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Original Article

Increased arterial stiffness in rheumatoid arthritis and Its relation to disease activity: A cross sectional study

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ABSTRACT

Background: Rheumatoid arthritis (RA) is associated with elevated plasma level of inflammatory markers. Chronic inflammation is known to predispose to endothelial dysfunction and increased arterial stiffness, which is an important marker of subclinical atherosclerosis and increased cardiovascular risk.

Objective: The aim is to test for the relationship between disease activity and arterial stiffness in RA patients.

Methods: The study included 90 RA patients, at different grades of disease activity and 45 healthy subjects, as a control group. Patients were subjected to full history taking and clinical examination, laboratory investigations including serum lipid profile and high sensitivity CRP (hs-CRP) measurements and plain x-rays of hands and feet. Modified Larsen method was used as radiographic scoring method. Disease activity score (DAS 28) was used for assessment of disease activity. Transthoracic echocardiography was performed to detect aortic stiffness parameters. Duplex ultrasound imaging of both common carotid arteries was performed to measure carotid stiffness parameters.

Results: The mean age of RA patients was 39.86 ± 9.39 years and most of them (83.3%) were females. RA patients had higher carotid stiffness index compared to control group patients (8.57 ± 4.83 vs 4.08 ± 1.13 , $p < .001$). Very poor correlation was found between DAS-28 and aortic ($r = 0.1$, $p = .28$) as well as carotid ($r = 0.05$, $p = .7$) stiffness indices. No statistically significant correlation was found between hs-CRP and aortic stiffness index ($r = 0.64$, $p = .55$). Disease duration was significantly correlated to intima-media thickness ($p < .01$) as well as with other carotid stiffness parameters. Age also show a statistically significant positive correlation with carotid stiffness parameters.

Conclusion: RA is associated with increased arterial stiffness, a well-recognized marker of cardiovascular risk. This is attributed to the inflammatory nature of the disease. It seems that the most important factors determining stiffness are patients' age and duration of illness.

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1. Introduction

Rheumatoid arthritis (RA) is characterized by inflammation of the synovial membrane and progressive destruction of the articular cartilage and bone, in addition to other extra-articular manifestations, with significant impact on morbidity and mortality.¹ Mortality rates are more than twice as high in patients with RA as in the general population, and this gap appears to be widening.²

The increased cardiovascular risk in RA patients is driven by several parameters, in particular ischemic heart disease and heart failure, mostly due to the long-standing inflammation and Framingham traditional risk factors.³

Additional contributing factors include pro-thrombotic state, insulin resistance,⁴ and immune system dysregulation with activation of T-cells. All of the above may lead to endothelial dysfunction and increased arterial stiffness, with accelerated atherosclerosis.⁵

Atherosclerosis increases the stiffness of large arteries but the increased intima-media thickening (IMT) is thought to represent one of the earliest stages of atherosclerosis and predicts plaque development.⁶

Increased carotid intima-media wall thickness (IMT) has been reported in patients with RA,⁷ even in RA patients without

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traditional cardiovascular risk factors.⁸ More importantly, an increased frequency of carotid plaques has been reported in patients with RA included in the category of moderate cardiovascular disease risk according to well-established risk algorithms.⁹

This study aims at evaluation of the increased vascular stiffness (aortic and carotid arteries) as an early, pre-plaque atherosclerotic change, in rheumatoid arthritis patients and correlates the stiffness parameters to RA disease activity.

2. Patients and methods

This is a cross sectional study that included 90 RA patients and 45 healthy subjects, who served as a control group. Patients fulfilled the 2010 ACR-EULAR classification criteria for RA.¹⁰ All patients gave their informed consent prior to their inclusion in the study.

Patients were subjected to full history taking (description of the joints involved, duration of the illness, present medications, extra-articular involvement... etc), clinical examination (blood pressure, weight and height measurements and body mass index calculation, general and cardiac examination). All joints of the body were examined thoroughly.

