The relationship between serum YKL-40 levels and arterial stiffness in patients with ankylosing spondylitis

Kucukali Turkyilmaz A[1], Devrimsel G[1], Serdaroglu Beyazal M[1], Kirbas A[2], Cicek Y[3], Capkin E[4], Karkucak M[4], Gokmen F[5]

ABSTRACT

Objective: Serum YKL-40 plays roles in inflammatory and vascular processes. Our aim was to evaluate serum YKL-40 levels in patients with ankylosing spondylitis (AS) and to investigate their potential relationship with arterial stiffness based on carotid-femoral pulse wave velocity (CF-PWV).

Methods: Forty-three patients with AS and 41 healthy controls with no history or current signs of cardiovascular disease were included in the study. All patients were administered nonsteroidal anti-inflammatory drugs (NSAIDs), and none were prescribed anti-tumor necrosis factor agents. Serum YKL-40 levels were measured. CF-PWV and intima-media thickness of the common carotid artery (IMT-C) were evaluated.

Results: The mean age of AS patients was 34.6 ± 10.2 years and of controls was 36.3 ± 9.0 years. CF-PWV was significantly higher in AS patients than in controls (8.2±2.7 vs. 7.0±1.6 m/s, respectively; P=0.015). However, the IMT-C was not significantly different between AS patients and controls (0.6±0.3 vs. 0.5±0.2 mm, P=0.501). YKL-40 levels were significantly higher in AS patients than in controls (78.9±37.9 vs. 58.4±21.2 ng/mL, P=0.003) and were strongly correlated with CF-PWV (r=0.773, P<0.001) and IMT-C (r=0.548, P<0.001). A multiple linear regression analysis revealed that CF-PWV could be explained by serum YKL-40 levels and IMT-C (adjusted R^2= 0.707, P=0.013 and P=0.001, respectively). AS patients with a higher disease activity score had higher YKL-40 levels, IMT-C, and CF-PWV than did those with a lower disease activity score (P<0.001, P=0.008, and P<0.001, respectively)

Conclusion: AS patients had higher serum YKL-40 levels, CF-PWV, and IMT-C than did healthy controls. Additionally, there was an association between increased CF-PWV and serum YKL-40 levels. Therefore, we conclude that CF-PWV and YKL-40 levels may be used for early diagnosis of atherosclerosis in AS patients.

Keywords: Ankylosing spondylitis; Arterial stiffness; Carotid-femoral pulse wave velocity; YKL-40 levels

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease of the spine and sacroiliac joints. AS is associated with some extra-articular manifestations, including cardiovascular diseases (CVDs)[1]. AS patients show increased mortality from CVDs, and it has been reported that their relative risk of developing atherosclerosis is 1.5-fold higher than that in the normal population[2,3]. Traditional cardiovascular risk factors, including smoking, dyslipidemia, hypertension, obesity, and diabetes mellitus, play an important role in the development of atherosclerosis[4]. However, these risk factors do not fully explain the increased risk of CVDs in patients with AS.

Chronic systemic inflammation seems to play a crucial role in the pathogenesis of atherosclerosis. It has been reported that the low-grade inflammation associated with AS has an influence on accelerating atherosclerosis[5]. Atherosclerosis has been associated with circulating inflammation biomarkers, such as C-reactive protein (CRP), fibrinogen, cytokines, and adhesion molecules[6]. Furthermore, YKL-40 has been suggested

1. Department of Physical Medicine and Rehabilitation, Recep Tayyip Erdoğan University, Medical School
2. Department of Biochemistry, Recep Tayyip Erdoğan University, Medical School
3. Department of Cardiology, Recep Tayyip Erdoğan University, Medical School
4. Department of Physical Medicine and Rehabilitation, Karadeniz Technical University, Medical School
5. Department of Physical Medicine and Rehabilitation, Canakkale Onsekiz Mart University, Medical School

as a potential biomarker of inflammation and endothelial dysfunction[7]. Studies have shown that elevated YKL-40 levels are associated with CVDs[8,9]. In addition, high serum YKL-40 levels have been found in patients with spondyloarthritis. That study suggested that YKL-40 might have potential value in monitoring disease activity[10].

The assessment of vascular dysfunction could be useful in identifying subclinical atherosclerosis and for predicting the risk of developing CVDs[11]. There are several methods for assessing vascular function. Arterial stiffness, which reflects arterial compliance, is an important indicator of the early stages of atherosclerosis. Carotid-femoral pulse wave velocity (CF-PWV) is considered the gold standard for assessing arterial stiffness[12]. In addition, the intima-media thickness of the common or internal carotid artery (IMT-C), as measured on high-resolution ultrasonography, is the standard method for assessing subclinical atherosclerosis. Recently, it has been reported that patients with AS have increased arterial stiffness (based on PWV) and IMT-C[13,14].

