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Original Article

Decreased Aortic Elasticity in Rheumatoid Arthritis: An Early Sign of Atherosclerosis and Predictive Factors

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Abstract

Background: Atherosclerosis is increased in patients with rheumatoid arthritis (RA) and early diagnosis of vascular disease leads to better outcome. Our aim was to evaluate whether aortic elasticity decreases in the subclinical stage of atherosclerosis in RA patients without any cardiovascular disease and to determine disease-related risk factors.

Methods: One hundred fourteen patients with RA, 50 patients with spondyloarthritis, and 50 healthy control were included in this study. Aortic elasticity was evaluated by echocardiography (ECHO). The relationship between atherosclerosis and vascular risk factors, including age, disease activity, C-reactive protein, and serum tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) levels was investigated.

Results: In ECHO evaluation, aortic stiffness was increased ($P = .01$), and aortic strain and elasticity were decreased ($P < .01$, $P = .01$) in RA patients compared to control groups. Serum tumor necrosis factor-like weak inducer of apoptosis levels were also significantly lower ($P < .01$) in RA, but no significant correlation was found with aortic strain measurement ($P > .05$). Aortic elasticity was shown to decrease significantly with age in all groups ($P < .05$).

Conclusion: In this study, we observed deterioration of aortic parameters indicating early atherosclerosis in RA. Aging was found to be the single predictive factor for vascular disease. Although a decrease in sTWEAK level was detected in the RA group, no statistically significant relationship could be demonstrated between sTWEAK level and aortic elasticity parameters. However, the cross-sectional design of the study and possible fluctuations in serum markers depending on disease activity make it difficult to draw a clear conclusion on this subject.

Keywords: Atherosclerosis, rheumatoid arthritis, TWEAK

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Introduction

Rheumatoid arthritis (RA) is an independent risk factor for cardiovascular disease (CVD). Atherosclerosis has an insidious course before clinical manifestations become relevant and is known to be associated with poor prognosis and increased mortality in RA.[1] Detection of CVD in the subclinical period is important in increasing survival rates, and this emphasizes the importance of early diagnosis of vascular diseases. Various methods can be used to reveal vascular damage at an early stage, and the most preferred method is echocardiography (ECHO) measurements, as they are non-invasive and easily accessible. Reduced arterial elasticity on ECHO evaluation is one of the first signs of atherosclerosis. Thus, prior small studies have shown increased arterial stiffness in patients with RA, and this has been accepted as a marker of subclinical vascular disease.[2,3]

Inflammation-induced endothelial dysfunction is the first event in the pathogenesis of vascular disease and is the most important cause of early vascular damage in RA patients. In the literature, there are some data showing that vascular inflammation decreases as a result of cytokine blocker therapies such as tumor necrosis factor alpha (TNF) alpha inhibitors.[4-6] Tumor necrosis factor alpha-like weak inducer of apoptosis (TWEAK) is an important cytokine in the pathogenesis of both atherosclerosis and RA.

Tumor necrosis factor alpha-like weak inducer of apoptosis is a type II transmembrane glycoprotein of the TNF superfamily with transmembrane and soluble forms; the latter can be detected both in the serum and body fluids.[7] Tumor necrosis factor alpha-like weak inducer of apoptosis induces stimulation of cell death or growth, angiogenesis, regulation of tissue formation and destruction, stimulation of the release of proinflammatory cytokines [matrix metalloproteinase-1 (MMP-1), interleukin 6 (IL-6), and IL-8], and damage of the bone or cartilage.[8,9] In addition to inflammation, there is also a potential

association between TWEAK and atherosclerosis pathogenesis.[10] Tumor necrosis factor alpha-like weak inducer of apoptosis acts by binding to 2 receptors, the inducible fibroblast growth factor 14 (Fn14) and the scavenger receptor cysteine-rich CD163 protein.[11,12] Expression of Fn14 is almost absent in healthy arteries; however, it is upregulated in acute stress and engagement of TWEAK/Fn14 triggers repair.[8,13] The TWEAK/Fn14 interaction is implicated in all stages of atherosclerosis development, starting from plaque formation to thrombosis.[11]

In this study, we aimed to investigate early atherosclerosis using non-invasive methods in RA patients without any CVD symptoms or signs. As a secondary endpoint, we aimed to evaluate whether there were any risk factors that could predict early vascular disease. For this purpose, we planned to evaluate sTWEAK level along with the classical vascular risk factors, since it has been shown to play an important role in both inflammation[14,15] and atherosclerosis, and there is no study revealing the role of serum TWEAK levels in determining cardiovascular risk in RA.

