Non-invasive assessment of coronary flow reserve and ADMA levels: a case–control study of early rheumatoid arthritis patients

Maurizio Turiel1, Fabiola Atzeni2, Livio Tomasoni1, Simona de Portu3, Luigi Delfino1, Bruno Dino Bodini1, Matteo Longhi1, Simona Sitia1, Mauro Bianchi4, Paolo Ferrario4, Andrea Doria5, Vito De Gennaro Colonna4,* and Piercarlo Sarzi-Puttini2,*

Objective. Plasma concentration of asymmetric dimethylarginine (ADMA), a major endogenous inhibitor of nitric oxide synthase, is considered a novel risk factor for endothelial dysfunction associated with enhanced atherosclerosis. Coronary microcirculation abnormalities have been demonstrated in patients with early rheumatoid arthritis (ERA) without any signs or symptoms of coronary artery disease (CAD). The aim of the study was to compare the ERA and control groups with ADMA, intima-media thickness (IMT) and coronary flow reserve (CFR) levels. It assessed whether ERA patients have more cardiovascular risk (endothelial dysfunction and coronary microvascular abnormalities), and evaluated whether any difference in IMT/CFR between ERA and controls can be explained by any difference in ADMA levels between the groups.

Methods. The study involved 25 ERA patients (female/male 21/4; mean age 52.04 years; disease duration ≤12 months) and 25 healthy volunteers with no history or current signs of CAD or other traditional risk factors. Dipyridamole trans-thoracic stress echocardiography was performed to evaluate CFR, and carotid ultrasound to measure the IMT of the common carotid arteries. Blood samples were obtained in order to assess ADMA levels before the patients had received any biological or non-biological DMARDs, or steroid therapy.

Results. CFR was significantly reduced in the ERA patients (2.5 ± 0.5 vs 3.5 ± 0.8; P < 0.01). In particular, 6/25 (24%) had a CFR of <2 consistent with potentially dangerous coronary flow impairment. Common carotid IMT was significantly greater in the ERA patients, although still within the normal range (0.68 ± 0.1 vs 0.56 ± 0.11 mm; P < 0.01). There was a significant correlation between CFR and plasma ADMA levels in the ERA population (r = −0.53; P < 0.01). IMT was negatively associated with CFR (P < 0.05).

Conclusions. Plasma ADMA levels were significantly higher in the ERA patients. A statistically significant negative effect of ADMA levels on CFR value was observed. The effect of ADMA levels on IMT is not significant.

Key words: Asymmetric dimethylarginine, Rheumatoid arthritis, Coronary artery disease, Coronary flow reserve, Trans-thoracic echocardiography.

Introduction

RA affects ~1% of the general adult population and is associated with a reduced life expectancy [1]. This increased mortality becomes apparent within a few years of the onset of the disease and increases with disease duration, and may be partially caused by infections, gastrointestinal, renal and respiratory diseases, or lung cancer and non-Hodgkin’s lymphoma (but not other cancers) [1]: recent epidemiological studies have shown that it is largely due to cardiovascular disease, primarily coronary artery disease (CAD) [2–4].

The high rate of cardiovascular mortality and morbidity in RA cannot be fully explained by traditional atherosclerosis risk factors because it is known that standard therapy (i.e. corticosteroids and MTX) may accelerate atherosclerosis [5, 6]. There is a considerable evidence suggesting that inflammation plays a pathogenic role in atherosclerosis [7, 8], including a number of recent studies [8–10]. Gerli et al. [11] have found that a subset of RA patients has an increased number of CD4+CD28null cells that produce IFN-γ, thus inducing Th1 cell activation and leading to a variety of cytokines and a long-term shift in immune activation; it is now recognized that this pathway is important in the evolution of atherosclerosis and often operates in unstable angina. Similarly, recent studies have demonstrated that neangiogenesis, which is an important factor in the pathogenesis of RA, is a major contributor to the development of atherosclerosis [12].

It has recently been found that asymmetric dimethylarginine (ADMA) is a predictor of cardiovascular risk [13, 14], and increased plasma ADMA levels have been observed in patients with diseases associated with enhanced atherosclerosis, such as hypercholesterolaemia [15], hypertriglyceridaemia [16], peripheral arterial disease [17], hypertension [18], type 2 diabetes mellitus [19], acute coronary syndromes [20], and end-stage renal failure [22]. It has also been hypothesized that ADMA is causally involved in the pathophysiology of atherosclerosis and its complications.

