ORIGINAL ARTICLE

Plasma asymmetric dimethylarginine in active rheumatoid arthritis: links with oxidative stress and inflammation

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KEY WORDS

asymmetric dimethylarginine, endothelium, inflammation, isoprostanes, rheumatoid arthritis

ABSTRACT

INTRODUCTION Endothelial dysfunction and accumulation of asymmetric dimethylarginine (ADMA) have been identified as independent predictors of future cardiovascular events in patients with coronary artery disease.

OBJECTIVES The aim of the study was to investigate the factors that determine increased accumulation of ADMA, an endogenous inhibitor of nitric oxide synthesis, in patients with rheumatoid arthritis (RA).

PATIENTS AND METHODS We studied 46 consecutive patients with RA (39 women, 7 men; mean age, 57 years [range, 23–75 years]) with active disease (mean Disease Activity Score 28 [DAS28], 5.2), without clinically overt cardiovascular disease and 50 controls matched for age, sex, hypertension, blood cholesterol, and glucose. We assessed the plasma levels of ADMA, symmetric dimethylarginine (SDMA), L-arginine, and the marker of oxidative stress, 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$).

RESULTS ADMA and SDMA levels were significantly higher in the RA group than in controls (0.58 ±0.081 vs. 0.46 ±0.045 μmol/l, P <0.0001; 0.45 ±0.07 vs. 0.36 ±0.046 μmol/l, P <0.0001; respectively). ADMA levels in the RA group correlated positively with fibrinogen (r = 0.70, P <0.00001), C-reactive protein (CRP; r = 0.88, P <0.00001), DAS28 (r = 0.44, P = 0.002) and Health Assessment Questionnaire scores (r = 0.39, P = 0.008), but not with age, renal function, or the medications used. 8-iso-$PGF_{2\alpha}$ correlated positively with ADMA (r = 0.82), SDMA (r = 0.72), CRP (r = 0.76), fibrinogen (r = 0.57) (all, P <0.0001) and DAS28 (r = 0.44, P = 0.003). Regression analysis models showed that CRP was the only independent predictor of 8-iso-$PGF_{2\alpha}$ and ADMA levels in RA.

CONCLUSIONS Our study is the first to show positive associations between plasma ADMA levels and the production of 8-isoprostanes and CRP in RA.

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INTRODUCTION In recent years, it has become clear that chronic inflammatory diseases such as rheumatoid arthritis (RA) are associated with an increased incidence of atherothrombotic cardiovascular events that cannot be fully explained by traditional risk factors.[1] Endothelial dysfunction is the initial step in atherogenesis.[2] Indeed, persistent endothelial cell activation and dysfunction in RA result from systemic inflammation that involves a number of inflammatory mediators.[3] However, molecular mechanisms leading to accelerated atherosclerosis in RA remain unclear. Vascular endothelium has several functions regulating vascular tone, blood-tissue exchange, and smooth muscle cell proliferation. Moreover, it also maintains blood fluidity and controls platelet aggregation as well as leukocyte adhesion and migration.[2] Dysregulation of hemostasis and local blood flow in the vessels is associated with an altered balance between nitric oxide (NO) and superoxide (0^{-2}) in endothelial cells.[4] Therefore, the suppression of endothelial NO synthase (NOS) activity has been considered a hallmark of endothelial injury[5] initiating atherosclerosis.[6] Endothelial dysfunction[7] and accumulation of asymmetric dimethylarginine (ADMA), an endogenous

inhibitor of NOS, have been identified as independent predictors of future cardiovascular events in patients with coronary artery disease.[8] Interestingly, it has been demonstrated that elevated ADMA levels can be detected in RA patients regardless of the presence of cardiovascular disease.[9] Moreover, a positive correlation between plasma ADMA levels and anticitrulinated protein antibodies has also been observed in RA patients without cardiovascular risk factors.[9] In earlier studies, elevated ADMA levels were found in RA patients with subclinical carotid atherosclerosis.[10] The activity of dimethylarginine dimethylaminohydrolase, the key enzyme in ADMA degradation, is downregulated by oxidative stress and tumor necrosis factor α (TNF-α),[11] which plays a crucial role in both RA and atherosclerotic vascular disease.[3,12] To our knowledge, it is unknown whether ADMA generation is associated with enhanced oxidative stress in RA patients. Therefore, the present study was performed to investigate the relationships between RA activity, oxidative stress, and ADMA. The assessment of treatment-associated changes in ADMA levels was beyond the scope of the current study.

