectives and procedures. The main exclusion criteria were as follows: self-reported or physician-diagnosed history of MI, heart failure, coronary artery revascularization, stroke, peripheral vascular disease, or current atrial fibrillation; body weight over 150 kg; or inflammatory diseases other than RA. None of the control participants met the criteria for RA or any other inflammatory disease.

Study protocol. Information was obtained by means of a structured interview, a physical examination, laboratory tests, multidetector computed tomography (MDCT), and a review of medical records. The demographic and clinical characteristics and the presence or absence of traditional CV risk factors were noted by a single physician experienced with managing patients with RA. The time since disease onset was recorded. Patients were rated according to the 28-joint Disease Activity Score (DAS28) adjusted for the high-sensitivity C-reactive protein (hs-CRP) level. The Health Assessment Questionnaire was also filled out. Current use of biologic and conventional synthetic disease-modifying antirheumatic drugs (cs-DMARD), nonsteroidal antiinflammatory drugs (NSAID), and aspirin was determined from both patient interviews and medical records.

Laboratory variables. Patients with RA and controls were required to fast overnight prior to the collection of blood for determination of a complete blood cell count, glycemia, creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, and hs-CRP levels. The estimated glomerular filtration rate (ml/min) was calculated using the Modification of Diet in Renal Disease formula. Clinical biochemistry variables were analyzed in an onsite laboratory using standard autoanalyzer techniques. The presence of rheumatoid factor and anticyclic citrullinated peptide antibody (anti-CCP) was determined for patients with RA only.

Traditional CV risk factors. Systolic blood pressure and diastolic blood pressure were determined as the average of 2 measurements obtained at an interval of 5 min after subjects had been resting in the supine position for at least 10 min. Current use of lipid-lowering drugs and antihypertensive agents was determined from both patient interviews and medical records. Diabetes mellitus was defined as fasting glycemia ≥ 1.26 g/l (7 mmol/l) or the current use of oral hypoglycemic agents and/or insulin. Smoking status (current smoker or nonsmoker) was self-reported. Height and weight were measured and body mass index was calculated as kg/m^2. A family history of coronary artery disease was defined as a first-degree relative having an MI before the age of 55 years in men and 65 in women.

CAC and AAC scores. To quantify the presence and extent of vascular calcification, each patient underwent a noncontrast-enhanced, 64-slice CT scan (Discovery CT750 HD, General Electric Healthcare). A prospective, electrocardiogram (ECG)-gated sequential scan of the whole heart was performed to measure CAC with the following variables: collimation 64 × 0.625 mm, slice thickness 2.5 mm, gantry rotation time 350 ms, tube voltage 120 kV, and tube current 200 mA. CAC scores were calculated according to the Agatston method[17], using dedicated software (Smart Score 4.0, GE Healthcare). AAC was evaluated without ECG gating. The volume acquisition started at the aortic hiatus of the diaphragm and ended below the aortic bifurcation. The CT variables were as follows: collimation 64 × 0.625 mm, slice thickness 0.625 mm, pitch 1, gantry rotation time 500 ms, tube voltage 120 kV, and tube current 300 mA. Image sets for all patients were analyzed on a commercially available external workstation (Advantage Windows 4.6, GE Healthcare). The abdominal aorta was segmented manually on 3-D maximum intensity projection images to remove bone and adjacent structures. Threshold segmentation was performed to keep only aortic calcifications. To reduce errors because of noise, a cutoff of 160 Hounsfield units was applied. The total calcification volume was calculated as the sum of all voxels in the remaining volume. Aortic wall surface area was calculated based on the cross-sectional area and length of the abdominal aorta measured on CT scan. The AAC score was calculated as follows: total calcification volume / aortic wall surface area × 100[18].

Statistical analysis. Statistical analysis was performed using SAS software (version 8.2, SAS Institute Inc.). Descriptive statistics used for quantitative variables were the mean, SD, minimum, maximum, median, and missing values; those used for qualitative variables were frequency and percentage. All tests were 2-sided with a significance threshold of $p < 0.05$. The different groups were compared using a chi-square test or Fisher's exact test for categorical variables, and either an analysis of variance (or Student t test for 2 groups) or a Kruskal-Wallis test (or Wilcoxon's rank test for 2 groups) for continuous variables. Univariate and multivariate logistic regressions were used to explain AAC and CAC scores, treated as categorical variables (no calcification: a calcification score of 0; calcification: a calcification score of 1 or more). Explanatory variables with $p < 0.1$ in a univariate analysis were included in a multivariate analysis. Using stepwise selection, explanatory variables with $p < 0.05$ were retained in the final multivariate model.