ADMA is released into plasma and inhibits nitric oxide (NO) production by NO synthase, thus causing endothelial dysfunction, which is closely associated with the development of atherosclerosis. It has recently been recognized as a major endogenous inhibitor of all three isoforms of NO synthase [23], and it is known that high plasma ADMA levels can impair NO generation and promote the progression of atherosclerosis [7].

Wisłowska et al. [24] found that RA patients with unknown cardiovascular disease had a high prevalence of silent CAD when assessed by means of 24-h electrocardiographic Holter monitoring, and a number of other authors have reported that CAD occurs rapidly in RA patients and at a younger age than in the general population [25, 26]. The importance of recognizing and treating patients with early RA (ERA) is therefore due to the risk that active disease may lead to progressive joint and cardiovascular damage [20, 27].
Trans-thoracic Doppler-derived coronary flow reserve (CFR) has been used to identify patients with known or suspected CAD [28], and its prognostic value has also been confirmed in various cardiovascular settings [28, 29]. Furthermore, the measurement of carotid artery intima-media thickness (IMT) is clinically useful in identifying early atherosclerosis and closely correlates with CAD [30].

The aim of the study was to compare the ERA and control groups with ADMA, IMT and CFR levels. It assessed whether ERA patients have more cardiovascular risk (endothelial dysfunction and coronary microvascular abnormalities), and evaluated whether any difference in IMT/CFR between ERA and controls can be explained by any difference in ADMA levels between the groups.

Patients and methods

Patients and controls

A case–control study was conducted in 25 consecutive outpatients (4 males and 21 females; mean age 52.04 ± 14.6 years) with ERA as defined by the ACR criteria [31] and no clinical history or signs of CAD or other cardiac diseases, recruited between March 2006 and August 2007 at the ERA referral centre of L. Sacco University Hospital (Milan, Italy). They all had active disease, defined as ≥6 swollen joints, six or more tender joints, an ESR of >28 mm/h or a global health assessment score of >20 on a 100 mm visual analogue scale (VAS: 0 = best and 100 = worst), and a maximum disease duration of 12 months. The control group consisted of 25 healthy volunteers overall matched with ERA patients, chosen as to ensure the two groups were similar in the distribution of the age and gender variables. The clinical and biochemical characteristics of the study population listed in Table 1 were collected cross-sectionally.

In order to avoid confusion with other known risk factors for atherosclerosis, the exclusion criteria were hypertension, defined as systolic/diastolic blood pressure of ≥140/90 mmHg or the use of antihypertensive medication; hyperlipidaemia, defined as total cholesterol levels of >200 mg/dl, low-density lipoprotein (LDL) cholesterol levels of ≥115 mg/dl or triglyceride levels of ≥150 mg/dl, or the use of lipid-lowering medication; diabetes mellitus, diagnosed on the basis of the World Health Organization criteria [32] or the use of anti-diabetic medication; and a history of ischaemic heart disease or cerebrovascular events. In order to avoid confusion with possible pharmacological risk factors for atherosclerosis, we also excluded RA patients who were already being treated with biological or non-biological DMARDs or steroid therapy.

Smoking habits were assessed by means of a questionnaire both in RA patients and in healthy controls.

The study was approved by our local ethics committee, and all of the subjects gave their written informed consent.

Assessment of RA. RA was defined on the basis of the ACR criteria using self-reports of morning stiffness and objective findings of synovitis and RF positivity [31]. Radiographs of the hands and wrists were obtained for all of the subjects. The clinical assessment included the number of tender and swollen joints, the duration of morning stiffness and ESR and CRP levels. Disease severity was assessed using the disease activity score (DAS28) criteria [33].

Cardiovascular assessment. The cardiovascular risk profile (standard ECG, conventional and stress trans-thoracic echocardiographic examinations with CFR measurement and carotid ultrasound evaluation) was assessed in all of the patients. The trans-thoracic Doppler-derived CFR and common carotid IMT data were collected and analysed by two independent echocardiographers not involved in patient care.

The exclusion criteria were: (i) a technically poor acoustic window precluding satisfactory two-dimensional (2D) Doppler echocardiographic imaging of the left ventricle or left anterior descending (LAD) coronary artery flow (for CFR assessment); (ii) an unwillingness to give informed consent; (iii) a history of CAD; (iv) congenital, valvular or hypertrophic cardiomyopathy, myocarditis or pericarditis, or thyroid diseases; (v) severe mental retardation; and (vi) lymphoproliferative disorders.