PATIENTS AND METHODS **Patients** The study included 46 consecutive patients with RA (39 women, 7 men; aged 57 years [range, 23–75 years], disease duration, 8.1 ±6.7 years; Disease Activity Score 28 [DAS28], 5.2 ±1.1) and 50 healthy control subjects matched for age, sex, hypertension, total cholesterol, and serum glucose. The Bioethics Committee of the Jagiellonian University approved the study protocol and written consent was obtained from all participants. All patients with RA fulfilled the American College of Rheumatology criteria for RA.[13]

The exclusion criteria were as follows: any acute illness, cancer, hepatic or renal dysfunction (creatinine >120 μmol/l), diabetes, previous myocardial infarction, stroke or another acute vascular event, venous thromboembolism, and current anticoagulation therapy. Patients receiving disease-modifying antirheumatic drugs (DMARDs) and biological treatment were eligible for the study.

Disease activity in RA patients was measured by the number of tender joints, number of swollen joints, duration of morning stiffness, patient's global assessment of disease activity, physician's global assessment of disease activity, and patient's assessment of pain using 100 mm visual analog scales (VAS). DAS28 was calculated by an experienced physician.[14] All RA patients completed the Health Assessment Questionnaire (HAQ).[15]

Laboratory investigations After an overnight fast, blood samples were taken from patients and controls. Blood cell count, serum glucose, creatinine, alanine aminotransferase (ALT), proteinogram, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and erythrocyte sedimentation rate (ESR) were assessed. Fibrinogen and C-reactive protein were measured by nephelometry (Dade Behring, Germany).

In the RA group, serum immunoglobulin M rheumatoid factor (RF) was assessed by quantitative nephelometry. RF levels above 15 IU/ml were considered elevated. Autoantibodies against citrullinated peptides (aCCP) were detected using an enzyme-linked immunosorbent assay, Immunoscan RA CCP2 (EuroDiagnostica, Sweden), according to the manufacturer's instructions. A concentration of aCCP above 5 mg//l was considered positive.

Plasma 8-iso-$PGF_{2\alpha}$ levels A commercially available immunoenzymatic assay was used to determine plasma 8-iso-$PGF_{2\alpha}$, a stable marker of oxidative stress (Cayman Chemicals, Ann Arbor, Michigan, United States).

Plasma ADMA levels Plasma ADMA, symmetric dimethylarginine (SDMA), and L-arginine levels were measured using high-performance liquid chromatography (HPLC) with precolumn derivatization, as previously described.[16] In brief, equilibrated carboxylic acid columns (Bond Elut, Varian Inc., California, United States) were used for 3-fold washing with 1 ml plasma samples with methanol and distilled water. Then, the samples were eluted with 10% ammonia and dried.

TABLE 1 Characteristics of rheumatoid arthritis and laboratory parameters in the study group (n = 46)

disease duration, y		8.1 ±6.7
morning stiffness, min		54 ±62
patient's assessment of pain (VAS, max. 100 mm)		47.4 ±21
patient's assessment of disease activity (VAS, max. 100 mm)		49 ±20.6
physician's assessment of disease activity (VAS, max.100 mm)		44.3 ±17.4
DAS28		5.2 ±1.1
HAQ		1.31 ±0.7
RF, n (%)		31/40 (78)
aCCP positive, n (%)		29/34 (85)
ESR, mm/1st h		28.1 ±20.03
treatment of RA, n (%)	methotrexate monotherapy	21 (48)
	leflunomide monotherapy	1 (2)
	leflunomide + methotrexate	4 (9)
	etanercept monotherapy	3 (6.5)
	etanercept + methotrexate	3 (6.5)
	sulfasalazine	2 (4)
	chloroquine	1 (2)
	cyclosporine	1 (2)
	prednisone	35 (76)
	NSAIDs	36 (78)

Values are expressed as mean ± standard deviation or number (percentage).

