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.5

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

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. 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.

Rheumatoid Factor was measured by latex agglutination method. 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.

Disease activity in the patients was assessed using the Disease Activity Score 28 (DAS 28). 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:

\[
\text{DAS28} = 0.56 \times \sqrt{(28 \times \text{Joint Count})} + 0.28 \times \sqrt{(28 \times \text{ESR})} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}.
\]

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, 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.

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.

Ultrasoundographic 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 > 0.99 mm.

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 quantitatively 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 ± 3.26 kg/m² and the mean BMI of patients had a mean of 26.46 ± 3.26 kg/m² and the mean of controls was 25.71 ± 2.57 kg/m². 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;
Carotid stiffness parameters in both study groups. Aortic stiffness parameters in both study groups. RA (group 1) patients. Clinical parameters, disease activity and laboratory data and treatment received by RA (group 1) patients. IMT; Intima-media thickness, PWV; Pulse wave velocity.

No statistically significant difference was found between IMT, 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.

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

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 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.

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

Variable RA patients (n = 90) Control group (n = 45) P

| Clinical parameters | No (%) | | |
|---------------------|--------|---|---|
| SC nodules | 5 (5.6%) | | |
| Dry eyes and mouth | 26 (28.8%) | | |
| Intestinal lung disease | 1 (1.1%) | | |
| Pulmonary nodule | 1 (1.1%) | | |
| Disease activity parameters | | Mean ± SD | No (%)
| DAS-28 | | | |
| High | (6.1 ± 0.6) | 43 (47.7%) | | |
| Moderate | (4.49 ± 0.72) | 40 (44.4%) | | |
| Low | (2.83 ± 0.29) | 6 (6.66%) | | |
| Remission | (2.46) | 1 (1.1%) | | |
| Modified Larsen score range | 20–65, (34.26 ± 5.71) | | |

Table 2
Aortic stiffness parameters in both study groups.

Variable RA patients (n = 90) Control group (n = 45) P

| Variable | Range | Mean ± SD | Range | Mean ± SD |
|----------|--------|-----------|--------|-----------|
| Aortic SI* | 0.58–15.97 | 4.83 ± 3.56 | 1.5–9.16 | 4.46 ± 1.83 |
| Aortic strain (%) | 4.21–27.78 | 12.12 ± 5.01 | 2.25–70.54 | 13.71 ± 10.69 |
| Aortic distensibility (cm²/dyne-1) | 2.81–18.18 | 7.38 ± 3.21 | 1.75–40.47 | 10.75 ± 8.95 |

Table 3
Carotid stiffness parameters in both study groups.

Variable RA patients (n = 90) Control group (n = 45) P

| Variable | Range | Mean ± SD | Range | Mean ± SD |
|----------|--------|-----------|--------|-----------|
| IMT (mm) | 0.32–0.96 | 0.49 ± 0.1 | 0.32–0.68 | 0.48 ± 0.07 |
| Carotid stiffness index | 2.19–4.14 | 8.57 ± 4.83 | 2.07–7.92 | 4.08 ± 1.13 |
| Carotid distension (μm) | 135.5–789.3 | 327.45 ± 136.03 | 314–939 | 649.77 ± 147.25 |
| Carotid PWV (m/s) | 3.51–1.83 | 6.39 ± 1.84 | 3.52–6.24 | 4.73 ± 0.64 |
| Distensibility coefficient (1/kpa) | 0.01–0.08 | 0.03 ± 0.01 | 0.02–0.08 | 0.04 ± 0.014 |
| Compliance coefficient (m³/kpa) | 0.34–2.55 | 1.13 ± 0.53 | 0.73–3.22 | 1.69 ± 0.56 |

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.

There was a poor correlation 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.

Variable RA patients (n = 90) Control group (n = 45) P

| Variable | Range | Mean ± SD | Range | Mean ± SD |
|----------|--------|-----------|--------|-----------|
| ESR (mm/hour) | 7–102, (41.16 ± 25.05) | | |
| Hb (gm/dl) | 8.3–15, (12 ± 1.4) | | |
| TLC (cell/mm³) | 3.6–18.3, (7.7 ± 2.79) | | |
| Platelets (platelet/mm³) | 163–651, (301.81 ± 97.2) | | |
| ALT (U/L) | 7–92, (24.04 ± 13.63) | | |
| AST (U/L) | 9–113, (22.88 ± 13.09) | | |
| Serum creatinine (mg/dl) | 0.3–1.4, (0.73 ± 0.19) | | |
| Serum cholesterol (mg/dl) | 96–295, (180.36 ± 41.54) | | |
| Serum triglycerides (mg/dl) | 32–352, (76.45 ± 46.49) | | |
| HDL-C (mg/dl) | 25–91, (48.09 ± 16.03) | | |
| LDL-C (mg/dl) | 43–255, (114.24 ± 36.24) | | |
| hs-CRP (mg/ml) | 0.1–13.7, (7.86 ± 4.7) | | |
| Treatment | | Mean ± SD | No(%) |
with some epidemiological studies showing an increased incidence of major CV events and clinical assessment of arterial stiffness.\textsuperscript{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.\textsuperscript{23,24} But we found a weak positive correlation between hs-CRP and carotid PWV.