Routine laboratory investigations as well as ESR and serum lipid profile including: total serum cholesterol (SC), low density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and serum triglyceride level. The value of SC > 200 mg/dl, HDL-C < 40 mg/dl, LDL-C > 130 mg/dl and TGs > 150 mg/dl according to the revised National Cholesterol Education Program 3 Guidelines.¹¹

Rheumatoid Factor was measured by latex agglutination method,¹² High sensitivity C-reactive protein (hs-CRP) was measured quantitatively using IBL International EU59151 Enzyme immunoassay. Expected ranges of values are interpreted as: CRP values < 1.0 µg/ml = Low risk for cardiovascular disease (CVD), CRP values 1.0–2.9 µg/ml = Intermediate risk for CVD, CRP values > 3.0 µg/ml = High risk for CVD.¹³

Disease activity in the patients was assessed using the Disease Activity Score 28 (DAS 28).¹⁴ DAS 28 with four variables were used, based on counts of tender and swollen joints (assessing 28 joints which are: 10 PIPs, 10 MCPs, 2 wrists, 2 elbows, 2 shoulders and 2 knees), ESR and a general health assessment on a visual analog scale. The value is the result of the following formula:

$$\text{DAS28-4} = 0.56 \times \sqrt{(28\text{TJC})} + 0.28 \times \sqrt{(28\text{SJC})} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH.}$$

The level of RA disease activity can be interpreted as: *Remission*: DAS 28 below 2.6, *Low disease activity*: 2.6 to levels below 3.2, *Moderate disease activity*: from 3.2 to levels below 5.1 or *High disease activity*: levels from and above 5.1.

Plain radiographs for hands, wrists and feet were taken for each patient in postero-anterior (PA) view. Modified Larsen method was used as the radiographic scoring method,¹⁵ where thirty-two joints are evaluated: eight proximal interphalangeal (PIP) joints, two interphalangeal joints of the thumbs, 10 metacarpo-phalangeal (MCP) joints, two wrists, and 10 metatarso-phalangeal (MTP) joints. Six stages are defined as follows: (0) = normal, (1) = soft tissue swelling and/or joint space narrowing/subchondral osteoporosis, (2) = erosions with destruction of the joint surface (DJS) < 25%, (3) = DJS 26–50%, (4) = DJS 51–75% and (5) = DJS > 75%. The score ranges from 0 to 160.¹⁵

Transthoracic echocardiography was performed using (Esaote MyLab60) machine with a 2.5 MHz phased-array transducer. The systolic and diastolic diameters of the ascending aorta were measured, 3 cm distal to the aortic valve, in the parasternal long axis

view by 2D guided M-mode tracing. An average of three consecutive measurements was calculated and recorded.

The aortic elastic properties were calculated by the following formulas:

- Aortic β stiffness index = $\ln(\text{SBP}/\text{DBP})/[(\text{SD}-\text{DD})/\text{DD}]$.¹⁶
- Aortic strain (%) = $(\text{SD}-\text{DD})/\text{DD}$.^{16–18}
- Aortic distensibility (cm^2/dyn) = $2 \times (\text{SD}-\text{DD})/[(\text{SBP}-\text{DBP}) \times \text{DD}]$.¹⁶

(Values obtained from the equation of aortic distensibility were to be multiplied with 1333 to convert mmHg to cm^2/dyn).

In (natural logarithm), SBP, DBP (systolic and diastolic blood pressures respectively), SD: aortic systolic diameter, DD: aortic diastolic diameter.

Ultrasonographic determination of the intima media-thickness (IMT) of the common carotid arteries was performed using (MyLab 60 Esaote) machine with linear 10 MHz probe. Three measurements were taken (2 cm proximal to the carotid bulb) on digitized still images that were obtained during ultrasound scanning. Values were then averaged and IMT was considered abnormal if > 0.09 cm.

Direct measurement of carotid stiffness implies the assessment of changes in carotid diameters and pressures at the same site. Also maximum and minimum carotid diameters were measured, and carotid distension was calculated. All these parameters were measured automatically by the machine, provided a good image quality and an expert operator.

2.1. Statistical analysis

The data were collected, tabulated and analyzed by SPSS package version 15 (SPSS corporation, USA). Qualitative data were presented in the form of frequency and percentage and quantitative data were presented in the form of mean and standard deviation.

Student t-test was used for comparative analysis of 2 quantitative normally distributed data. Correlation between variables was performed using Pearson's correlation test; this test detects if change in one variable is accompanied by corresponding change in the other variables. A significant correlation may be positive or negative. A chi-square test was used to compare categorical data. Results were considered significant if $P < .05$.