RESULTS

Characteristics of the patient and control groups. The clinical and demographic characteristics of the patients with RA and the control subjects are shown in Table 1 and Table 2. All patients were white. The RA and control groups did not differ significantly in terms of age (RA: 60.7 ± 8.5, controls: 61.1 ± 7.0), sex (women: 74.7% in both groups), or the prevalence of traditional CV risk factors. In the patient group, the mean time since onset of RA was 12.9 ± 9.2 years. Most of the patients (n = 57, 76.0%) were treated with methotrexate (MTX), and only 5 (6.7%) were taking leflunomide and 3 (4.0%) were taking sulfasalazine. The mean number of previous cs-DMARD used was 1.6 ± 0.9, and 43 of the 75 patients with RA (57.3%) had been treated by only 1 cs-DMARD. Fifty patients (66.6%) were being

treated with biological DMARD: 31 (41.3%) with anti-tumor necrosis factor-α (TNF-α), 12 (16.0%) with tocilizumab, 4 (5.3%) with abatacept, and 3 (4.0%) with rituximab. Ten (13.3%) patients were taking biologic DMARD, but not cs-DMARD. Twenty-two patients (29.3%) were taking low-dose GC and 21 (28.0%) were taking NSAID. Remission or low disease activity (defined as a DAS28-hs-CRP ≤ 3.2) was observed in 54 patients (72.0%). The patients and controls did not differ significantly in terms of serum total, HDL and LDL cholesterol, and triglyceride levels. However, glycemia was higher in controls than in patients ($p < 0.01$).

Vascular calcification. The prevalence of vascular calcification and the CAC and AAC scores in patients with RA and control subjects are shown in Table 3. CAC was more prevalent in patients with RA (65.3%) than in controls (49.3%; $p = 0.04$). The mean CAC score was 197 ± 470 in patients with RA and 109 ± 297 in controls ($p = 0.07$). The median CAC score was 15.5 (0–122) in patients with RA and 0 (0–104) in controls. Abdominal aorta calcification scores were not available for 2 patients with RA because of abdominal aorta aneurysm. However, AAC was also more prevalent in patients with RA (71.2%) than in controls (54.7%; $p = 0.04$). The mean AAC score was 1.0 ± 1.3 in patients with RA and 0.7 ± 1.4 in controls ($p = 0.02$). The median AAC score was 0.6 (0–1.5) in patients with RA and 0.2 (0–0.7) in controls.

Analyses based on RA cases and controls combined. To establish whether a relationship exists between RA and the presence and extent of vascular calcification, we performed an analysis of vascular calcification (CAC and AAC) according to disease status (RA or not) and traditional risk factors in the combined population. Appendices 1, 2, and 3 show a strong relationship between RA, and the presence and extent of vascular calcification.

Determinants of vascular calcification in patients with RA. Comparisons of traditional CV risk factors, disease characteristics, and concomitant treatments in patients with RA with or without CAC and/or AAC are shown in Table 4 and Table 5. Patients with CAC were older ($p < 0.01$) and more likely to be men ($p = 0.01$) than patients without CAC. In a multivariate logistic regression analysis, older age [OR per year, 95% CI 1.11 (1.03–1.20), $p < 0.01$] and male sex [OR = 7.65 (1.42–41.32), $p = 0.02$] were independently associated with CAC (Table 6). Current use of MTX [OR = 0.20 (0.05–0.91), $p = 0.04$] was independently associated with the absence of CAC. Patients with AAC were older ($p < 0.01$), had higher LDL and total cholesterol levels ($p = 0.03$ for both), and were more likely to have erosive arthritis ($p = 0.02$) than patients without AAC. The presence of subcutaneous rheumatoid nodules approached statistical significance ($p = 0.05$) for AAC. In a multivariate logistic regression analysis, older age [OR per year = 1.17 (1.07–1.27), $p < 0.001$] and erosive arthritis [OR = 3.78 (1.12–12.8), $p = 0.03$] were found to be independently associated with AAC (Table 6).