Abbreviations: aCCP – autoantibodies against citrullinated peptides, DAS28 – disease activity score, ESR – erythrocyte sedimentation rate, HAQ – health assessment questionnaire, NSAIDs – nonsteroidal anti-inflammatory drugs, RA – rheumatoid arthritis, RF – rheumatoid factor, VAS – visual analogue scale

TABLE 2 Demographic, clinical, and laboratory variables in patients with rheumatoid arthritis and controls

Variable	RA patients (n = 46)	Controls (n = 50)	*P*
age, y	57 (23–75)	56 (35–73)	NS
female gender, n (%)	39 (85)	43(86)	NS
current smokers, n (%)	4 (8.7)	17 (34)	0.004
hypertension, n (%)	22 (48)	16 (32)	NS
TC, mmol/l	4.89 (2.45–7.39)	4.88 (4.13–6.72)	NS
LDL cholesterol, mmol/l	2.91 (1.40–4.51)	2.97 (2.00–4.72)	NS
HDL cholesterol, mmol/l	1.53 (0.98–2.68)	1.36 (0.90–1.62)	0.03
TG, mmol/l	1.27 (0.5–3.1)	1.35 (0.66–2.34)	NS
glucose, mmol/l	4.5 (3.7–8.1)	5.3 (4.1–6.6)	NS
creatinine, µmol/l	65.33 ±15.23	66.6 0 ±11.45	NS
CRP, mg/l	7.84 (0.18–103.0)	1.99 (0.22–3.51)	<0.0001
fibrinogen, g/l	4.18 (2.43–10.20)	2.56 (1.97–4.22)	<0.0001

Values are expressed as mean ± standard deviation, median (interquartile range), or number (percentage).

Abbreviations: CRP – C-reactive protein, HDL – high-density lipoprotein, LDL – low-density lipoprotein, NS – nonsignificant, TC – total cholesterol, TG – triglycerides

TABLE 3 L-arginine metabolites and 8-iso-prostaglandin $F_{2\alpha}$ in patients with rheumatoid arthritis and controls

	RA patients (n = 46)	Controls (n = 50)	*P*
ADMA, µmol/l	0.58 ±0.081	0.46 ±0.045	<0.00001[a]
SDMA, µmol/l	0.45 ±0.07	0.36 ±0.046	<0.00001[a]
L-arginine, µmol/l	69.76 ±9.33	63.98 ±8.90	0.003[b]
8-iso-$PGF_{2\alpha}$, pg/ml	249.52 ±51.20	100.06 ±21.57	<0.00001[a]

Values are expressed as mean ± standard deviation.

a *t* test
b Mann-Whitney test

Abbreviations: ADMA – asymmetric dimethylarginine, SDMA – symmetric dimethylarginine, 8-iso-$PGF_{2\alpha}$ – 8-iso-prostaglandin $F_{2\alpha}$

The sediment obtained was dissolved in 1 ml of water, the solution was centrifuged, and the supernatant was subjected to HPLC using ODS column (Fisher Scientific, St. Louis, Missouri, United States), used as the internal standard.

Statistical analysis The statistical analysis was performed using STATISTICA 8.0.

Data are expressed as mean values (± standard deviation) or median (interquartile range). The Shapiro-Wilk test was used to determine normal distribution. Intergroup differences for continuous variables were assessed by the *t* test for normally distributed variables or by the Mann-Whitney test for nonnormally distributed variables. The Pearson or Spearman rank correlation coefficients were calculated to test the associations between 2 variables with a normal or nonnormal distribution, respectively. A multiple linear regression analysis (the forward stepwise method) was used to determine predictors of ADMA and 8-iso-$PGF_{2\alpha}$. The independent variables included RA duration, DAS28, CRP, and fibrinogen. A *P* value less than 0.05 was considered statistically significant.

RESULTS A total of 46 consecutive patients with RA were included in the final analysis. The mean value of DAS28 in the RA group was 5.2 ±1.1 indicating high activity of the disease.

Both groups did not differ with regard to age, sex, and most cardiovascular risk factors except the higher percentage of cigarette smokers in the control group (17 [34%] vs. 4 [8.7%], $P = 0.0035$) and higher HDL cholesterol in the RA group (1.53 [0.98–2.68] mmol/l vs. 1.36 [0.90–1.62] mmol/l, $P = 0.026$). As expected, fibrinogen and CRP were elevated in patients with RA. The patient characteristics are presented in TABLES 1 and 2.