Because of the high risk of CVDs in patients with AS, it is very important to identify atherosclerosis in its early stages. Accordingly, the aims of this study were to evaluate the possible role of serum YKL-40 level as a biomarker of subclinical CVDs in AS patients and to investigate its potential relationship with subclinical atherosclerosis based on CF-PWV and IMT-C measurements.

PATIENTS AND METHODS

In this study, 43 AS patients and 41 healthy controls were enrolled. Patients who fulfilled the modified New York criteria for AS[15] were consecutively recruited from a rheumatology outpatient clinic between February and October 2012. Healthy controls were selected from among hospital personnel who volunteered to participate as the control group. Patients and controls with any reported cardiovascular diseases (coronary angina, heart failure, myocardial infarction, peripheral vascular disease, stroke) as well as patients who were receiving anti-hypertensive medications, lipid-lowering therapies, corticosteroid treatments, or had any other chronic disease were excluded from the study. All patients were using nonsteroidal anti-inflammatory drugs (NSAIDs), and none had taken anti-tumor necrosis factor (TNF) agents, sulfasalazine, or other disease-modifying anti-rheumatic drugs (DMARDs) for at least 3 months. The local ethical committee approved the study protocol, and informed consent was obtained from all participants before the examination.

CLINICAL ASSESSMENT
Clinical features, symptom duration, height, weight, and body mass index (BMI) were recorded. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used to assess disease activity (0:no activity and 10:highest level of activity). A BASDAI score of ≥4 was considered to indicate active disease. Visual analogue scale (VAS) was utilized to record pain scores. If there was no pain, the score was 0 point and the most severe pain was recorded as 10 points. All patients answered questions about their medications. A single experienced cardiologist who was blinded to patient clinical data performed the vascular assessments. These assessments were performed in the morning after an overnight fast of at least 8 h. Resting blood pressure was recorded with a mercury column sphygmomanometer.

BIOCHEMICAL ANALYSIS
Blood samples, which were drawn after 8 h of fasting, were measured for serum glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), CRP, and the erythrocyte sedimentation rate (ESR).

SERUM YKL-40 MEASUREMENT
Venous blood samples were drawn in the morning after 8 h of fasting. The samples were centrifuged at 2,500×g for 10 minutes at 4°C. Serum was obtained after centrifugation and stored at -80°C until analysis. Serum YKL-40 level was measured using a commercially available enzyme immunoassay (EIA) kit (MicroVue YKL-40; Quidel, San Diego, CA, USA) according to the manufacturer's instructions, which indicated that the normal range of YKL-40 levels was 35–83 ng/mL.

PULSE WAVE VELOCITY MEASUREMENT
CF-PWV was measured in the carotid-femoral segment using a validated non-invasive device (SphygmoCor, AtCor Medical, Sydney, Australia) that sequentially records the carotid and femoral artery pulse waves with an application tonometer and electrocardiogram. The

measurements were performed after the subjects had rested for 15 min in the supine position in a quiet room. The distances from the sternal notch to the right carotid artery and from the sternal notch to the right femoral artery were measured. At least 10 consecutive pulse waves were recorded over the common carotid and right femoral arteries. The time difference (t) was measured as the difference between the start of each waveform. Using a tape measure, the total distance between the carotid and femoral artery was measured, and the CF-PWV was calculated automatically. The results were expressed in m/s.

CAROTID ULTRASONOGRAPHY

Carotid arterial ultrasonography was performed using a high-resolution ultrasonography scanner (VingMed Vivid 3;GE Medical System, Horten, Norway) with a 7-MHz linear-array transducer. Measurements were performed on the right common carotid artery with the subject in the supine position. The region 1 cm proximal to the carotid bifurcation was identified, and the IMT-C of the far wall was evaluated as the distance between the lumen–intima and the media–adventitia interfaces. The IMT-C measurement was obtained from four adjacent sites at 1-mm intervals, and the average of all measurements was used for analysis. Mean values were calculated, and the results were presented in mm.

STATISTICAL ANALYSIS

Values obtained by measurement were expressed as mean ± standard deviation (SD), and those obtained by counting were expressed as a percentage. The appropriateness of the normal distribution of the acquired data was tested with the Kolmogorov–Smirnov test. For comparison of the measurement values of the two groups, the Student t-test and the Mann–Whitney U test were utilized for values with normal and non-normal distributions, respectively. The chi-squared test was used for the comparison of qualitative data. A correlation analysis for continuous variables was performed using the Spearman's correlation coefficient. A multiple backward linear regression analysis was performed in order to identify the parameters accounting for the CF-PWV. We evaluated the factors that could affect the CF-PWV dependent variable in the multivariate linear regression analysis. Independent factors were age, symptom duration, CRP, BASDAI, YKL-40, and IMT-C. The number of independent factors was determined according to study sample size. Statistical significance was considered as P < 0.05.