Material and Methods

This cross-sectional study includes randomly selected RA patients who met the 2010 American College of Rheumatology/European League Against Rheumatism criteria and matched to (1 : 2) spondyloarthritis (SpA) patients and healthy control groups according to age and gender.[16,17] Patients with a history of CVD, including myocardial infarction, ischemic cerebrovascular events, and peripheral arterial disease; cardiac valvular disease; uncontrolled hypertension; diabetes; and those aged less than 18 years or above 70 years were excluded. The study protocol was approved by the Ethics Committee of the Medical Faculty of the Demiroğlu Bilim University (Approval Number: 44140529/2016-10; Date: March 16, 2016). All the patients' written informed consent was obtained.

Main Points

- The risk of subclinical atherosclerosis is increased in rheumatoid arthritis (RA).
- Aortic elasticity has been shown to be impaired in RA patients.
- Decreased serum TWEAK level is a useful indicator of vascular damage, but it has not been found to be sufficiently reliable in predicting atherosclerosis in RA.

Patients and Controls

Between 2016 and 2017, we consecutively recruited 177 patients with RA, and 61 patients were screened. After excluding patients who had diabetes mellitus (31 in RA, 8 in SpA), CVD (11 in RA, 2 in SpA), cerebrovascular disease (1 in RA) and advanced age (20 in RA, 1 in SpA), 114 patients with RA, 50 patients with SpA (ankylosing spondylitis: 37, psoriatic arthritis: 10, inflammatory bowel disease-associated arthritis: 3), and 50 healthy controls were enrolled.

Data Collection

During outpatient visits, we evaluated the clinical characteristics [disease activity, using the Disease Activity Score 28 joint count (DAS28) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score], presence of extra-articular involvement, and medication), laboratory data (acute phase reactants, complete blood count, fasting glucose, lipid profile, and uric acid), as well as CVD-related conditions (hypertension, hyperlipidemia, family history of coronary artery disease, and smoking history). In addition, the body mass index (BMI) was calculated, and blood pressure was recorded for each subject, followed by venous blood sampling. Thereafter, ECHO was performed by 2 blinded cardiologists.

Assessment of Atherosclerosis

Atherosclerosis was noninvasively assessed with ECHO by measuring the aortic elasticity parameters (aortic stiffness and aortic strain). All the patients underwent transthoracic ECHO in the left lateral decubitus position using 2.5 to 4 MHz transducers and a "General Electric Vivid S6" (New York, NY, USA) echocardiography device.

For the assessment of aortic stiffness, ascending aorta images were obtained at 3 cm above the aortic valve using M-mode ECHO from the parasternal long axis view and recorded. The systolic aortic diameter (AoS) was measured at the maximal anterior motion of the aorta, whereas the diastolic aortic diameter (AoD) was measured at the peak of the QRS wave complex on the simultaneously recorded electrocardiography. The average value of 5 consecutive measurements was calculated. The aortic elasticity parameters were calculated according to the following formulas by using these average values, systolic blood pressure (SBP), and diastolic blood pressure (DBP) measurements:

$$\text{Aortic strain (\%)} = 100 \times (\text{AoS} - \text{AoD})/\text{AoD}$$

$$\text{Aortic stiffness} = \text{Logarithm (SBP/DBP)/aortic strain}$$

$$\text{Aortic elasticity} = 2 \times \text{aortic strain/SBP} - \text{DBP}$$

The optimal cutoff value of aortic strain was taken as ≤9.22% (sensitivity, 86%; specificity, 70%) for the prediction of atherosclerosis.[18]

Collection and Evaluation of Venous Blood Samples

°Blood samples were collected at the time of outpatient visits, and the serum was separated via centrifugation at 1000 rpm for 10 minutes; thereafter, it was refrigerated at −20°C. Tumor necrosis factor alpha-like weak inducer of apoptosis (EBIOSCIENCE, San Diego, Calif, USA) (pg/mL) and Fn14 (ELABSCIENCE, Houston, Tex, USA) (pg/mL) levels were determined using the enzyme-linked immunosorbent assay (ELISA) method.

Statistical Analysis

The statistical analysis was performed using *t*-tests and one-way analysis of variance (ANOVA) for normally distributed continuous variables, and the Kruskal–Wallis and Mann–Whitney *U*-tests for non-normally distributed continuous variables. The chi-square test was used for categorical variables. *P*-value of $P < .05$ was considered to be statistically significant. For 3-group comparisons, the significance level for the *P*-value was reduced to <0.01 in post-hoc analysis to rule out potential type 1 errors. The Spearman correlation test was used to identify correlations between 2 continuous variables. The possible predictors of atherosclerosis such as age, disease activity score, disease duration, hyperlipidemia, hypertension, BMI, and serum ELISA measurements (TWEAK, Fn14) were examined by univariate and multiple logistic regression analysis. The analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows, version 14.0 software (SPSS Inc.; Chicago, IL, USA).