As shown in TABLE 3, the plasma levels of ADMA and SDMA were significantly higher in the RA group compared with controls, which might suggest increased inhibition of NOS activity. Plasma L-arginine levels were also slightly higher in the RA group. Moreover, 8-iso-$PGF_{2\alpha}$ levels were higher in this patient group.

Methotrexate was administered in 28 patients with RA (61%). We did not find any significant differences in ADMA, SDMA, and 8-iso-$PGF_{2\alpha}$ levels between patients receiving and not receiving methotrexate treatment. All 3 parameters did not

TABLE 4 Independent predictors of asymmetric dimethylarginine and 8-iso-prostaglandin $F_{2\alpha}$ in patients with rheumatoid arthritis in multiple stepwise regression analysis models

Independent predictors	
of ADMA	of 8-iso-$PGF_{2\alpha}$
CRP	CRP
$R^2 = 0.64$	$R^2 = 0.53$
slope estimate = 0.66	slope estimate = 0.73
standard error = 0.12	standard error = 0.13
$P < 0.00001$	$P < 0.00001$

Abbreviations: see TABLES 2 and 3

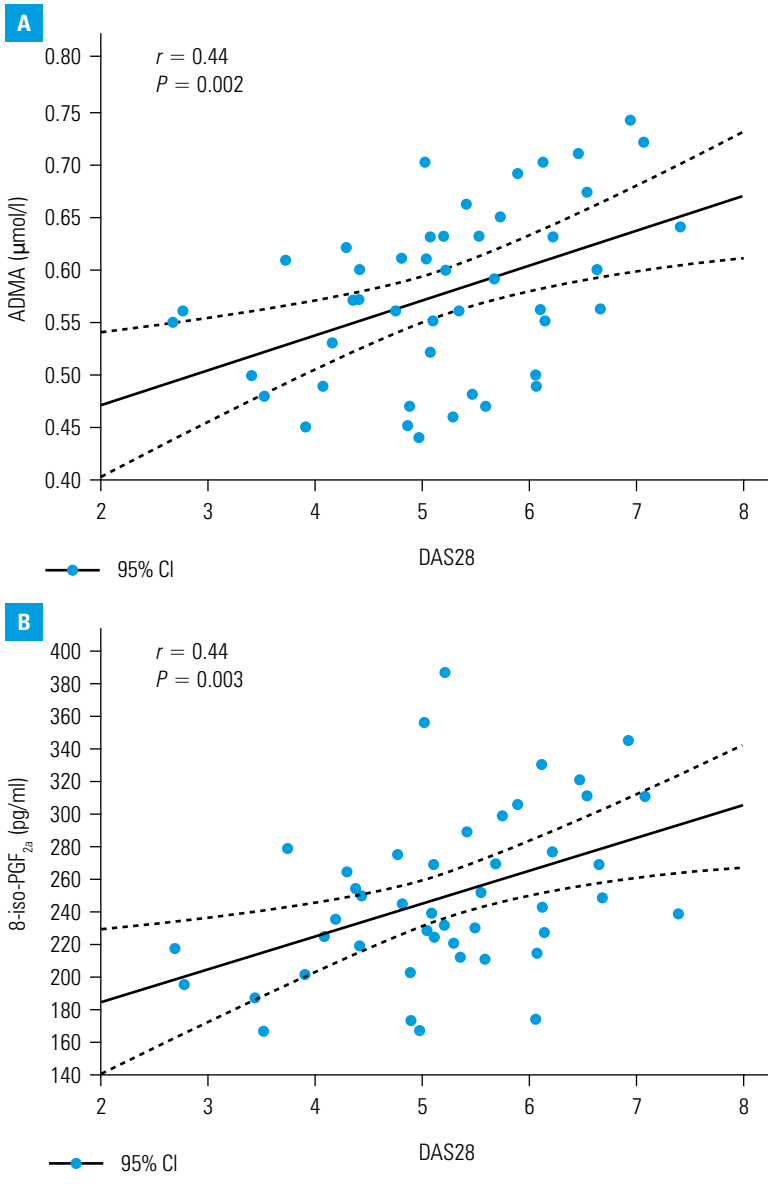

FIGURE 1 Examples of the strongest correlations of L-arginine metabolites, 8-iso-prostaglandin $F_{2\alpha}$, and markers of inflammatory activity in patients with rheumatoid arthritis; **A** – correlations between ADMA and DAS28; **B** – correlations between 8-iso-$PGF_{2\alpha}$ and DAS28
Abbreviations: CI – confidence interval, others – see TABLES 1–3

differ between the groups of patients receiving (76%) and not receiving corticosteroids and no correlations have been observed (data not shown).