DISCUSSION

Our present results demonstrate that CAC and AAC (as evaluated by CT) are more prevalent and severe in patients with RA than in age-matched and sex-matched controls. To the best of our knowledge, this is the first time that AAC has

Table 1. Demographic and clinical characteristics. Values are the mean ± SD unless otherwise specified.

Characteristics	Patients with RA, n = 75	Control Subjects, n = 75	p
Age, yrs	60.7 ± 8.5	61.1 ± 6.9	0.73
Female sex (%)	56 (74.6)	56 (74.6)	1.00
Weight, kg	73.7 ± 19.0	73.4 ± 19.4	0.84
Height, cm	164.8 ± 8.9	163.8 ± 8.9	0.42
Body mass index, kg/m^2	27.0 ± 5.9	27.2 ± 6.4	0.88
Current smokers (%)	14 (18.6)	13 (17.3)	0.83
Diabetes mellitus (%)	3 (4.0)	4 (5.3)	1.00
Family history of CVD (%)	12 (16.0)	14 (18.6)	0.66
Antihypertensive drugs (%)	31 (41.3)	27 (36.0)	0.50
Lipid-lowering drugs (%)	26 (34.7)	24 (32.0)	0.72
Total cholesterol, g/l	2.2 ± 0.4	2.2 ± 0.3	0.43
LDL cholesterol, g/l	1.3 ± 0.3	1.3 ± 0.3	0.09
HDL cholesterol, g/l	0.6 ± 0.1	0.7 ± 0.2	0.93
Triglycerides, g/l	1.1 ± 0.5	1.1 ± 0.5	0.53
Glycemia, g/l	4.4 ± 1.0	4.8 ± 1.2	**< 0.01**
Current use of aspirin, %	7 (9.3)	5 (6.6)	0.54
Creatinine clearance, ml/min	98.2 ± 20.5	94.3 ± 16.1	0.19
hs-CRP, mg/l	4.6 ± 6.9	3.1 ± 4.4	0.48

Significant results are indicated in bold face. RA: rheumatoid arthritis; CVD: cardiovascular disease; LDL: low-density lipoprotein; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein.

Table 2. Characteristics of patients with RA. Values are the mean ± SD unless otherwise specified.

Characteristics	n = 75
Disease duration, yrs	12.9 ± 9.2
Positive for RF (%)	48 (64.0)
Positive for anti-CCP (%)	50 (66.6)
Erosive arthritis (%)	44 (56.8)
Rheumatoid nodules (%)	16 (21.3)
Tender joint count, 28 joints	1.9 ± 3.2
Swollen joint count, 28 joints	1.7 ± 2.6
HAQ score	1.0 ± 0.7
DAS28-hs-CRP	2.7 ±1.0
DAS28-hs-CRP ≤ 3.2 (%)	54 (72.0)
Current cs-DMARD users (%)	62 (82.6)
Current methotrexate users (%)	57 (76.0)
Dose of methotrexate used, mg/week	13.2 ± 4.6
Current bDMARD users (%)	50 (66.6)
Current anti-TNF-α users (%)	31 (41.3)
Current NSAID users (%)	21 (28.0)
Current GC users (%)	22 (29.3)
Dose of GC used, mg/day	5.7 ± 2.1

RA: rheumatoid arthritis; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide; HAQ: Health Assessment Questionnaire; DAS28-hs-CRP: Disease Activity Score 28-high-sensitivity C-reactive protein; cs-DMARD: conventional synthetic disease-modifying antirheumatic drug; bDMARD: biologic DMARD; TNF-α: tumor necrosis factor-α; NSAID: nonsteroidal antiinflammatory drug; GC: glucocorticoid.

been assessed by CT in patients with RA; the most commonly used method is a validated, visual, semiquantitative score based on lateral lumbar radiographs. We hypothesized that the presence of vascular calcification in RA was related to clinical characteristics and concomitant treatments as well as traditional CV risk factors. Although traditional factors [such as age and hypertension (HTN)] were independently associated with CAC in our patient population, our study's striking finding concerned MTX; patients with RA, but not CAC, were more likely to be treated with MTX than were patients with RA and CAC. For AAC, the major determinants were age and (somewhat surprisingly) erosive arthritis.