Results

All 3 groups were similar in terms of sex, age, and disease duration. The mean DAS28 score was 3.6 ± 1.37 in the RA group, with most patients (86%) having mild or moderate disease activity, whereas only 14% of RA patients had a high disease activity score. The demographic features of the RA patients in our study are shown in Table 1.

The study groups did not differ significantly with respect to hyperlipidemia, impaired glucose intolerance, obesity, family history of coronary artery disease, smoking, and uric acid

Table 1. Demographic Characteristics of Rheumatoid Arthritis Patients

Rheumatoid Arthritis (n = 114)	
The mean duration of disease (months) (mean ± SD)	107.7 ± 92.5
Autoantibodies n (%)	
Rheumatoid factor	60 (52.6)
Anti CCP	70 (61.4)
DAS28 (mean ± SD)	3.6 ± 1.37
Remission n *(%)*	32 (28)
Low disease activity n (%)	13 (11.4)
Moderate disease activity n (%)	53 (46.5)
High disease activity n (%)	16 (14)
Erythrocyte sedimentation rate (mm/h) (mean ± SD)	24.5 ± 19.7
C-reactive protein *(mg/dL) (mean ± SD)*	0.68 ± 1.29
Extra-articular signs n (%)	50 (43.8)
Sicca syndrome	34 (29.8)
Anemia of chronic disease	12 (10.5)
Interstitial lung disease	3 (2.6)
Pleural effusion	2 (1.7)
Pericardial effusion	1 (0.8)
Rheumatoid nodule	1 (0.8)
Drug use n (%)	
Disease modifying antirheumatic drugs	81 (71.1)
Biological antirheumatic drugs	28 (24.6)
Drug-naïve	5 (4.3)

levels. Although more patients in RA group had a diagnosis of hypertension, all of the patient' blood pressure values were in the normal range. Table 2 shows the clinical characteristics of the patients.

Enzyme-Linked Immunosorbent Assay Measurements

Serum TWEAK concentration was significantly lower in RA patients than in SpA patients and healthy controls (HCs) ($P < .01$), whereas the serum Fn14 levels were significantly higher ($P < .01$) (Table 3, Figure 1A and B). Seropositive RA patients had significantly higher Fn14 (721 ± 1066 vs. 185 ± 233 pg/mL, $P < .01$) levels that also correlated positively with disease duration ($r = 0.38$, $P < .01$).

Echocardiographic Evaluations

The aortic assessments showed a significant decrease in the aortic elasticity in RA patients compared with the subjects from other groups ($P = .01$) (Table 4). Both univariate and multivariate analysis revealed that age was the main predictor of atherosclerosis in all groups. Serum TWEAK level was found as the other independent factors of aortic strain measurement in the HC group ($P < .01$). But, no significant correlation was found between aortic elasticity parameters and sTWEAK levels or traditional risk factors in RA and AS patients ($P > .05$).

Discussion

It is a well-known fact that the risk of inflammation-related CVD increases in RA patients. Early detection of coronary artery disease is crucial for the prevention of mortality and morbidity. Here, we aimed to investigate the presence of subclinical atherosclerosis in RA patients with noninvasive methods and to demonstrate the deterioration in aortic elastic parameters that exhibit vascular damage.

Carotid intima-media thickness (CIMT) and aortic elasticity parameters are important methods for noninvasive detection of atherosclerosis in the subclinical phase.[19,20] Carotid intima-media thickness is the oldest technique used to identify subclinical atherosclerosis, which has been reported to increase in RA patients.[20] However recent meta-analyses have shown that CIMT measurement is not a sensitive method because it does not provide sufficient information about the plaque structure.[21] One of the other methods that can be used in the earliest stages of structural and functional changes in the vascular wall is the evaluation of aortic elasticity parameters, wherein arterial compliance can be measured. Arterial stiffness is the first finding detected in vascular wall structural disorder and increases with age.[22,23] Some studies reported that the arterial stiffness of RA patients is higher than that of age-matched controls,[2,4] and that aortic elasticity increases and CIMT decreases after anti-TNF treatment,[4,5,24] with improvement in aortic elasticity parameters beginning earlier than CIMT.[4] This finding suggests that aortic elasticity parameters may be more sensitive indicators of subclinical atherosclerosis. In our study, which is planned in line with this information, we found impaired aortic elasticity parameters (stiffness and strain) in the RA group without any CVD symptoms or signs, and this finding suggested there was significant early vascular damage in the RA group compared to the healthy and patient control groups.