3. Results

Fifteen patients were males (16.7%) and 75 were females (83.3%), while the control group included 8 males (17.8%) and 37 females (82.2%). Age of patients ranged from 19 to 55 years with a mean of 39.86 ± 9.39 years, while the age of the control group ranged from 23 to 54 years with a mean of 37.82 ± 9.62 years. BMI of patients had a mean of $26.46 \pm 3.26 \text{ kg/m}^2$ and the mean of controls was $25.71 \pm 2.57 \text{ kg/m}^2$. The disease duration ranged between 0.5–33 years with a mean of 7.51 ± 7.1 years. Arthritis was reported in 78/90 patients (86.7%) with morning stiffness duration ranging from 5 to 120 min with a mean of 17.83 ± 26.29 min and joint deformities were recorded in 25/90 (27.8%) patients. The clinical parameters, disease activity, laboratory data and treatment received are shown in Table 1.

RA patients showed statistically significant lower values regarding aortic distensibility ($p = .002$), however no significant difference was found between RA patients and control group regarding aortic stiffness index ($p = .4$) and aortic strain ($p = .2$), Table 2.

RA patients showed statistically significant lower values regarding carotid distension ($p < .001$), distensibility coefficient ($p < .001$) and compliance coefficient ($p < .001$) and higher values regarding carotid stiffness index ($p < .001$) and carotid pulse wave velocity;

Table 1

Clinical parameters, disease activity and laboratory data and treatment received by RA (group 1) patients.

Clinical parameters	No (%)
<i>Extra-articular Manifestations</i>	
SC nodules	5 (5.6%)
Dry eyes and mouth	26 (28.8%)
Interstitial lung disease	1 (1.1%)
Pulmonary nodule	1 (1.1%)
<i>Disease activity parameters</i>	
(Mean \pm SD), No (%)	
<i>DAS-28</i>	
High	(6.1 \pm 0.67), 43 (47.7%)
Moderate	(4.49 \pm 0.72), 40 (44.4%)
Low	(2.83 \pm 0.29), 6 (6.66%)
Remission	(2.46), 1 (1.1%)
Modified Larsen score range, (Mean \pm SD)	20-65, (34.26 \pm 5.71)
<i>Laboratory findings</i>	
Range, (Mean \pm SD)	
ESR (mm/hour)	7-102, (41.16 \pm 25.05)
Hb (gm/dl)	8.3-15, (12 \pm 1.4)
TLC (cell/mm ³)	3.6-18.3, (7.7 \pm 2.79)
Platelets (platelet/mm ³)	163-651, (301.81 \pm 97.2)
ALT (U/L)	7-92, (24.04 \pm 13.63)
AST (U/L)	9-113, (22.88 \pm 13.09)
Serum creatinine (mg/dl)	0.3-1.4, (0.73 \pm 0.19)
Serum cholesterol(mg/dl)	96-295, (180.36 \pm 41.54)
Serum triglycerides(mg/dl)	32-352, (76.45 \pm 46.49)
HDL-C(mg/dl)	25-91, (48.09 \pm 16.03)
LDL-C(mg/dl)	43-255, (114.24 \pm 36.24)
hs-CRP(μ g/ml)	0.1-13.7, (7.86 \pm 4.7)
<i>Treatment</i>	
(Mean \pm SD), No(%)	
Methotrexate (mg/w)	20.19 \pm 3.65, 65 (72.2%)
Leflunomide (mg/d)	20 \pm 0, 29 (32.2%)
Antimalarials (mg/day)	330 \pm 97.87, 27 (30%)
Salazopyrine (gm/day)	1.35 \pm 0.475, 7 (7.8%)
Steroids (mg/day)	5.5 \pm 1.73, 62 (68.9%)

SC nodules: Subcutaneous nodules, DAS-28: disease activity score, ESR: erythrocyte sedimentation rate, Hb: hemoglobin, TLC: total leucocyte count, ALT: alanine transaminase, AST: aspartate transaminase, HDL-C: high density lipo-protein cholesterol, LDL-C: low density lipo-protein cholesterol, hs-CRP:high sensitivity C-reactive protein.

PWV ($p < .001$) in comparison to control group. As regards IMT, no statistically significant difference was found between RA patients and control group ($p = .33$), Table 3.

Age and disease duration showed a statistically significant correlation with IMT and carotid stiffness parameters, but failed to

show a statistically significant correlation with aortic stiffness parameters as shown in Table 4.