Patients with RA are known to develop early-onset, widespread calcification in various vascular beds[9,19]. Recent advances in MDCT allow rapid, effective, and noninvasive detection of the prevalence and severity of vascular calcification. This is of particular interest because vascular calcification is both a marker and a cause of elevated CV morbidity and mortality[16,20,21]. Only a few studies have used CT to measure vascular calcification in patients with RA[9,19]. In 1 such study, CT was used to measure the distribution and extent of vascular calcification in 85 patients with RA and 85 age-matched and sex-matched controls[19]; patients with RA had a significantly higher relative risk (vs controls) of developing calcification in the thoracic aorta, carotid arteries, and coronary arteries. However, adjustment for age and sex, HTN was the only factor found to be independently associated with the presence or absence of vascular calcification[19]. In another study, CT was used to measure the extent of CAC in 227 subjects, of whom 70 had recent-onset RA (disease duration < 5 yrs, mean age: 51 yrs), 71 had established RA (disease duration > 10 yrs, mean age: 58 yrs), and 86 were controls (matched for age, sex, and race)[9]. The investigators found that CAC occurred more frequently in patients with established RA (60.6%) than in patients with recent-onset RA (42.9%) or control subjects (38.4%; p = 0.02). In patients with RA (and after adjustment for age and sex), current smoking, an elevated erythrocyte sedimentation rate, and disease duration > 10 years were associated with more severe CAC (defined as an Agatston score > 109)[9]. Like Wang, *et al*[19], we found that age and male sex were independently associated with CAC in patients with RA. However, this was not true for disease duration, smoking status, HTN, and hs-CRP in our study. These results are surprising because HTN is usually a major determinant of CAC, and is underdiagnosed and undertreated in patients with RA[22]. Our starting hypothesis was that the presence of vascular calcification was related to the characteristics of RA and concomitant treatments. However, no such relationships were found for CAC. In contrast, to the best of our knowledge, our present study is the first to observe that MTX prescription was independently associated with the absence of CAC. This result is especially interesting because the effects of therapeutics used in RA (other than anti-TNF-α therapy[23,24,25]) on CV disease are not well known. However, MTX has an effect on CV disease in RA[26,27,28]. In a systematic review and metaanalysis, MTX use was associated with a 21% lower CV disease risk in patients with systemic inflammation (mainly RA)[26]. Indeed, the study by Choi, *et al*[27], showing the largest reduction (70%) in CV deaths, was awarded the highest quality score. Although the mechanisms by which MTX reduces CV disease and vascular calcification in RA are

Table 3. Prevalence of vascular calcification and mean calcification scores in patients with RA and in controls.

Site	Prevalence of Vascular Calcification			Mean ± SD Calcification Score		
	RA	Controls	p	RA	Controls	p
Coronary	65.3%	49.3%	0.04	197 ± 470	109 ± 297	0.07
Aorta	71.2%	54.7%	0.04	1.0 ± 1.3	0.7 ± 1.4	0.02

RA: rheumatoid arthritis.

Table 4. Univariate analysis of the relationships between traditional cardiovascular risk factors, disease characteristics, concomitant treatments, and coronary artery calcification in patients with RA. Values are the mean ± SD unless otherwise specified.

