Scandinavian Journal of Rheumatology

ISSN: 0300-9742 (Print) 1502-7732 (Online) Journal homepage: http://www.tandfonline.com/loi/irhe20

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To cite this article: A Tuttolomondo, R Pecoraro, C Buttà, D Di Raimondo, A Ferrante, V Della Corte, F Ciccia, C Bellia, A Giardina, A Raffa, M Ciaccio & A Pinto (2015) Arterial stiffness indexes and serum cytokine levels in seronegative spondyloarthritis: relationships between stiffness markers and metabolic and immunoinflammatory variables, Scandinavian Journal of Rheumatology, 44:6, 474-479, DOI: 10.3109/03009742.2015.1030449

To link to this article: http://dx.doi.org/10.3109/03009742.2015.1030449

Published online: 14 Jul 2015.

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Arterial stiffness indexes and serum cytokine levels in seronegative spondyloarthritis: relationships between stiffness markers and metabolic and immunoinflammatory variables

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Objective: The aim of this study was to investigate the relationship between immunoinflammatory markers and indexes of arterial stiffness in patients with seronegative spondyloarthritis (SpA).

Method: We enrolled consecutive patients with inflammatory seronegative SpA referred to a rheumatology outpatient clinic. Control subjects were patients admitted in the same period for any cause other than chronic inflammatory disease or acute cardiovascular and cerebrovascular events. Carotid-femoral pulse wave velocity (PWV) was measured and the aortic pressure waveform was used to calculate the augmentation index (Aix). We also evaluated plasma levels of C-reactive protein (CRP), interleukin (IL)-1β, tumour necrosis factor (TNF)-α, and interleukin (IL)-6 as markers of immunoinflammatory activation.

Results: This study enrolled 53 patients with SpA and 55 control subjects. After adjustment for blood glucose, cholesterol, and triglyceride levels, and systolic (SBP) and diastolic blood pressure (DBP), patients with seronegative SpA showed higher mean PWV and Aix compared to controls. Moreover, in patients with seronegative SpA, we observed higher mean plasma levels of IL-6, IL-1β, and TNF-α in subjects with mean PWV > 8 m/s in comparison with those with PWV < 8 m/s. Multivariate analysis revealed a significant association between PWV > 8 m/s and male gender, age, diabetes, hypertension, low density lipoprotein cholesterol (LDL-C) > 120 mg/dL, total cholesterol (TC) > 200 mg/dL, coronary artery disease (CAD), microalbuminuria, carotid plaque, and plasma levels of IL-6, IL-1β, and TNF-α.

Conclusions: These findings emphasize the role of inflammatory variables and metabolic factors in indexes of high arterial stiffness. Thus, an inflammatory-metabolic background may influence the pathogenesis of increased arterial stiffness in seronegative inflammatory arthritis.

Seronegative spondyloarthritis (or spondylarthropathy, SpA) comprises a family of inflammatory rheumatic diseases involving the axial skeleton and having a negative serostatus. Entities included in the spondylarthropathies are ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, undifferentiated SpA, and irritable bowel disease (IBD). Cytokines are thought to play a vital role in the immune dysregulation of SpA. Despite their importance, cytokine profiles in SpA, either in serum or within inflammatory cells, are largely unknown. Aortic stiffness, wave-reflection intensity, and endothelial function are independent predictors of cardiovascular risk in various patient groups (1–4) and may also directly accelerate the atherosclerotic process (5). Some studies have reported an association between SpA and cardiovascular risk (6, 7). Few studies have examined the role of arterial stiffness and immunoinflammatory variables in patients with seronegative SpA (8–10). On this basis, the aim of our study was to investigate the relationship between immunoinflammatory markers and arterial stiffness in patients with seronegative SpA.

Method

We enrolled all consecutive patients with inflammatory SpA referred to the rheumatology outpatient clinic of our Biomedical Department of Internal Medicine and Specialties at the University of Palermo from September 2012 to December 2013.