In the current study, a statistically significant correlation was found between disease duration and different parameters of carotid stiffness. This supports that disease duration is an important risk factor for arterial stiffness.\textsuperscript{25}

In addition, a statistically significant correlation was found between serum cholesterol, TGs and different carotid stiffness parameters. Concerning aortic stiffness parameters, a statistically significant negative correlation was found between serum cholesterol and aortic distensibility. This comes in concordance with the fact that dyslipidemia is another major risk factor for arterial stiffness.\textsuperscript{19}

Two studies assessed the relationship between serum lipids and arterial stiffness in RA patients, they found that hyperlipidemia did not significantly correlate with aortic stiffness as measured by carotid femoral pulse wave velocity (cPWV).\textsuperscript{27,28} But when the components of the lipids were considered separately, aortic stiffness showed direct associations only with triglycerides.\textsuperscript{29}

We found no significant correlation between DAS-28 and arterial stiffness parameters measured in the aorta and common carotid arteries. The current findings are in agreement with a study that assessed arterial stiffness by augmentation index and PWV.\textsuperscript{30}

The current findings suggest that the increased arterial stiffness in patients under study reflected the cumulative inflammatory disease process rather than the degree of acute systemic inflammation as measured by hs-CRP and DAS-28. In addition IMT may be dependent on serial measurements of CRP levels so the measurement of serum CRP at a single point failed to be associated with IMT of common carotid artery.

In the present study, no statistically significant correlation was found between modified Larsen score and carotid IMT. However, a

**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 |
|---------------------------------|--------------|------------------|-----------------------|--------|
|                                 | p           | r               | p          | r       | p        | r      | p       | r     |
| 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 (cm²/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    | 0.02     | -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 (m²/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 |
|---------------------------------|--------|
|                                 | p      | r     |
| Carotid stiffness parameters    |        |       |
| 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 (m²/kpa) | 0.48   | -0.075|
| Local systolic blood pressure (mmHg) | 0.13   | 0.16  |
| Local diastolic blood pressure (mmHg) | 0.32   | 0.11  |
| Aortic stiffness parameters     |        |       |
| Aortic SI                       | 0.28   | 0.11  |
| Aortic strain (%)               | 0.89   | -0.15 |
| Aortic distensibility (cm²/dyne-1) | 0.45             | -0.08 |

**Table 6**

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

| Variable                        | Cholesterol | TG | HDL-C | LDL-C |
|---------------------------------|-------------|----|-------|-------|
|                                 | p           | r  | p      | r     |
| Aortic stiffness index          | 0.33        | 0.11| 0.11  | 0.11  |
| Aortic strain (%)               | 0.09        | -0.18| -0.18| -0.18|
| Aortic distensibility (cm²/dyne-1) | 0.03             | -0.22| -0.22| -0.19|
| IMT (mm)                        | <0.001\textsuperscript{-}\textsuperscript{1} | 0.37| 0.006\textsuperscript{-}\textsuperscript{2} | 0.29|
| Carotid distension(µm)          | 0.06        | -0.2 | 0.009\textsuperscript{-}\textsuperscript{3} | -0.27|
| Carotid stiffness index         | 0.29        | 0.11| 0.08  | 0.19  |
| Carotid PWV (m/s)               | 0.15        | 0.15| 0.04  | 0.21  |
| Distensibility coefficient (1/kpa) | 0.006            | -0.29| 0.07  | -0.19|
| Compliance coefficient (m²/kpa) | 0.009\textsuperscript{-}\textsuperscript{1} | -0.272| 0.07  | -0.19|
| Local carotid systolic pressure (mmHg) | 0.54        | 0.07| 0.61  | 0.05  |
| Local carotid diastolic pressure (mmHg) | 0.89        | 0.01| 0.31  | 0.11  |

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).
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.1

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 hyperhomocysteinemia 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.

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