No statistically significant correlation was found between hs-CRP and aortic stiffness index ($p = .55$, $r = 0.6$), aortic strain ($p = .91$, $r = -0.01$) or aortic distensibility ($p = .78$, $r = 0.03$). But a statistically significant positive correlation was found between hs-CRP and carotid PWV ($p = .04$, $r = 0.2$), however, no statistically significant correlation was found between hs-CRP and the rest of the carotid elastic parameters, as shown in Table 4.

There was a poor correlation between DAS-28 score and aortic and carotid stiffness parameters, as seen in Table 5

A statistically significant negative correlation was found between serum cholesterol level and aortic distensibility ($p = .03$). A statistically significant positive correlation was found between carotid IMT and serum cholesterol ($p < .01$), serum TGs ($p = .006$) and LDL-C ($p = .001$) as shown in Table 6.

No statistically significant correlation was found between DAS-28 and aortic stiffness index ($p = .28$, $r = 0.1$), aortic strain ($p = .89$, $r = -0.2$) or aortic distensibility ($p = .45$, $r = -0.1$). No statistically significant correlation was found between DAS-28 and IMT ($P = .64$, $r = 0.1$), or any of the carotid stiffness parameters as carotid distension ($p = .9$, $r = -0.004$), carotid stiffness index ($p = .7$, $r = 0.05$), carotid PWV ($p = .4$, $r = 0.1$), carotid distensibility coefficient ($p = .2$, $r = -0.2$) and carotid compliance coefficient ($p = .5$, $r = -0.08$).

No statistically significant correlation was found between doses of different disease modifying anti-rheumatic drugs received by RA patients under study and any of the aortic or carotid stiffness parameters, as shown in Table 7.

4. Discussion

Pulse Wave Velocity (PWV) is an arterial stiffness marker that has shown association with cardiovascular morbidity in the general population. Studies conducted in patients with RA also describe an increase of arterial stiffness.¹⁹ In a population-based study PWV in patients with RA was associated to central Systolic Blood Pressure and carotid intima-media wall thickness (IMT).²⁰ Moreover, RA patients with atherosclerotic plaques showed higher PWV.²⁰

Rheumatoid arthritis patients had statistically significant lower values of aortic distensibility, yet insignificant higher aortic stiffness index and less aortic strain than control group. This coincides

Table 2

Aortic stiffness parameters in both study groups.

Variable	RA patients (n = 90)		Control group(n = 45)		P
	Range	Mean \pm SD	Range	Mean \pm SD	
Aortic SI [†]	0.58-15.97	4.83 \pm 3.56	1.5-9.16	4.46 \pm 1.83	0.43
Aortic strain (%)	4.21-27.78	12.12 \pm 5.01	2.25-70.54	13.71 \pm 10.69	0.24
Aortic distensibility (cm ² dyne-1)	2.81-18.18	7.38 \pm 3.21	1.75-40.47	10.75 \pm 8.95	0.002

SI: Stiffness index.

Table 3

Carotid stiffness parameters in both study groups.

Variable	RA patients (n = 90)		Control group (n = 45)		P
	Range	Mean \pm SD	Range	Mean \pm SD	
IMT (mm)	0.32-0.96	0.49 \pm 0.1	0.32-0.68	0.48 \pm 0.07	0.33
Carotid stiffness index	2.19-4.14	8.57 \pm 4.83	2.07-7.92	4.08 \pm 1.13	<0.001**
Carotid distension (μ m)	135.5-789.5	327.45 \pm 136.03	314-939	649.77 \pm 147.25	<0.001**
Carotid PWV (m/s)	3.51-1.83	6.39 \pm 1.84	3.52-6.24	4.73 \pm 0.64	<0.001**
Distensibility coefficient (1/kpa)	0.01-0.08	0.03 \pm 0.01	0.02-0.08	0.04 \pm 0.014	<0.001**
Compliance coefficient (m ² /kpa)	0.34-2.55	1.13 \pm 0.53	0.73-3.22	1.69 \pm 0.56	<0.001**

IMT; Intima-media thickness, PWV; Pulse wave velocity.

Table 4
Correlation between demographic and radiological characteristics and hs-CRP of RA patients and aortic and carotid stiffness parameters.