Arterial blood pressure and ECG were evaluated using standard procedures [34].

Standard echocardiography. The trans-thoracic echocardiographic images were recorded using a commercially available ultrasound unit (Sonos 5500, Philips Medical Systems, Andover, USA) equipped with 1.3–2.6 MHz (S3) transducer capability and a 3.5–7 MHz broad band high-frequency trans-thoracic transducer (S8) with second harmonics. Left ventricular diameters and wall thicknesses were measured from the 2D targeted M-mode echocardiographic trace in accordance with the recommendations of the American Society of Echocardiography [35]. The left ventricle was divided into 16 segments, and segmental wall motion was graded as 1 = normal, 2 = hypokinetic, 3 = akinetic or 4 = dyskinetic. A wall motion score index was obtained by dividing the sum of the segment scores by the number of visualized segments [36].

Left ventricular mass was calculated using Devereux’s formula [37]; the Doppler indices of left ventricular diastolic function were measured using standard techniques [38].

Dipyridamole echocardiography and CFR

In order to make the trans-thoracic Doppler-derived CFR evaluation, all of the study subjects were asked to abstain from xanthine-containing food and drinks for ≥24 h. With the subjects in a stable 90° left lateral recumbent position, LAD CFR was evaluated before and during dipyridamole infusion (0.56 mg/kg over 4 min + 0.28 mg/kg over the next 2 min) using a modified two-chamber view to identify the distal LAD.

 Coronary blood flow in the mid-distal portion of the LAD artery was measured under the guidance of colour Doppler flow mapping synchronized by ECG.
CFR was calculated as the ratio between peak diastolic velocity during hyperaemia and baseline diastolic velocity. We performed three measurements which were averaged. At the same time, segmental left ventricular wall motion, ECG and symptom arousal were evaluated.

The left ventricular wall motion score index was calculated during stress [36]. At the end of the protocol, 125–250 mg of aminophylline was administered to counteract the effect of dipyridamole. All of the recordings were digitally stored in order to simplify their off-line review and measurement.

The previously assessed intra- and inter-observer variability in measuring the Doppler recordings was <10%.

Carotid artery ultrasound

Carotid artery ultrasound was performed using a Sonos 5500 (Philips Medical Systems) with a 7-11 MHz linear array transducer. The patients lay supine with the neck extended and chin turned contralaterally to the examined side, and the carotid arteries were scanned in the transverse and longitudinal planes. The IMT of the common carotid artery was measured 1 cm distal to the carotid bifurcation in the posterior wall, with the measurements being made over both the right and left carotid arteries. IMT was defined as the distance between the leading edges of the lumen interfaces and the media-adventitia interface of the far wall [30, 39]. We performed three measurements which were averaged.

Biochemical analysis

The laboratory variables relevant to RA activity (ESR, white blood cell and platelet cell counts and CRP levels) were measured using routine methods. IgM RF was measured by means of immunonephelometry using the quantitative N Latex RF system (Dade Behring, Marburg, Germany), with RF titres of >15 IU/ml being considered positive. Anti-CCP autoantibodies were tested using a commercially available second-generation ELISA kit (Menarini Diagnostics, Florence, Italy).

Serum levels of total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were determined using an autoanalyzer. LDL cholesterol was calculated by means of Friedewald's formula [40]. Other standard clinical laboratory tests were performed under fasting conditions on the same day as the other evaluations. The mean glomerular filtration rate (GFR) was calculated using the Cockcroft–Gault formula.

Plasma ADMA concentrations

Plasma ADMA concentrations were determined using the HPLC method described by Teerlink [41] with minor modifications. Briefly, a Millipore Waters Model 590 liquid chromatograph (Waters Ass., Milford, MA, USA) equipped with an injection valve (Model 7125 Rheodyne, Cotati, CA, USA) and a Waters 474 Scanning Fluorescence Detector was connected to a Hitachi-Merck D-2000 Chromato-integrator (Merek Darmstadt, Germany), and a Waters Symmetry C18 3.5 µm column (150 × 4.6 mm internal diameter) coupled to a Waters Sentry Symmetry C18 guard column was operated at room temperature. The mobile phase was 9:91 (v/v) acetonitrile:50 mM potassium phosphate buffer (K2HPO4 pH = 6.50). The flow rate was 1.1 ml/min, and the column effluent was monitored at excitation and emission wavelengths of 340 and 455 nm, respectively.