The mean levels of ADMA in a group of 6 patients (15%) treated with etanercept did not differ from those observed in the remaining patients.

Elevated ADMA levels in the RA group correlated positively with CRP ($r = 0.88$, $P < 0.00001$), fibrinogen ($r = 0.70$, $P < 0.00001$) (FIGURE 1A), DAS28 ($r = 0.44$, $P = 0.002$), HAQ scores ($r = 0.39$, $P = 0.008$), ESR ($r = 0.50$, $P = 0.0004$), and platelet count ($r = 0.39$, $P = 0.04$). In RA patients, ADMA showed no associations with age or creatinine ($P > 0.1$). Plasma SDMA levels correlated positively with CRP ($r = 0.82$, $P < 0.00001$), ESR ($r = 0.57$, $P = 0.00003$) fibrinogen ($r = 0.63$, $P < 0.00001$), DAS28 ($r = 0.40$, $P = 0.005$), and HAQ scores ($r = 0.35$, $P = 0.02$),

The regression analysis model showed that CRP was the only independent predictor of ADMA levels in RA patients ($R^2 = 0.64$; $P < 0.00001$) (TABLE 4).

Plasma 8-iso-$PGF_{2\alpha}$ levels correlated positively with DAS28 ($r = 0.44$, $P = 0.003$) (FIGURE 1B), CRP ($r = 0.76$, $P < 0.00001$), ADMA ($r = 0.82$, $P < 0.00001$), SDMA ($r = 0.72$, $P = 0.00001$), fibrinogen ($r = 0.57$, $P = 0.0001$), HAQ scores ($r = 0.44$, $P = 0.002$), ESR ($r = 0.38$, $P = 0.01$), and platelet count ($r = 0.45$, $P = 0.01$).

No correlations with age and disease duration were observed. Moreover, there were no correlations of ADMA or 8-isoprostane with RF and aCCP levels.

The regression analysis model showed that CRP was the only independent predictor of 8-iso-$PGF_{2\alpha}$ levels ($R^2 = 0.53$; $P < 0.00001$) (TABLE 4).

DISCUSSION To our knowledge, this study is the first to have demonstrated associations between the markers of active inflammation, oxidative stress in vivo, and ADMA in RA. In previous studies, endothelial dysfunction, which is the initial step in atherosclerosis,[7] has been shown in patients with early[9,17] and long-term RA.[12,18] It is well established that atherosclerosis starts with endothelial injury[2] and its causes are multiple.[2-4] In animal models, reduced NO bioavailability and oxidative stress contribute to endothelial dysfunction.[4,5] It has been observed in human endothelial cells in vitro that CRP increases the expression of cell adhesion molecules, endothelin-1, and plasminogen activator inhibitor-1, and it decreases endothelial NOS expression and activity.[19] Since most cardiovascular deaths occur in RA patients with high disease activity,[1] the pathogenic role of CRP and several soluble inflammatory mediators involved in RA-associated atherosclerosis has been intensively studied.[3] The results of the present study support the view that oxidative stress and the inhibition of NOS by ADMA may participate in the pathogenesis of vascular injury in RA. Reactive oxygen species and reactive nitrogen species have been observed to cause tissue injury and to have systemic pathophysiological consequences in chronic inflammatory conditions including RA).[20] However, Ames PR et al.[21] reported raised plasma levels of