Variable	Age at onset		Disease duration		Modified Larsen score		hs-CRP	
	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>R</i>
Aortic stiffness index	0.63	−0.052	0.07	0.192	0.44	−0.08	0.55	0.64
Aortic strain (%)	0.65	0.05	0.19	−0.14	0.15	0.15	0.91	−0.01
Aortic distensibility (cm ² dyne ^{−1})	0.94	−0.01	0.11	−0.17	0.11	0.17	0.78	0.03
IMT (mm)	0.003	0.31	<0.001	0.41	0.11	0.17	0.72	−0.04
Carotid distension (μm)	0.005	−0.29	0.004	−0.3	0.01	−0.27	0.09	−0.18
Carotid stiffness index	0.04	0.21	0.01	0.27	0.02	0.25	0.05	0.2
Carotid PWV (m/s)	0.04	0.21	0.001	0.35	0.02	0.237	0.04	0.22
Distensibility coefficient (1/kpa)	0.04	−0.22	0.004	−0.3	0.27	−0.12	0.72	−0.04
Compliance coefficient (m ² /kpa)	0.14	0.16	0.01	−0.27	0.13	−0.16	0.54	−0.07
Local carotid systolic pressure (mmHg)	0.74	0.04	0.01	0.26	0.71	0.04	0.18	0.14
Local carotid diastolic pressure (mmHg)	0.47	0.078	0.02	0.24	0.44	0.08	0.11	0.16

SI; stiffness index, IMT; intima-media thickness, PWV; pulse wave velocity.

Table 5
Correlation between DAS-28 and aortic and carotid stiffness parameters.

Variable	DAS-28	
	<i>p</i>	<i>r</i>
<i>Carotid stiffness parameters</i>		
IMT (mm)	0.64	0.05
Carotid distension (μm)	0.97	−0.004
Carotid stiffness index	0.65	0.048
Carotid PWV (m/s)	0.35	0.1
Distensibility coefficient (1/kpa)	0.15	−0.153
Compliance coefficient (m ² /kpa)	0.48	−0.075
Local systolic blood pressure (mmHg)	0.13	0.16
Local diastolic blood pressure (mmHg)	0.32	0.11
<i>Aortic stiffness parameters</i>		
Aortic SI	0.28	0.11
Aortic strain (%)	0.89	−0.15
Aortic distensibility (cm ² dyne ^{−1})	0.45	−0.08

with some epidemiological studies showing an increased incidence of major CV events and clinical assessment of arterial stiffness.^{21,22}

RA patients had statistically significant lower values regarding carotid distension, distensibility coefficient and compliance coefficient and higher values regarding carotid stiffness index and carotid pulse wave velocity (PWV), this means that RA patients had higher carotid stiffness compared to control group.

We found no statistically significant correlation neither between current hs-CRP levels and aortic stiffness parameters nor carotid IMT. This comes in agreement with many studies.^{23,24} But we found a weak positive correlation between hs-CRP and carotid PWV.

Table 6
Correlation between lipid profile of RA patients and different aortic and carotid stiffness parameters.

Variable	Cholesterol		TG		HDL-C		LDL-C	
	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>
Aortic stiffness index	0.33	0.11	0.11	0.11	0.56	−0.06	0.31	0.11
Aortic strain (%)	0.09	−0.18	−0.18	−0.18	0.92	−0.01	0.22	−0.13
Aortic distensibility (cm ² dyne ^{−1})	0.03*	−0.22	−0.22	−0.19	0.84	−0.022	0.11	−0.17
IMT (mm)	<0.001**	0.37	0.006**	0.29	0.89	−0.02	0.001**	0.339
Carotid distension(μm)	0.06	−0.2	0.009**	−0.27	0.23	−0.13	0.52	−0.07
Carotid stiffness index	0.29	0.11	0.08	0.19	0.59	0.06	0.96	−0.01
Carotid PWV (m/s)	0.15	0.15	0.04*	0.21	0.52	0.07	0.73	0.04
Distensibility coefficient (1/kpa)	0.006**	−0.29	0.07	−0.19	0.16	−0.15	0.09	−0.18
Compliance coefficient (m ² /kpa)	0.009**	−0.272	0.07	−0.19	0.31	−0.11	0.09	−0.18
Local carotid systolic pressure (mmHg)	0.54	0.07	0.61	0.05	0.72	−0.04	0.63	0.05
Local carotid diastolic pressure (mmHg)	0.89	0.01	0.31	0.11	0.85	−0.02	0.92	−0.01

TG; triglycerides, HDL-C; high density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol, IMT; intima-media thickness, PWV; pulse wave velocity.

* Statistically significant (*p* < .05).

** Statistically highly significant (*p* < .01).

Table 7

Correlation between doses of medications received by RA patients and different aortic and carotid stiffness parameters.