The plasma samples were purified by means of solid phase extraction (SPE), with HN3-monomethylamine (760 ng/100 µl) being added (200 µl) as an internal standard, as well as 700 µl of PBS (10 mM sodium phosphate, 140 mM NaCl, pH = 7.0). The samples were extracted using disposable cartridges (Waters Oasis MCX SPE 1 ml, 100 mg) pre-conditioned with one volume of eluting solvent, followed by one volume of water. After washing with one volume of HCl 100 mM and one volume of methanol, the elution was carried out with two fractions of 0.5 ml of concentrated ammonia,0.1 M NaOH/water/methanol (10/0.5/10/80). The eluate was evaporated to dryness at 40°C under nitrogen flow, and the residue was reconstituted with 100 µl of bidistilled water and the addition of 100 µl of the o-phthalaldehyde (OPA) reagent. Previously, this was prepared by dissolving 10 mg OPA in 0.2 ml methanol, followed by the addition of 1.8 ml of a 200 mM potassium borate buffer (pH 9.5) and 10 µl 3-mercaptopropionic acid, and then diluted 1/5 with borate buffer. Five minutes after the addition of the OPA reagent, aliquots (20 µl) of the solution were injected into the HPLC system. Linearity was assessed in the range 0.1–20 µM of ADMA. The mean correlation coefficient was >0.99. The ADMA limit of quantitation (LOQ) was 0.01 µM. Analytical recovery was 98%, and the interassay CV was better than 3%.

Statistical analysis

The descriptive data are shown as mean values ± s.d., which were compared using Student's t-test. Exact inference for the Hodges–Lehman estimate was used to evaluate the shift in CFR, IMT and ADMA between the control and the ERA groups. Multiple linear regression was used to adjust for ADMA levels in comparing mean coronary outcomes (CFR and IMT) between case and control groups. The univariate correlations were assessed by means of Pearson's correlation coefficient and evaluating P-values using exact Monte Carlo tests based on 10,000 samples from the dataset [42]. All of the tests were two-sided and a P-value of <0.05 was considered statistically significant. The analyses were made using SPSS statistical software (version 14.0) and StatXact-7 (version 7, Cytel Software Corporation, Cambridge, MA, USA) [43].

Results

Clinical characteristics of the ERA patients and healthy controls

Table 1 shows the descriptive statistics and haemodynamic data of the study population. The two groups were comparable in terms of age, sex, blood pressure, serum lipid levels, menopause status, smoking status, renal function and the BMI. All ERA patients had normal thyroid function tests.

The ERA patients had significantly higher CRP and ESR levels than the healthy controls (P < 0.01 for both), and increased IMT (P = 0.01), but there were no significant differences in heart rate or blood pressure at rest or during dipyridamole infusion.

Standard 2D echocardiography at baseline showed that the ERA patients had normal left ventricular wall thickness, dimension, mass and systolic function; carotid plaques were detected in two patients (8%) and none in the healthy controls.

Plasma ADMA levels correlated with anti-CCP antibody levels (R = 0.59, P < 0.01), with the number of swollen (R = 0.45, P = 0.02) and tender joints (R = 0.51, P = 0.01), but did not vary significantly by gender (P = 0.794) or smoking habits (P = 0.656).

Endothelial dysfunction and coronary microvascular abnormalities in ERA patients

CFR was successfully measured in all patients and the dipyridamole infusion was generally well tolerated. None of the patients undergoing dipyridamole stress echocardiography showed any changes in clinical or electrocardiographic characteristics, or global or regional wall motion.

The Hodges–Lehman shift estimate in CFR, IMT and ADMA between the control and the ERA groups is estimated to be −1.11, 0.08 mm and 0.09 µM/l. The 95% exact CI on the magnitude of the shift are (−1.52, −0.6), (0.01, 0.17) and (0.04, 0.12), respectively.
TABLE 2. Mean values and mean difference values of IMT, CFR and ADMA between controls and ERA patients

<table>
<thead>
<tr>
<th></th>
<th>Controls (mean ± s.d.)</th>
<th>ERA patients (mean ± s.d.)</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFR</td>
<td>3.5 ± 0.8</td>
<td>2.5 ± 0.8*</td>
<td>−0.98 (−1.36, −0.60)</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.56 ± 0.13</td>
<td>0.67 ± 0.13*</td>
<td>0.11 (0.03, 0.18)</td>
</tr>
<tr>
<td>ADMA, μM/l</td>
<td>0.58 ± 0.07</td>
<td>0.66 ± 0.07*</td>
<td>0.08 (0.04, 0.12)</td>
</tr>
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*P < 0.01.