Control subjects were patients admitted, in the same period, to our Internal Medicine Department, for any

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Accepted 13 March 2015

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DOI: 10.3109/03009742.2015.1030449

cause other than chronic inflammatory disease or acute cardiovascular and cerebrovascular events. To match patients with inflammatory SpA and controls for cardiovascular risk and previous cardiovascular morbidity, subjects were included among possible controls if they had cardiovascular risk factors or previous cardiovascular or cerebrovascular events. Controls were excluded if they had one of the following exclusion criteria: rheumatological disorders, chronic inflammatory disease, acute systemic infections, recent venous thrombosis, recent acute myocardial infarction (AMI) (within 3 months), or recent cerebrovascular event [transient ischaemic attack (TIA) or stroke within 6 months]; all these conditions may influence inflammatory cytokine and cell levels.

Cardiovascular risk factors were evaluated for both cases and controls on the basis of the following criteria. Hypercholesterolaemia was defined as the presence of total cholesterol (TC) blood levels ≥ 200 mg/dL. Hypertension was defined as present if subjects had been previously diagnosed according to the World Health Organization/International Society of Hypertension guidelines (11) and were routinely receiving antihypertensive therapy. Patients were defined as type 2 diabetics if they had known diabetes treated by diet, oral hypoglycaemic drugs, or insulin. Previous coronary artery disease (CAD) was determined on the basis of a history of physician-diagnosed angina, MI, or any previous revascularization procedure assessed by a questionnaire. Previous cerebrovascular disease (TIA/ischaemic stroke) was assessed by history, specific neurological examination performed by specialists, and hospital or radiological (brain computer tomography or brain magnetic resonance imaging) records of definite previous stroke. Subjects were classified as having previous peripheral artery disease (PAD) when they had a history of ankle-brachial index (ABI) < 0.9 and/or intermittent claudication or critical limb ischaemia, or when they had undergone a peripheral arterial bypass or amputation.

The study protocol was approved by the local ethics committee and all participants gave written informed consent. Every subject with inflammatory SpA was matched for age (±3 years), sex, and cardiovascular risk factor prevalence with one control subject.

Pulse wave velocity (PWV) measurement

Carotid-femoral PWV was measured in the supine position using an automatic device (SphygmoCor version 7.1). Distance was measured in millimetres on the skin surface, subtracting the distance of the carotid artery to the sternal notch from the distance measured between the sternal notch and the peripheral artery of choice. Pulse wave analysis (PWA) was performed at each arterial site in sequence and the time difference was determined by identifying the foot of the pulse waveform in relation to the QRS complex on a simultaneous three-lead electrocardiogram (ECG).

PWV was calculated as the distance travelled by the arterial pulse wave (in metres) divided by the time delay between the two arterial points (in seconds), thus expressed as m/s. Applanation tonometry was used to record the radial artery pressure waveform continuously, and mean values of ≥ 2 screens of pulse waves of good quality were used for analysis. The aortic pressure waveform was used to calculate the augmentation index (Aix), as the difference in height between the first and second systolic peaks expressed as a percentage of pulse pressure.

Laboratory evaluation

Blood samples were obtained at rest in the supine position. We evaluated plasma levels of C-reactive protein (CRP), interleukin (IL)-1β, tumour necrosis factor (TNF)-α, and IL-6 as markers of immunoinflammatory activation. IL-1β, TNF-β, and IL-6 were measured using a sandwich enzyme-linked immunosorbent assay (Quantikine, R&D Systems, VWF ELISA kitdurian, Instrumentation Laboratory, Milan, Italy). The minimum detectable concentrations for the diagnostic tests are: 1.6 pg/mL for TNF-α, < 1 pg/mL for IL-1β, and < 0.70 pg/mL for IL-6. Intra- and interassay coefficients of variation were, respectively, 4.2% and 4.6% for TNF-α, 3.3% and 4.2% for IL-1β, and 1.6% and 3.3% for IL-6.

Statistical analysis

The results are expressed as mean ± sd for continuous variables and percentages for categorical data, with $p \geq 0.05$ considered significant.