Characteristics	No CAC, Score = 0, n = 26	CAC, Score ≥ 1, n = 49	p
Age, yrs	56.6 ± 8.0	62.8 ± 8.1	**< 0.01**[c]
Male, n (%)	2 (7.7)	17 (34.7)	**0.01**[b]
Weight, kg	69.8 ± 20.8	75.8 ± 17.9	0.15[d]
Height, cm	163.5 ± 7.7	165.6 ± 9.5	0.33[d]
Erosive arthritis, n (%)	12 (46.2)	32 (65.3)	0.11[a]
Positive for RF and/or anti-CCP, n (%)	21 (80.8)	42 (85.7)	0.58[a]
Disease duration, mos	160 ± 100	152 ± 118	0.54[d]
Current prednisolone use (%)	5 (19.2)	17 (34.7)	0.16[a]
Current methotrexate use, n (%)	23 (88.5)	34 (69.4)	0.09[b]
Current anti-TNF-α use, n (%)	10 (38.5)	21 (42.9)	0.71[a]
Rheumatoid nodules, n (%)	7 (26.9)	9 (18.4)	0.39[a]
Hypertension, n (%)	7 (26.9)	24 (49.0)	0.06[a]
SBP	130 ± 21	129 ± 15	0.85[c]
DBP	83 ± 15	80 ± 9	0.28[d]
Current smoker, n (%)	6 (23.1)	8 (16.3)	0.47[a]
Current aspirin use, n (%)	1 (3.8)	6 (12.2)	0.41[b]
Hypercholesterolemia, n (%)	7 (26.9)	19 (38.8)	0.30[a]
Total cholesterol, g/l	2.2 ± 0.5	2.1 ± 0.3	0.81[c]
LDL, g/l	1.2 ± 0.4	1.3 ± 0.3	0.70[c]
HDL, g/l	0.7 ± 0.2	0.6 ± 0.1	0.10[c]
Triglycerides, g/l	1.1 ± 0.7	1.2 ± 0.5	0.16[d]
Glycemia, g/l	4.3 ± 0.6	4.4 ± 1.1	0.75[d]
EGFR-MDRD, ml/min	102.2 ± 22.7	96.1 ± 19.2	0.22[c]
hs-CRP, mg/l	4.8 ± 8.1	4.5 ± 6.4	0.37[d]

Significant results are indicated in bold face. [a]Chi-square test. [b]Fisher's exact test. [c]Student t test. [d]Wilcoxon signed-rank test. RA: rheumatoid arthritis; CAC: coronary artery calcification; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; TNF-α: tumor necrosis factor-α; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; EGFR-MDRD: estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula; hs-CRP: high-sensitivity C-reactive protein.

likely to be complex, decreasing systemic inflammation appears to be a major determinant[28]. It is important to note that (1) MTX exerts its antiinflammatory effects (at least in part) through adenosine receptors, and (2) adenosine signaling decreases vascular inflammation[29,30,31]. This is consistent with the concept whereby inflammation promotes atherosclerosis and vascular calcification[32]. However, medication effects could be confounded by indication in our observational study and causality cannot be inferred. It has been shown that the presence of anti-CCP is associated with an increased risk of CV disease in RA[33]. However, to the best of our knowledge, this is the first time that a major disease characteristic such as erosive arthritis has been linked to atherosclerosis (assessed by the AAC score).

Our present study had a number of limitations. First, our study's cross-sectional design prevented us from proving the existence of a chronological or causal relationship between traditional/novel risk factors on one hand and vascular calcification on the other. Indeed, the potential influence of the duration and dosage of MTX prescription on CAC could not be validly evaluable. Second, we did not observe an association between vascular calcification on one hand, and anti-TNF-α and GC use on the other — even though these concomitant treatments are known to be related to CV disease in RA[23,24,25,14,34]. Third, the prognostic significance of vascular calcification, as a subclinical marker of atherosclerosis, is a matter of debate[35,36,37]. In atherosclerotic plaque (more than 90% of atherosclerotic fatty plaques undergo calcification), the contribution of focal calcification to plaque vulnerability remains unclear, but atherosclerotic plaque calcification is currently used as a subclinical marker of atherosclerosis. Medial artery calcification contributes to vascular stiffness and is strongly correlated with coronary artery disease and future CV events in patients with chronic kidney disease and in diabetic subjects[38,39]. One of the most important limitations of MDCT scoring of CAC is the difficulty in distinguishing between superficial, focal atherosclerotic calcification and deep, concentric medial calcification[35]. Moreover, noncalcified atherosclerotic plaques cannot be diagnosed by MDCT[40].

Our present results demonstrate that in patients with RA, (1) HTN, age, and MTX use are associated with the presence or absence of CAC, and (2) age and the presence of erosive arthritis are associated with AAC. Our identification of a strong, independent association between MTX use and the absence of CAC emphasizes the need for prospective, randomized clinical studies of the effects of MTX on vascular calcification and CV events, and

Table 5. Univariate analysis of the relationships between traditional cardiovascular risk factors, disease characteristics, concomitant treatments, and abdominal aorta calcification in patients with RA. Values are the mean ± SD unless otherwise specified.