TABLE 3. Adjusted 95% CI of the difference in mean levels of CFR and IMT between cases and controls by ADMA levels

<table>
<thead>
<tr>
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<th>Adjusted mean differencea (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT, mm</td>
<td>0.11 (0.02, 0.20)</td>
</tr>
<tr>
<td>CFR</td>
<td>−0.49 (−0.84, −0.15)</td>
</tr>
</tbody>
</table>

aCoefficient of the linear regression of IMT and CFR on group label adjusting for ADMA values.

TABLE 4. Effect of ADMA levels on coronary outcomes (CFR and IMT)

<table>
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<th>Unadjusted effect (95% CI)</th>
<th>Adjusted effect (95% CI)</th>
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<tbody>
<tr>
<td>IMT, mm</td>
<td>0.34 (−0.16, 0.83)</td>
<td>−0.02 (−0.58, 0.53)</td>
</tr>
<tr>
<td>CFR</td>
<td>−7.76 (−9.80, −5.72)</td>
<td>−6.15 (−8.36, −3.95)</td>
</tr>
</tbody>
</table>

aCoefficient of the linear regression of IMT and CFR on ADMA values adjusting for group label.

Resorting to Gaussian approximation (Table 2), CFR was significantly reduced in the ERA patients (2.5 ± 0.5 vs 3.5 ± 0.8; P < 0.01). In particular, the smallest CFR value in the control group was 2.1, while 6/25 (24%) ERA patients had a CFR of <2 consistent with potentially dangerous coronary flow impairment (Fisher’s exact test, P = 0.02). Common carotid IMT was significantly greater in the ERA patients, although still within the normal range (0.68 ± 0.10 vs 0.56 ± 0.11 mm; P < 0.01) (Table 2). These results reasonably overlap those obtained by means of the non-parametric Hodges–Lehman statistic.

Association between CFR, IMT and plasma ADMA levels

Tables 2 and 3 show unadjusted and adjusted 95% CIs of the difference between mean levels of CFR and IMT by ADMA levels. Plasma ADMA levels were significantly higher in the ERA patients (0.66 ± 0.07 vs 0.58 ± 0.07; P < 0.01) (Table 2). ADMA appears to behave as an effect modifier by influencing the value of the CFR outcome. In particular, Table 4 reports a statistically significant negative effect of ADMA levels on CFR value. The effect of ADMA levels on IMT is not significant.

There was a significant correlation between CFR and plasma ADMA levels in the ERA population (r = −0.53; P < 0.01). IMT was negatively associated with CFR (P < 0.05).

Discussion

Our results indicate that ADMA levels that may contribute to accelerate atherogenesis were significantly higher in the ERA patients. High ADMA levels in RA may be due to a number of mechanisms: (i) a reduction in the activity of dimethylarginine dimethylaminohydrolase, a key enzyme governing ADMA (but not symmetric dimethyl-L-arginine) degradation; (ii) increased protein arginine type I N-methyltransferase expression due to oxidative stress [44]; (iii) increased endothelial cell turnover and the consequent liberation of free ADMA during protein catabolism; and (iv) decreased dimethylarginine dimethylaminohydrolase expression due to hypoxia within the inflamed synovium [45].

However, the high value of ADMA in ERA patients seems to be unrelated to co-existing abnormalities in these patients because the conditions that have been previously reported to be associated with high plasma ADMA levels were excluded from the study. In particular, different authors have previously observed high plasma ADMA levels in patients with mild renal failure [46].

Stafford-Smith [47] found that ADMA accumulates as renal function declines and closely correlated with cardiovascular events. Our patients had normal renal function, and so we can exclude the possibility that their high plasma ADMA levels may have been due to reduced renal clearance.