8-iso-$PGF_{2\alpha}$ in systemic lupus erythematosus and in some other rheumatic diseases, though no increase was found in RA. Basu et al.[22] examined the markers of oxidative injury at inflamed joints and in circulating blood. In their study, all rheumatic patients had significantly higher baseline levels of serum 8-iso-$PGF_{2\alpha}$ and serum prostaglandin $F_{2\alpha}$ metabolite. They observed a strong correlation between the levels of 8-iso-$PGF_{2\alpha}$ and 15-keto--dihydro-prostaglandin $F_{2\alpha}$ in both serum and synovial fluid. More recently, a significant reduction in oxidative stress markers associated with decreased disease activity (DAS28 and CRP levels) has been reported in RA patients treated with anti-TNF-α antibody,[23] indicating a close relationship between TNF-α, systemic inflammation, and oxidative stress. In the present study, we found a significant positive correlation between the parameters reflecting disease activity and elevated plasma levels of ADMA, an endogenous inhibitor of NOS and 8-iso-$PGF_{2\alpha}$, a marker of oxidative stress. In contrast to the previous reports,[9,10] in our group of RA patients, we observed positive correlations between serum CRP and both plasma ADMA and SDMA levels. In addition, there was a positive correlation between plasma 8-iso-$PGF_{2\alpha}$ and ADMA levels. ADMA, an indicator of endothelial dysfunction,[16] competes with L-arginine at the level of NOS and inhibits NO generation.[5] The role of SDMA is not as clear. Some studies suggest that it may decrease L-arginine uptake by endothelial cells.[24]

CRP has been considered a direct proinflammatory factor,[3] which predicts myocardial infarction[25] and stroke,[26] and its elevated levels in active RA indicate a higher risk of cardiovascular mortality.[27] Hannawi et al.[28] demonstrated that in early RA, age and baseline CRP are the key determinants of carotid intima-media thickness (IMT). Our cohort of RA patients was characterized by high clinical activity of the disease (DAS28, 5.2 ±1.1) and elevated levels of serum CRP (14 ±18.2 mg/l). Interestingly, Surdacki et al.[9] showed that neither ADMA nor its stereoisomer, SDMA, correlated with CRP or other parameters reflecting disease activity. The reason for the discrepancies between the studies is not clear. However, there were 2 different groups of RA patients involved. Surdacki et al.[9,10] excluded patients with lower disease activity (DAS28 <3.2) and those treated with corticosteroids. In contrast, we enrolled 46 consecutive RA patients with lower or higher disease activity scores, who better reflect the whole spectrum of the RA population in everyday practice. In such patient group, we found correlations between the clinical parameters (DAS28, HAQ, VAS), biochemical markers, and ADMA levels. Importantly, in RA patients without chronic renal disease, there was no correlation between ADMA and serum creatinine, which underlies the strong effect of inflammation on ADMA generation and degradation in the disease. Our findings expand the current knowledge on the links between RA activity and ADMA accumulation.

Our observation indicating the association between RA activity and ADMA levels appears to be particularly important, even if statistical associations reported here do not necessarily mean the cause-effect relationships. It seems convincing that the inhibition of the L-arginine-NO pathway, the hallmark of endothelial dysfunction, is likely to be caused by inflammatory factors. There is one report showing that anti-TNF-α treatment decreases ADMA levels in patients with ankylosing spondylitis.[29] It provides additional evidence for the direct role of proinflammatory mediators in the regulation of NOS activity; however, Turiel et al.,[30] in a much smaller group of RA patients without any evidence of cardiovascular involvement (10 patients treated with methotrexate, 10 with adalimumab), failed to show a direct effect of DMARD treatment on carotid IMT and ADMA levels.

Our another novel finding is a strong association between oxidative stress and the increase of natural NO inhibitors in RA. Oxidative stress leads to the modification of various proteins, and other authors[10] speculated that it decreases the activity of the enzyme governing degradation of ADMA.[11] An imbalance of NO and reactive oxygen species (so called oxidative stress), plays an important role in the pathogenesis of RA[31] and in cardiovascular diseases.[4] So far, enhanced NO inactivation caused by superoxide radicals, rather than decreased NO production, was observed in experimental models of atherosclerosis.[32] Our findings suggest that both mechanisms leading to NO depletion could be involved in RA-associated endothelial dysfunction. Since dysregulation of endothelial NOS may enhance oxidative stress,[33] we could propose the hypothetical mechanism of a vicious cycle of inflammation, namely, depletion NO and oxidative stress which causes vascular disease in RA. Despite many potential causes of premature atherosclerosis in RA, our findings indicate that inhibition of the L-arginine-NOS pathway by ADMA and enhanced oxidative stress are associated with active inflammatory process in RA. Therefore, it might be speculated that elevated ADMA and oxidative stress are associated with an increased risk for cardiovascular events in RA.[1,3]