Another aim of our study is to reveal patient- or disease-related factors that can predict early atherosclerosis. For this purpose, age, disease activity, traditional CVD risk factors, and inflammatory markers (CRP and sTWEAK) were evaluated, and similar to previous studies, aortic elasticity was found to be only inversely related to age in both the RA and control groups.[2] Consistent with other studies, we did not find a relationship with traditional risk factors that could explain the vascular findings observed in RA patients.[2,25] This result supports the hypothesis that the current vascular findings are mainly related to chronic inflammation. On the other hand, although acute-phase proteins have been reported to be associated with CAD in the general population and CRP to be inversely associated with aortic elasticity in RA patients, we could not show any relationship between CRP levels and aortic stiffness in this study. This finding is probably related to the fact that CRP levels were within the normal range in 85% of our RA patients, meaning that inflammation was kept under tight control.

Tumor necrosis factor alpha-like weak inducer of apoptosis/Fn14 axis is another known factor playing an role in atherosclerotic plaque development.[26] and decreased sTWEAK levels in patients with atherosclerosis and associated conditions, such as diabetes mellitus, chronic renal failure, hypertension, and peripheral arterial disease, have been reported in different studies.[27-29] Although its pathogenic effect, and the reason for its decrease in atherosclerosis, have not yet been fully elucidated, among the possible mechanisms is reduction by binding to Fn14 or scavenger receptor CD163. Some studies have shown that Fn14 is highly upregulated after vessel wall injury and that it decreases serum sTWEAK levels.[28,29] Conversely, autoimmune and chronic inflammatory conditions lead to increased sTWEAK levels, such as RA, systemic lupus erythematosus (SLE), and multiple sclerosis, especially in active disease

Table 2. Characteristics of the Study Population

	RA (n = 114)	SpA (n = 50)	HC (n = 50)	*P*
Gender n (%)				.43
Female	93 (81.6)	39 (78)	44 (88)	
Male	21 (18.4)	11 (22)	6 (12)	
Age (mean ± SD) (years)	48.1 ± 11.5	45.1 ± 10.4	47.4 ± 7.3	.30
Disease duration (mean ± SD) (months)	107.2 ± 92.5	90.4 ± 95.8	-	.34
Systolic blood pressure (mean ± SD) (mm/Hg)	128.2 ± 23.4	124.7 ± 18.9	123.1 ± 17.7	.30
Diastolic blood pressure (mean ± SD) (mm/Hg)	79.6 ± 11.8	78.2 ± 9.5	77.3 ± 9.2	.42
Hypertension n (%)	38 (33.3)	10 (20)	7 (14)	.01
Hyperlipidemia n (%)	12 (10.5)	8 (16)	1 (2)	.06
Impaired fasting glucose n (%)	8 (7)	6 (12)	3 (6)	.46
Family history of cardiovascular disease n (%)	53 (46.5)	22 (44)	28 (56)	.62
Smoking n (%)	44 (38.6)	24 (48)	16 (32)	.29
Obesity n (%)	30 (26.3)	16 (32)	17 (34)	.52
Body mass index (mean ± SD) (kg/m^2)	27.3 ± 5.4	27.7 ± 5.0	28.4 ± 5.7	.11
ESR (mean ± SD) (mm/h)	24.5 ± 19.7	21.2 ± 14	20.4 ± 13.7	.28
CRP (mean ± SD) (mg/dL)	0.68 ± 1.29	0.76 ± 1.03	0.29 ± 0.38	.04
Total cholesterol (mean ± SD) (mg/dL)	199.1 ± 41.8	214.5 ± 32.6	196.7 ± 31.7	.04
Triglyceride (mean ± SD) (mg/dL)	112.9 ± 60	125.3 ± 62	114.6 ± 64.9	.48
LDL (mean ± SD) (mg/dL)	115.5 ± 35.2	133.1 ± 27	113.9 ± 27.7	<.01
HDL (mean ± SD) (mg/dL)	61 ± 17.1	56.5 ± 14.3	59.8 ± 19.5	.26
Blood glucose (mean ± SD) (mg/dL)	89.2 ± 8.1	92.2 ± 6.8	88.3 ± 10.1	.05
Uric acid (mean ± SD) (mg/dL)	4.0 ± 1.2	4.4 ± 1.2	4.4 ± 1.4	.11
Leukocyte (mean ± SD) (per mm^3)	7518 ± 2324	7557 ± 2843	6800 ± 2100	.17
Hemoglobin (mean ± SD) (mg/dL)	12.8 ± 1.4	12.8 ± 1.7	12.9 ± 1.5	.91
Platelet (mean ± SD) (×10^3/μL)	275 ± 69	278 ± 81	296 ± 76	.22