All data were analysed using the SAS 9.1 statistical program. Clinical characteristics were compared among the four groups using a one-way analysis of variance (ANOVA). Pearson's correlation coefficients were calculated to evaluate the relationship between arterial stiffness indexes and immunoinflammatory (plasma cytokine levels) and metabolic variables. Significance was defined at the 0.05 confidence level. Analysis of normality was performed with the Shapiro–Wilk W test. Non-normally distributed data were logarithmically (log 10) transformed before analysis. The relationships between immunoinflammatory markers, PWV, Aix, and other parameters were analysed using non-parametric methods (Spearman p correlations) after correction for age and gender.

Logistical regression analysis was conducted with data presented as odds ratios (ORs) with 95% confidence intervals (CIs). Initial univariate analyses identified demographic and clinical variables that independently predicted arterial stiffness as PWV > 8 m/s. Significant variables were entered into subsequent multivariate logistical regression analysis with the variables included in the models using forward stepwise selection, with a

probability value of 0.05 required for entry into the model. A probability value ≤ 0.05 was considered significant.

Results

We enrolled 53 patients with SpA and 55 control subjects without SpA matched for cardiovascular risk and previous cardiovascular morbidity. Demographic and clinical variables are listed in Table 1. Among the patients with SpA, 18 (33.96%) had AS and 35 (66.04%) had psoriatic arthritis.

After adjustment for blood glucose, cholesterol, and triglyceride levels, systolic (SBP) and diastolic blood pressure (DBP), patients with SpA showed a higher mean PWV (9.98 ± 2.9 vs. 6.79 ± 3.1 m/s, $p < 0.05$) and Aix (94.3 ± 3.5% vs. 88 ± 4.6%) compared to control subjects. SpA patients showed higher mean plasma levels of IL-6, IL-1β, and TNF-α in comparison with controls.

In particular, in SpA patients we observed higher mean plasma levels of IL-6 (8.21 vs. 6.14 pg/mL, $p = 0.011$), IL-1β (4.11 vs. 2.14 pg/mL, $p = 0.032$), and TNF-α (31.11 vs. 10.74 pg/mL, $p < 0.001$) among those with mean PWV > 8 m/s in comparison with those with PWV < 8 m/s (Table 2).

In patients with SpA, we observed a significant correlation between PWV and SBP ($R = 0.38$, $p = 0.040$), hypertension ($R = 0.36$, $p < 0.05$), blood glucose levels ($R = 0.31$, $p < 0.05$), plasma low density lipoprotein cholesterol (LDL-C) plasma ($R = 0.30$, $p = 0.011$), plasma TC levels ($R = 0.31$, $p = 0.010$), CAD ($R = 0.29$, $p = 0.022$), microalbuminuria ($R = 0.30$, $p < 0.05$), carotid plaque ($R = 0.29$, $p = 0.030$), left ventricular

Table 1. Demographic and clinical characteristics of patients with spondyloarthritis (SpA) and controls.

	Patients with SpA	Controls	p-value
n	53	55	0.71
Males/Females	28/25	30/25	0.55
Age (years)	52.28 ± 4.2	54.28 ± 2.7	0.63
Type of SpA			
Ankylosing spondylitis (AS)	18 (33.96)		
Psoriatic arthritis	35 (66.04)		
Duration of disease (years)	7 ± 2.5		
SBP (mmHg)	142.06 ± 7.4	141.05 ± 4.4	0.33
DBP (mmHg)	90.88 ± 4.8	89.46 ± 3.6	0.25
HR (beats/min)	76.75 ± 9.2	78.25 ± 7.2	0.18
Medications			
ACE inhibitors	2 (3.77)	3 (5.44)	0.31
ARBs	1 (1.88)	1 (1.86)	0.40
Methotrexate	7 (13.20)	–	0.29
Cox-2 inhibitors	3 (5.66)	–	0.77
Steroids	4 (7.54)	–	
Biologics	8 (15.09)	–	
ASA	3 (5.66)	4 (7.27)	
Statins	5 (9.43)	2 (3.66)	
Hypertension	8 (15.09)	7 (12.72)	0.81
Diabetes	5 (9.43)	6 (10.90)	0.55
Metabolic syndrome	3 (5.56	4 (7.27)	0.61
CAD	3 (5.56)	4 (7.27)	0.59
PWV (m/s)	9.98 ± 2.9	6.79 ± 3.1	**< 0.05**
Aix (%)	94.3 ± 3.5	88 ± 4.6	**0.021**
CHF	10 (18.86)	10 (18.80)	0.065
LVH	11 (20.14)	9 (16.36)	0.071
Carotid plaque	9 (16.98)	10 (18.18)	0.56
IL-6 (pg/mL)	7.18 (4.24–10.95)	2.22 (1.04–3.25)	**0.001**
TNF-α (pg/mL)	20.94 (6.71–42.70)	8.38 (6.78–8.55)	**< 0.001**
IL-1β (pg/mL)	3.13 (1.08–5.01)	1.49 (1.01–2.76)	**0.033**
ABI	0.85	0.88	0.52
Glucose (mg/dL)	101 ± 2.3	99 ± 2.8	0.43
LDL-C (mg/dL)	112 ± 4.5	109 ± 5.5	0.55
TC (mg/dL)	214 ± 11.5	202 ± 9.4	0.77
Triglycerides (mg/dL)	159 ± 11.5	161 ± 8.7	0.89