Characteristics	No AAC, Score = 0, n = 21	AAC, Score ≥ 1, n = 52	p
Age, yrs	54.4 ± 5.9	63.1 ± 8.2	**< 0.01**[c]
Male, n (%)	3 (14.3)	16 (30.8)	0.24[b]
Weight, kg	77.2 ± 22.8	72.5 ± 17.8	0.32[d]
Height, cm	163.9 ± 8.6	165.4 ± 9.2	0.50[d]
Erosive arthritis, n (%)	8 (38.1)	35 (67.3)	**0.02**[a]
Positive for RF and/or anti-CCP, n (%)	17 (81.0)	44 (84.6)	0.73[b]
Disease duration, mos	132 ± 107	160 ± 108	0.25[d]
Current prednisolone use (%)	4 (19.0)	17 (32.7)	0.39[b]
Current methotrexate use, n (%)	17 (81.0)	38 (73.1)	0.56[b]
Current anti-TNF-α use, n (%)	10 (47.6)	20 (38.5)	0.47[a]
Rheumatoid nodules, n (%)	1 (4.8)	14 (26.9)	0.05[b]
Hypertension, n (%)	6 (28.6)	25 (48.1)	0.13[a]
SBP	127 ± 17	130 ± 18	0.49[c]
DBP	82 ± 11	80 ± 12	0.24[d]
Current smoker, n (%)	3 (14.3)	11 (21.2)	0.74[b]
Current aspirin use, n (%)	2 (9.5)	4 (7.7)	1.00[b]
Hypercholesterolemia, n (%)	6 (28.6)	19 (36.5)	0.52[a]
Total cholesterol, g/l	2.0 ± 0.4	2.2 ± 0.4	**0.03**[c]
LDL, g/l	1.1 ± 0.3	1.3 ± 0.3	**0.03**[c]
HDL, g/l	0.6 ± 0.2	0.7 ± 0.1	0.34[c]
Triglycerides, g/l	1.1 ± 0.7	1.1 ± 0.5	0.78[d]
Glycemia, g/l	4.3 ± 0.7	4.4 ± 1.0	0.92[d]
EGFR-MDRD, ml/min	97.6 ± 23.9	98.1 ± 19.6	0.93[c]
hs-CRP, mg/l	5.5 ± 8.3	4.2 ± 6.5	0.79[d]

Significant results are indicated in bold face. [a]Chi-square test. [b]Fisher's exact test. [c]Student t test. [d]Wilcoxon signed-rank test. RA: rheumatoid arthritis; AAC: abdominal aorta calcification; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; TNF-α: tumor necrosis factor-α; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; EGFR-MDRD: estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula; hs-CRP: high-sensitivity C-reactive protein.

Table 6. Univariate and multivariate logistic regression analysis of determinants of vascular calcification in patients with RA.

Vascular Calcification			Univariate Analysis			Multivariate Analysis		
		Unit Increment	OR	95% CI	p	OR	95% CI	p
CAC								
	Age	Yrs	**1.10**	1.03–1.18	< 0.01	**1.11**	1.03–1.20	< 0.01
	Male sex	Yes vs no	**6.37**	1.34–30.3	0.02	**7.65**	1.42–41.3	0.02
	Methotrexate	Yes vs no	**0.30**	0.08–1.14	0.07	**0.20**	0.05–0.91	0.04
AAC								
	Age	Yrs	**1.17**	1.07–1.27	< 0.001	**1.17**	1.07–1.27	< 0.001
	Erosive arthritis	Yes vs no	**3.35**	1.17–9.60	0.02	**3.78**	1.12–12.8	0.03

Significant results are indicated in bold face. RA: rheumatoid arthritis; CAC: coronary artery calcification; AAC: abdominal aorta calcification.

preclinical studies of the mechanisms underlying this effect. Further studies will be needed to confirm the potential influence of erosive arthritis on CV disease.