Our study has several limitations. First, the study population is limited, which may have introduced type II errors, especially in the calculation of correlation coefficients. Second, in our analysis, we determined each variable at a single time point and some changes in the levels during follow-up cannot be excluded. Third, clinical outcomes, including cardiovascular events, were not evaluated and clinical consequences of increased ADMA in RA remain to be established in a long-term follow-up of a large RA population. Finally, it is unknown whether patients with low-activity RA have elevated ADMA levels compared with well-matched controls.

In conclusion, our study shows that, the inflammatory state, disease activity, oxidative stress, and ADMA accumulation are closely interrelated in RA. The findings suggest that inflammation in RA might be directly or indirectly associated with mediators causing endothelial dysfunction, thus contributing to a cardiovascular risk in patients affected by the disease.

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ARTYKUŁ ORYGINALNY

Asymetryczna dimetyloarginina w aktywnym reumatoidalnym zapaleniu stawów – związek ze stresem oksydacyjnym i zapaleniem

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SŁOWA KLUCZOWE

asymetryczna dimetyloarginina, isoprostany, śródbłonek, reumatoidalne zapalenie stawów, zapalenie

STRESZCZENIE

WPROWADZENIE Dysfunkcję śródbłonka oraz nadmierną produkcję asymetrycznej dimetyloargininy (ADMA) uznaje się za niezależny predyktor wystąpienia zdarzeń sercowo-naczyniowych u osób z chorobą niedokrwienną serca.

CELE Celem badania była ocena czynników wpływających na zwiększoną produkcję ADMA, endogennego inhibitora syntazy tlenku azotu, u chorych na reumatoidalne zapalenie stawów (RZS).

PACJENCI I METODY Przebadaliśmy 46 chorych na RZS (39 kobiet, 7 mężczyzn; średnia wieku: 57 lat [23–75 lat]) z aktywnym przebiegiem choroby (średni wskaźnik aktywności choroby [*disease activity score* – DAS28]: 5,2), bez klinicznych objawów chorób układu krążenia oraz grupę kontrolną 50 pacjentów dobranych pod względem wieku, płci, nadciśnienia tętniczego, stężenia cholesterolu i glukozy we krwi. Ocenialiśmy stężenie ADMA, symetrycznej dimetylargininy (SDMA), L-argininy (Arg) i markera stresu oksydacyjnego, 8-iso-prostaglandyny $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$), w osoczu krwi.

WYNIKI Stężenia ADMA i SDMA były znamiennie większe w grupie chorych na RZS w porównaniu z grupą kontrolną (odpowiednio, 0,58 ±0,081 *vs* 0,46 ±0,045 µmol/l; p <0,0001 i 0,45 ±0,07 *vs* 0,36 ±0,046 µmol/l; p <0,0001). W grupie RZS stężenia ADMA dodatnio korelowały ze stężeniem fibrynogenu (r = 0,70; p <0,00 001), białka C -reaktywnego (*C-reactive protein* – CRP) (r = 0,88; p <0,00 001), DAS28 (r = 0,44; p = 0,002) i wynikiem kwestionariusza oceny zdrowia (Health Assessment Questionnaire) (r = 0,39; p = 0,008), natomiast nie korelowały z wiekiem pacjentów, funkcją nerek i zastosowanym leczeniem. Wartości 8-iso-$PGF_{2\alpha}$ dodatnio korelowały z ADMA (r = 0,82), SDMA (r = 0,72), CRP (r = 0,76), fibrynogenem (r = 0,57; wszystkie, p<0,0001) i DAS28 (r = 0,44; p = 0,003). Analiza modeli regresji wykazała, że CRP jest jedynym niezależnym predyktorem 8-iso-$PGF_{2\alpha}$ i stężenia ADMA w RZS.

WNIOSKI Nasze badanie jako pierwsze pokazuje dodatnią korelację między stężeniem ADMA w osoczu a produkcją 8-isoprostanów i CRP w RZS.

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