HC, healthy control; RA, rheumatoid arthritis, SpA, spondyloarthritis (ankylosing spondylitis (AS): 37, psoriatic arthritis: 10, and inflammatory bowel disease-associated arthritis: 3).

Table 3. Serum Tumour Necrosis Factor Alpha-Like Weak Inducer of Apoptosis and Fibroblast Growth Factor 14 Results in Rheumatoid Arthritis, Spondyloarthritis, and Healthy Control Groups

	RA (n = 114)	SpA (n = 50)	HC (n = 50)	*P**
TWEAK (pg/mL)	937.4 ± 291.7**	1075.2 ± 312.1	1061.3 ± 402.8	<.01
Fn14 (pg/mL)	557 ± 929.4***	148.7 ± 211.6	91.6 ± 67.9	<.01

Values were given as mean ± SD.
HC, healthy control; RA, rheumatoid arthritis, SpA, spondyloarthritis.
*Kruskal–Wallis test.
**Mann–Whitney *U*-test; RA vs. SpA, *P* < .01, RA vs. healthy controls, *P* = .02; SpA vs. healthy controls, *P* = .4.
***Mann–Whitney *U*-test, RA vs. SpA, *P* < .01; RA vs. healthy controls, *P* < .01; SpA vs. healthy controls, *P* = .5.

Table 4. Doppler Ultrasonography Results in Rheumatoid Arthritis, Spondyloarthritis, and Healthy Control Groups

	RA (n = 114)	SpA (n = 50)	HC (n = 50)	*P**
Ao Strain	9.4 ± 4.6*	10.8 ± 4.6	11.7 ± 4.5	<.01
Ao Stiffness	6.6 ± 4.3**	5.2 ± 3	4.9 ± 3	.01
Ao elasticity	4.3 ± 2.7***	5.05 ± 2.7	5.5 ± 2.7	.01

Values were given as mean ± SD.
HC, healthy control; RA, rheumatoid arthritis, SpA, spondyloarthritis.
*Mann–Whitney *U*-test; RA vs. healthy controls, *P* < .01; RA vs. SpA, *P* = .06; SpA vs. healthy controls, *P* = .3.
**Mann–Whitney *U*-test; RA vs. healthy controls, *P* = .01; RA vs. SpA, *P* = .05; SpA vs. healthy controls, *P* = .04.
***Mann–Whitney *U*-test; RA vs. healthy controls, *P* < .01; RA vs. SpA, *P* = .09; SpA vs. healthy controls, *P* = .2.

duration.[14,15,30] On the other hand, it has been shown that sTWEAK levels decrease with microvascular damage in patients with lupus nephritis and systemic sclerosis.[15,31,32] Therefore, the main factor determining the serum TWEAK level in inflammatory diseases seems to depend on whether disease activity or vascular damage is more pronounced. Within this information, it can be thought that decreased TWEAK levels in RA patients with low disease activity may be related to vascular damage. Although we detected a decrease in sTWEAK levels and deterioration in aortic elasticity parameters in RA patients in this study, the relationship between aortic tension and sTWEAK levels was revealed only in the healthy control group. As mentioned above, TWEAK/Fn14 are influenced by many factors in inflammatory diseases, such as fluctuation of serum markers by disease activity and ongoing treatments especially biological drugs. Therefore, the absence of statistically significant relationship between sTWEAK and aortic parameters in the RA group may be related to the cross-sectional design of our study.

In conclusion, this study showed impaired aortic elasticity and reduced sTWEAK levels in RA patients. Vascular damage was found to be associated only with aging. Although it is thought that the decrease in sTWEAK level is related to vascular damage, no significant relationship could be shown between sTWEAK level and aortic tension in our patients with RA. Therefore, prospective designed and large sample size studies will be more useful to demonstrate whether there is a relationship between atherosclerosis and these biomarkers.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Medical Faculty of the Demiroğlu Bilim University (Approval Number: 44140529/2016-10; Date: 16.03.2016).

Informed Consent: Informed consent was obtained from the participants who agreed to take part in the study.

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