Variable	Methotrexate		Anti-malarials		Salazopyrine		Steroids	
	p	r	p	r	P	r	p	r
Aortic stiffness index	0.84	−0.02	0.32	0.19	0.65	−2	0.62	0.06
Aortic strain (%)	0.69	−0.05	0.89	0.02	0.95	0.02	0.6	0.06
Aortic distensibility (cm ² dyne ^{−1})	0.45	−0.09	0.64	0.09	0.94	−0.03	0.79	0.03
IMT (mm)	0.77	0.03	0.85	−0.03	0.9	0.05	0.15	0.18
Carotid distension (μm)	0.93	0.01	0.91	0.02	0.33	0.43	0.23	−0.15
Carotid stiffness index	0.46	0.09	0.46	0.14	0.37	−0.4	0.61	0.06
Carotid PWV (m/s)	0.57	0.07	0.74	0.06	0.59	−0.24	0.42	0.1
Distensibility coefficient (1/kpa)	0.62	−0.06	0.5	0.13	0.9	0.05	0.2	−0.16
Compliance coefficient (m ² /kpa)	0.91	−0.01	0.92	0.01	0.93	−0.03	0.59	−0.06
Local carotid systolic pressure (mmHg)	0.97	−0.004	0.84	−0.04	0.08	0.69	0.5	0.08
Local carotid diastolic pressure (mmHg)	0.57	−0.07	0.77	0.05	0.08	0.7	0.23	0.15

*Statistically significant (p < .05).

-IMT; intima-media thickness, PWV; pulse wave velocity.

statistically significant positive correlation was found between modified Larsen score and carotid stiffness index and carotid PWV. This relationship between cumulative disease activity and severity of arterial stiffness supports the notion that chronic inflammation plays a role in RA associated atherosclerosis.

In the present study, no statistically significant correlation was found between doses of steroids and different DMARDs received by RA patients and aortic or carotid stiffness parameters. These findings are in agreement with a study documented that common carotid artery IMT was not significantly different between RA patients who were taking and those who were not taking NSAIDs, corticosteroids, or methotrexate.³¹

The current study has some limitations one of these is being a cross-sectional study; single determination of serum lipid profile and inflammatory markers in particular may not accurately represent concentrations over time and cumulative inflammatory burden. In addition, there is only one control per two RA patients, which could decrease the statistical power in the control group.

Another limitation could be that all individuals were already on treatment including DMARDs, as the majority of our RA patients were on methotrexate and folic acid which may be responsible for the insignificant values of arterial stiffness parameters. Folic acid supplementation taken by study subjects receiving methotrexate may prevent hyperhomocysteinaemia during methotrexate treatment in RA. In addition, a previous study suggested that methotrexate treatment reduces overall and cardiovascular mortality in rheumatoid patients.³²

Moreover, we have to consider the differences among assessment techniques and devices used in previous studies, as well as the lack of comparable age-adjusted normal values which may limit the validity of arterial stiffness parameters as markers of early atherosclerosis.³³

5. Conclusion

This study demonstrated increased arterial stiffness in patients with RA free from cardiovascular risk factors and overt cardiovascular disease, secondary to the effect of inflammatory process associated with RA. We recommend further longitudinal studies involving larger sample sizes which will provide insight into the relative contribution of RA and treatment variables to arterial stiffness.

Conflict of interest

The authors have no conflicts of interest.