SBP, Systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid (Aspirin); CAD, coronary artery disease; PWV, pulse wave velocity; Aix, augmentation index; CHF, congestive heart failure; LVH, left ventricular hypertrophy, IL-6, interleukin-6; TNF-α, tumour necrosis factor α; IL-1β, interleukin 1β; ABI, ankle brachial index; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol.
Values are given as mean ± sd, n (%), or median (IQR).
Ankle brachial index (ABI).
Statistically significant variables are expressed in bold type.

Table 2. Immunoinflammatory variables in patients with spondyloarthritis (SpA) and in controls in relation to PWV values.

	Patients with SpA (n = 53)			Controls (n = 55)		
	PWV < 8 m/s	PWV > 8 m/s	p-value	PWV < 8 m/s	PWV > 8 m/s	p-value
n (%)	15 (28.30)	38 (71.69)		39 (70.90)	16 (29.09)	
IL-6 (pg/mL)	6.14 (4.84–7.95)	8.21 (6.24–10.95)	**0.0011**	2.11 (1.04–3.25)	2.34 (1.32–3.27)	0.77
IL-1β (pg/mL)	2.14 (1.08–3.77)	4.11 (2.24–5.01)	**0.032**	1.14 (1.01–2.47)	1.84 (1.21–2.76)	0.22
TNF-α (pg/mL)	10.74 (6.71–6.84)	31.11 (16.24–2.70)	**< 0.001**	8.77 (6.78–8.65)	7.99 (5.04–8.55)	**0.045**

PWV, Pulse wave velocity; IL-6, interleukin-6; TNF-α, tumour necrosis factor alpha; IL-1β, interleukin 1β.
Values are given as median (IQR).
Statistically significant variables are expressed in bold type.

hypertrophy (LVH; R = 0.24, p = 0.039), IL-6 (R = 0.38, p < 0.05), TNF-α (R = 0.44, p < 0.001), IL-1β (R = 0.39, p < 0.05) (Table 3).

With regard to logistical regression analysis of demographic and clinical variables associated with PWV > 8 m/s in patients with SpA, at univariate analysis we observed a significant association with male gender, age, diabetes, hypertension, atrial fibrillation, blood glucose levels > 150 mg/dL, LDL-C > 120 mg/dL, plasma TC > 200 mg/dL, CAD, microalbuminuria, and carotid plaque (Table 4).

At multivariate analysis, we observed a significant association between PWV > 8 m/s and male gender (OR 1.45, 95% CI 0.98–2.77, p = 0.044), age (OR 3.09, 95% CI 2.21–4.01, p < 0.001), diabetes (OR 2.86, 95% CI 1.21–3.69, p = 0.032), hypertension (OR 3.01, 95% CI 2.01–4.01, p < 0.005), LDL-C levels > 120 mg/dL (OR 1.85, 95% CI 1.12–2.88, p = 0.038), plasma TC levels > 200 mg/dL (OR 1.72, 95% CI 1.01–2.35, p = 0.041), CAD (OR 2.43, 95% CI 1.31–2.87, 1.31–2.87, p = 0.023), microalbuminuria (OR 2.51, 95% CI 1.24–2.79, p = 0.020), carotid plaque (OR 2.91, 95% CI 1.54–4.01, p = 0.027), IL-6 (OR 3.09, 95% CI 2.02–5.01, p = 0.009), IL-1β (OR 3.11, 95% CI 1.54–4.01, p < 0.05), and TNF-α (OR 3.99, 95% CI 3.17–5.33, p < 0.001) (see Table 4).