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APPENDIX 1. Univariate analysis of the relationships between traditional cardiovascular risk factors, disease status, and vascular calcification presence (coronary artery calcification and abdominal aorta calcification). All data are represented as n (%) unless specified otherwise.

Characteristics	No CAC, Score = 0, n = 64	CAC, Score ≥ 1, n = 86	p	No AAC, Score = 0, n = 55	AAC, Score ≥ 0.1, n = 93	p
Age, yrs, mean ± SD	57.4 ± 6.5	63.5 ± 7.6	**< 0.001[c]**	57.1 ± 6.6	63.1 ± 7.6	**< 0.001[c]**
Male	7 (10.9)	31 (36.0)	**< 0.001[a]**	9 (16.4)	29 (31.2)	**0.046[a]**
Hypertension	12 (18.8)	46 (53.5)	**< 0.001[a]**	16 (29.1)	42 (45.2)	0.053[a]
Current smoker	10 (15.6)	17 (19.8)	0.514[a]	7 (12.7)	20 (21.5)	0.181[a]
Hypercholesterolemia	13 (20.3)	37 (43.0)	**0.004[a]**	10 (18.2)	39 (41.9)	**0.003[a]**
Total cholesterol, g/l, mean ± SD	2.2 ± 0.4	2.2 ± 0.3	0.830[c]	2.1 ± 0.4	2.2 ± 0.4	0.530[c]
LDL, g/l, mean ± SD	1.3 ± 0.3	1.3 ± 0.3	0.744[c]	1.3 ± 0.3	1.3 ± 0.3	0.899[c]
HDL, g/l, mean ± SD	0.7 ± 0.2	0.6 ± 0.1	**0.029[d]**	0.6 ± 0.1	0.7 ± 0.2	0.579[d]
Rheumatoid arthritis	26 (40.6)	49 (57.0)	**0.048[a]**	21 (38.2)	52 (55.9)	**0.037[a]**

Significant results are indicated in bold face. [a]Chi-square test. [c]Student t test. [d]Wilcoxon signed-rank test. CAC: coronary artery calcification; AAC: abdominal aorta calcification; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

APPENDIX 2. Multivariate logistic regression analysis of determinants of vascular calcification presence (coronary artery calcification and abdominal aorta calcification).

Vascular Calcification Presence			Multivariate Analysis	
	Unit Increment	OR	95% CI	p
CAC				
Age	Yrs	**1.14**	1.07–1.21	< 0.0001
Male sex	Yes vs no	**3.49**	1.20–10.2	0.02
Hypertension	Yes vs no	**4.07**	1.73–9.59	0.001
HDL	g/l	**0.06**	0.01–0.93	0.04
Rheumatoid arthritis	No vs yes	**0.41**	0.18–0.92	0.03
AAC				
Age	Yrs	**1.16**	1.09–1.24	< 0.0001
Current smoker	Yes vs no	**4.26**	1.40–12.98	0.01
Hypercholesterolemia	Yes vs no	**3.72**	1.51–9.16	0.004
Rheumatoid arthritis	No vs yes	**0.39**	0.17–0.87	0.02

Significant results are indicated in bold face. CAC: coronary artery calcification; HDL: high-density lipoprotein; AAC: abdominal aorta calcification.

APPENDIX 3. Univariate and multivariate analysis of the relationships between traditional cardiovascular risk factors, disease status, and vascular calcification extent (coronary artery calcification and abdominal aorta calcification).

Characteristics	CAC Univariate Analysis, p	CAC Multivariate Analysis, p	AAC Univariate Analysis, p	AAC Multivariate Analysis, p
Age	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.0001**
Sex	**< 0.001**	**< 0.001**	0.133	—
Hypertension	**< 0.001**	**< 0.001**	**< 0.001**	—
Current smoker	0.558	—	0.170	**0.001**
Hypercholesterolemia	**0.002**	—	**0.001**	**0.001**
Total cholesterol	0.512	—	0.862	—
LDL	0.861	—	0.831	—
HDL	**0.031**	—	0.760	—
Rheumatoid arthritis	0.071	**0.037**	**0.015**	**0.003**

Significant results are indicated in bold face. CAC: coronary artery calcification; AAC: abdominal aorta calcification; LDL: low-density lipoprotein; HDL: high-density lipoprotein.