References

- Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum.* 2003;48:54–58.
- Gonzalez A, Maradit KH, Crowson CS, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. *Arthritis Rheum.* 2007;56:3583–3587.
- Rubbert-Roth A. Assessing the safety of biologic agents in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2012;51:38–47.
- El Sayed AM, El Bakry SA, Mobasher SA, et al. Insulin resistance as a risk factor for subclinical atherosclerosis in rheumatoid arthritis. *The Egyptian Rheumatologist*. 2014;36:7–13.
- Dhawan SS, Quyyumi AA. Rheumatoid arthritis and cardiovascular disease. *Curr Atheroscler Rep*. 2008;10:128–133.
- Cecelja M, Chowienzyk P. Role of arterial stiffness in cardiovascular disease. *J. R. Soc. Med. Cardiovasc. Dis.* 2012;1:11–21.
- Van Sijl AM, Peters MJ, Knol DK, et al. Carotid intima media thickness in rheumatoid arthritis as compared to control subjects: a meta-analysis. *Semin. Arthritis Rheum.* 2011;40:389–397.
- Gonzalez-Juanatey C, Llorca J, Testa A, et al. Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease. *Medicine (Baltimore)*. 2003;82:407–413.
- Corrales A, González-Juanatey C, Peiró ME, et al. Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. *Ann. Rheum. Dis.* 2014;73:722–727.
- Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62:2569–2581.
- Grundt S, Becker D, Clark L, et al. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation*. 2002;106:3143.
- Singer JM, Plotz CM. The latex fixation test. I. Application to the serologic diagnosis of rheumatoid arthritis. *Am. J. Med.* 1956;21:888–892.
- Mitra B1, Panja M. High sensitive C-reactive protein: a novel biochemical markers and its role in coronary artery disease. *J. Assoc. Physicians India*. 2005;53:25–32.
- Prevoo ML, Van Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum.* 1995;38:44–48.
- Rau R, Herborn G. A modified version of Larsen's scoring method to assess radiologic changes in rheumatoid arthritis. *J. Rheumatol.* 1995;22:1976–1982.
- Fahy M, Ko H, Srivastava S, et al. A comparison of echocardiographic techniques in determination of arterial elasticity in the pediatric population. *Echocardiography*. 2009;26:567–573.
- Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European society of cardiology. *J. Am. Soc. Echocardiogr.* 2005;18:1440–1463.
- Dernellis J, Panaretou M. Aortic stiffness is an independent predictor of progression to hypertension in non-hypertensive subjects. *Hypertension*. 2005;45:426–431.
- Klocke R, Cockcroft JR, Taylor GJ, et al. Arterial stiffness and central blood pressure, as determined by pulse wave analysis, in rheumatoid arthritis. *Ann. Rheum. Dis.* 2003;62:414–418.

20. Robustillo-Villarino M, Alegre-Sancho JJ, Rodilla-Sala E, et al. Pulse wave velocity and augmentation index are not independently associated with carotid atherosclerosis in patients with rheumatoid arthritis. *Clin. Rheumatol.* 2017;36:2601–2606.
21. Marasini B, De Monti M, Ghilardi G. Risk factors for accelerated atherosclerosis in patients with systemic lupus erythematosus. *Ann. Rheum. Dis.* 2005;64:163–164.
22. Minaur NJ, Jacoby RK, Cosh JA, et al. Outcome after 40 years with rheumatoid arthritis: a prospective study of function, disease activity, and mortality. *J. Rheumatol. Suppl.* 2004;69:3–8.
23. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, et al. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum.* 2008;59:1690–1697.
24. Turesson C, Jacobsson L, Ryden Ahlgren A, et al. Increased stiffness of the abdominal aorta in women with rheumatoid arthritis. *Rheumatology (Oxford)*. 2005;44:896–901.
25. Roman MJ, Devereux RB, Schwartz JE, et al. Arterial stiffness in chronic inflammatory diseases. *Hypertension*. 2005;46:194–199.
26. Karp G, Wolak A, Baumfeld Y, et al. Assessment of aortic stiffness among patients with systemic lupus erythematosus and rheumatoid arthritis by magnetic resonance imaging. *Int. J. Cardiovasc. Imaging*. 2016;32:935–944.
27. Triantafyllias K, De Blasi M, Hoffmann I, et al. The count of tender rather than swollen joints correlates with aortic stiffness in patients with rheumatoid arthritis. *Springer Plus*. 2016;5:428–435.
28. Sliem H, Nasr G. Change of the aortic elasticity in rheumatoid arthritis: Relationship to associated cardiovascular risk factors. *J. Cardiovasc. Dis. Res.* 2010;1:110–115.
29. Ferreira I, Snijder MB, Twisk JW, et al. Central fat mass versus peripheral fat and lean mass: opposite (adverse versus favorable) associations with arterial stiffness? The amsterdam growth and health study. *J. Clin. Endocrinol. Metab.* 2004;89:2632–2639.
30. Cypiene A, Laucevicius A, Venalis A, et al. Increased arterial stiffness in young patients with rheumatoid arthritis. *Semin. Cardiol.* 2006;12:141–148.
31. Choi HK, Hernan MA, Seeger JD, et al. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet*. 2002;359:1173–1177.
32. Kerekes G, Soltesz P, Nurmohamed MT, et al. Validated methods for assessment of subclinical atherosclerosis in rheumatology. *Nat. Rev. Rheumatol.* 2012;8:224–234.