Table 3. Correlations between PWV and clinical variables in patients with spondyloarthritis (n = 53).

Variable	R	p-value
Age	0.41	0.85
SBP	0.38	**0.04**
DBP	0.36	0.52
Hypertension	0.36	**< 0.05**
Diabetes	0.38	**< 0.05**
Atrial fibrillation	0.21	0.74
Glucose blood levels	0.31	**< 0.05**
LDL-C plasma levels	0.30	**0.011**
TC plasma levels	0.31	**0.01**
Triglyceride plasma levels	0.23	0.52
CAD	0.29	**0.022**
CHF	0.21	0.55
Microalbuminuria	0.30	**< 0.05**
Carotid plaque	0.29	**0.03**
LVH	0.24	**0.039**
IL-6	0.38	**< 0.05**
IL-1β	0.39	**< 0.05**
TNF-α	0.44	**< 0.001**

PWV, Pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; CAD, coronary artery disease; CHF, congestive heart failure; LVH, left ventricular hypertrophy; IL-6, interleukin-6; IL-1β, interleukin 1β; TNF-α, tumour necrosis factor α.
Statistically significant variables are expressed in bold type.

Discussion

Our study shows that subjects with SpA have higher median serum levels of immunoinflammatory markers such as IL1-β, IL-6, and TNF-α in comparison with controls. Several studies (12–14) have shown that TNF-α levels are raised at baseline in patients with SpA. Gratacos et al (15) showed that TNF-α and IL-6 levels were raised in patients with AS compared with patients with non-inflammatory back pain. No significant difference in interferon (IFN)-γ levels was found. However, several trials no found increased levels of other serum pro-inflammatory or anti-inflammatory cytokines in SpA (12–15).

In our patients with SpA, we observed higher median values of arterial stiffness markers such as PWV and Aix in comparison with control subjects. In general, arterial stiffness indexes represent a subclinical marker of atherosclerosis. Hence it is possible to hypothesize that patients affected by SpA could be prone to atherosclerosis.

Atherosclerosis and arthritis share several pathophysiological characteristics. Both conditions seem to be provoked by initial cell injury (to endothelial cells in atherosclerosis and to synovial cells in rheumatoid arthritis) and a central role is played by macrophages, T lymphocytes and connective tissue cells, accompanied by the formation of an extracellular matrix (16). Thus, a possible link between arthritis or spondyloarthritis and arterial stiffness could be represented by immunoinflammatory activation.

Analogously, some data suggest that inflammation may play a direct role in mediating arterial stiffness (17). Reactive oxygen species (ROS) constitute another category of compounds that exert effects on

Table 4. Univariate and multivariate logistic regression analysis of demographic and clinical variables associated with PWV > 8 m/s in patients with seronegative spondyloarthritis (SpA).