We found that CFR was significantly reduced in the ERA patients. Recently it has been demonstrated that CFR is a highly sensitive (>90%) diagnostic marker of CAD and that a CFR of <2 accurately predicts the presence of severe coronary stenosis (i.e. >70% coronary narrowing) [48, 49]. During stress echocardiography, an abnormal CFR in the presence of a normal regional wall motion score index also becomes highly specific in reflecting an impaired coronary microcirculation in the absence of epicardial coronary stenosis, as for example in reperfused myocardial infarction, diabetes mellitus, hypercholesterolaemia, syndrome X or CTDs [28, 50, 51]. Furthermore, Hirata et al. [52] have described a significant reduction in CFR in SLE patients.

Our results showed a significant correlation between CFR and plasma ADMA levels in the ERA patients, while IMT that was significantly greater in the ERA patients, although still within the normal range was negatively associated with CFR. The first results are similar to a recent study of 200 patients with SLE and subclinical atherosclerosis by Kiani et al. [53] that reported in SLE patients with high plasma ADMA levels a significant correlation between plasma ADMA levels and coronary calcium (considered a marker of atherosclerosis) both of which are associated with a poor prognosis.

Our IMT data, which agree with the findings of Kumeda et al. [54] who reported that the IMT of the common carotid and femoral arteries was increased in RA patients, provide only slight support for the detection of preclinical atherosclerosis. At the same time, Kumeda et al. [54] reported that the increased femoral artery IMT of the common carotid and subclinical atherosclerosis by Kiani et al. [53] that reported in SLE patients with high plasma ADMA levels a significant correlation between plasma ADMA levels and coronary calcium (considered a marker of atherosclerosis) both of which are associated with a poor prognosis. Our IMT data, which agree with the findings of Kumeda et al. [54] who reported in SLE patients with high plasma ADMA levels a significant correlation between plasma ADMA levels and coronary calcium (considered a marker of atherosclerosis) both of which are associated with a poor prognosis. Our IMT data, which agree with the findings of Kumeda et al. [54] who reported in SLE patients with high plasma ADMA levels a significant correlation between plasma ADMA levels and coronary calcium (considered a marker of atherosclerosis) both of which are associated with a poor prognosis. Our IMT data, which agree with the findings of Kumeda et al. [54] who reported in SLE patients with high plasma ADMA levels a significant correlation between plasma ADMA levels and coronary calcium (considered a marker of atherosclerosis) both of which are associated with a poor prognosis.
such as anti-TNF-α agents. Jiang et al. [56] observed that ADMA significantly increases TNF-α levels in human endothelial cells, and that this is inhibited by simvastatin in accordance with the concomitant reduction in the ADMA-induced inflammatory reaction [56, 57], and Hurlimann et al. [58] have found that TNF-α antagonism not only reduces RA activity, but also improves endothelial function. It is also known that 3-hydroxy-3-methylglutaryl Co enzyme A (HMG-CoA) reductase inhibitors have a protective effect on vascular endothelium, which seems to be mediated by an enhanced NO synthase system [59]. However, the possible effectiveness of statins and biological therapies in changing the course of CAD in RA patients remains to be investigated.

As pointed out by Scott [60], it seems to be necessary to identify RA patients rapidly because aggressive therapy is more effective in patients at risk of severe CAD, and there is some evidence that combined therapy with TNF-α inhibitors may be the most effective [38].

In addition to the fact that the generalizability of our results would require evidence from other populations, one of the limitations of a cross-sectional design is the lack of information concerning the time course of risk factors such as cholesterol and other lipids.

In conclusion, this study is the first case-control study looking at coronary vasomotor function and ADMA levels in ERA patients before receiving DMARDs or biological therapy. Our findings suggest that part of the CFR variability might be explained by ADMA, where higher levels of ADMA associated with decreased CFR values. ERA patients exhibited worse clinical outcome (CFR and IMT) than controls independently from ADMA. However, ADMA levels might represent an important effect modifier of the relation between ERA disease and CFR outcome. Hence, ADMA and CFR could be useful diagnostic aids to detect early phases of cardiovascular damage in this population, when traditional screening tests are still normal. However, future researches are necessary to define the diagnostic and prognostic role of plasma ADMA levels and CFR measurement as simple methods of screening ERA patients with high risk of CAD in which a more aggressive therapy (such as statins, anti-TNF drugs, etc.) should be suggested.

Rheumatology key messages

- Plasma concentration of ADMA is considered a novel risk factor for endothelial dysfunction associated with enhanced atherosclerosis.
- In our study, the plasma AMDA levels correlated with CFR and with disease severity indices.
- Plasma ADMA levels in association with CFR may be useful to assess endothelial dysfunction.

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

References