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender (male)	2.12 (1.23–4.78)	0.016	1.45 (0.98–2.77)	0.044
Age	3.34 (2.67–4.02)	< 0.001	3.09 (2.21–4.01)	< 0.001
Diabetes	3.09 (1.87–3.33)	< 0.005	2.86 (1.21–3.69)	0.032
Hypertension	3.78 (2.76–4.98)	< 0.001	3.01 (2.01–4.01)	< 0.005
Atrial fibrillation	1.67 (0.93–2.23)	0.039	0.92 (0.22–2.41)	0.44
Blood glucose > 150 mg/dL	1.66 (0.71–2.34)	0.023	0.67 (0.12–2.56)	0.57
Plasma LDL-C > 120 mg/dL	2.62 (1.44–3.00)	0.019	1.85 (1.12–2.88)	0.038
Plasma TC > 200 mg/dL	2.01 (1.11–2.78)	0.033	1.72 (1.01–2.35)	0.041
Plasma triglyceride > 200 mg/dL	0.99 (0.23–1.67)	0.77	0.88 (0.37–1.78)	0.79
CAD	2.66 (1.56–3.11)	0.011	2.43 (1.31–2.87)	0.023
CHF	0.89 (0.51–1.55)	0.67	0.81 (0.47–1.42)	0.59
Microalbuminuria	2.85 (1.37–3.09)	< 0.005	2.51 (1.24–2.79)	0.020
Carotid plaque	3.23 (2.13–3.79	< 0.001	2.91 (1.54–4.01)	0.027
LVH	0.80 (0.11–1.54)	0.61	0.66 (0.33–1.69)	0.53
IL-6	3.71 (2.22–4.45)	< 0.001	3.09 (2.02–5.01)	0.009
IL-1β	4.19 (3.01–5.67)	< 0.001	3.11 (2.45–4.98)	< 0.05
TNF-α	5.32 (3.99–6.01)	< 0.001	3.99 (3.17–5.33)	< 0.001

PWV, Pulse wave velocity; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; CAD, coronary artery disease; CHF, congestive heart failure; LVH, left ventricular hypertrophy; IL-6, interleukin-6; IL-1β, interleukin 1β; TNF-α, tumour necrosis factor α; OR, odds ratio; CI, confidence interval.

both cartilage and the vasculature. Free radical species have been implicated in cartilage degeneration and the pathogenesis of osteoarthritis, for example, by causing chondrocyte lipid peroxidation, a reaction that has been directly linked to collagen oxidation and degradation. Similarly, oxidative stress has been shown to promote vascular disease (18) and experimental evidence has demonstrated that reducing oxidative stress may reduce aortic stiffness (19).

Our findings also showed higher plasma cytokine levels in patients with SpA and mean PWV > 8 m/s in comparison with those with PWV < 8 m/s and this finding could represent a further confirmation of the relationship between immunoinflammatory activation and arterial stiffness.

Nevertheless, inflammation cannot be the only pathogenetic background of arterial stiffness in subjects with inflammatory arthropathies. In a recent study that enrolled patients with AS after 24 weeks of anti-TNF-α therapy, despite significant improvements in patients symptoms, clinical activity parameters, and CRP levels, no significant change was seen in arterial stiffness parameters (9). On this basis, other factors in addition to inflammatory markers such as metabolic variables (blood glucose, cholesterol, and triglyceride levels) or endothelial damage variables such as ROS and nitric oxide (NO) may play a role in the pathogenesis of arterial stiffness in patients with inflammatory arthritis.

Our findings show, in addition to a significant correlation between arterial stiffness and markers of immunoinflammatory variables such as plasma cytokine values, a correlation between PWV and clinical and metabolic variables such as hypertension, blood glucose, plasma LDL-C and TC levels, CAD, and microalbuminuria. Hence, metabolic variables could also have a role in influencing arterial stiffness indexes even in the clinical context of an inflammatory disease (20–26).

Moreover, in our study we evaluated predictive variables of arterial stiffness in SpA. Our findings show that age, diabetes, hypertension, LDL-C > 120 mg/dL, plasma TC levels, CAD, microalbuminuria, carotid plaque and, in particular, plasma IL-6, IL-1β, and TNF-α levels are significant predictive variables of arterial stiffness in SpA patients with PWV > 8 m/s.

The strengths of our study lie in the decision to evaluate a control group of subject also matched for cardiovascular risk factors and subclinical atherosclerosis prevalence; thus we have limited possible bias due to the effects of atherosclerosis burden on inflammatory markers.

Our study also has some limitations: the relatively small sample size, the possible effects of clinical disease activity on inflammatory markers, and our assessment of vascular stiffening by PWV, which reflects central and not peripheral arterial stiffness.

In conclusion, our findings emphasize the role of inflammatory variables and metabolic factors as determinants of high arterial stiffness markers. Thus, an inflammatory-metabolic background may influence the pathogenesis of increased arterial stiffness in seronegative inflammatory arthritis.

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