RESULTS

The clinical characteristics and cardiovascular and laboratory parameters of the AS patients and healthy controls are shown in Table I. The mean age was 34.6±10.2 years among the AS patients and 36.3±9.0 years among the controls. There were 28 (53.7%) and 22 (65.1%) male patients in the AS and control groups, respectively. There were no differences in the TC, TG, LDL-C, and HDL-C values or systolic and diastolic blood pressure readings between the patients and controls (all $P>0.05$). ESR and CRP levels (both $P<0.001$) as well as serum YKL-40 levels (78.9±37.9 vs. 58.4±21.2 ng/mL, respectively, $P=0.003$) were significantly higher in the AS patients than in the control subjects. The CF-PWV values were also higher in the AS patients than in the controls (8.2±2.7 vs. 7.0±1.6 m/s, respectively, $P=0.015$). However, the IMT-C values were not significantly different between groups (0.6±0.3 vs. 0.5±0.2 mm, $P=0.501$).

The CF-PWV and IMT-C values were correlated with indexes of disease activity, such as CRP, ESR, VAS, and BASDAI (Table II). Furthermore, for AS patients, the serum YKL-40 level was significantly correlated with IMT-C, CRP, ESR, VAS, and BASDAI ($r=0.548$, $r=0.711$, $r=0.767$, $r=0.802$, $r=0.807$, respectively; all $P<0.001$). The YKL-40 level in the AS patients also demonstrated a strong correlation with CF-PWV values ($r=0.773$, $P<0.001$; Figure 1).

A multiple backward linear regression analysis was used in order to adjust for any potential confounding influences of factors such as age, symptom duration, CRP, BASDAI, YKL-40, and IMT-C on AS patients. The linear regression analysis revealed that CF-PWV values were explained by serum YKL-40 levels and IMT-C values (adjusted $R^2= 0.707$, $P=0.013$, and $P=0.001$, respectively; Table III).

AS patients with a higher disease activity score (BASDAI≥4) had higher YKL-40, IMT-C, and CF-PWV values than those with a low disease activity score (BASDAI<4) ($P<0.001$, $P=0.008$ and $P<0.001$, respectively; Table IV).

DISCUSSION

Atherosclerosis is a strong predictor of future CVDs. AS patients have an increased risk of CVDs and mortality compared with the general population[16]. Mechanisms underlying AS-associated atherosclerosis are not

TABLE I. CLINICAL CHARACTERISTICS, CARDIOVASCULAR AND LABORATORY PARAMETERS OF PATIENTS WITH ANKYLOSING SPONDYLITIS (AS) AND CONTROL SUBJECTS (MEAN ± SD)

	AS (n=43)	Controls (n=41)	P
Age, years	34.6 ± 10.2	36.3 ± 9.0	0.412
Male/female, n (%)	28/15 (65.1/34.9)	22/19 (53.7/46.3)	0.397
Symptom duration, years	9.3 ± 7.0	–	
BMI, kg/m²	24.8 ± 1.9	25.3 ± 2.1	0.233
Current smokers, n(%)	16 (37.2)	13 (31.7)	0.596
HLA-B27 positive, n(%)	35 (81.4)	–	
BASDAI score	3.7 ± 1.9	–	
VAS, cm	5.1 ± 2.8	–	
YKL-40, ng/ml	78.9 ± 37.9	58.4 ± 21.2	0.003
CF-PWV, m/s	8.2 ± 2.7	7.0 ± 1.6	0.015
IMT-C, mm	0.6 ± 0.3	0.5 ± 0.2	0.501
ESR, mm/h	27.3 ± 13.8	14.6 ± 6.1	<0.001
CRP, mg/dl	1.7 ± 1.3	0.4 ± 0.3	<0.001
TC, mg/dl	150.1 ± 16.4	142.0 ± 27.2	0.104
LDL-C, mg/dl	96.6 ± 13.2	95.5 ± 24.1	0.787
HDL-C, mg/dl	52.0 ± 13.8	53.8 ± 14.2	0.563
TGs, mg/dl	106.0 ± 29.9	100.3 ± 30.5	0.389
SBP, mmHg	122.1 ± 4.9	121.6 ± 7.1	0.505
DBP, mmHg	65.6 ± 4.8	64.5 ± 5.6	0.189

BMI: Body mass index; VAS: Visual analogue scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CF-PWV: Carotid–femoral pulse wave velocity; IMT-C: Intima-media thickness-carotid; LDL: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; TGs: Triglycerides; TC: Total cholesterol; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

TABLE II. CORRELATION BETWEEN DISEASE ACTIVITY AND CAROTID-FEMORAL PULSE WAVE VELOCITY (CF-PWV), INTIMA-MEDIA THICKNESS-CAROTID (IMT-C) IN PATIENTS WITH ANKYLOSING SPONDYLITIS

	CF-PWV r	IMT-C r
BASDAI	0.675*	0.461**
VAS, cm	0.657*	0.485**
YKL-40, ng/ml	0.773*	0.548*
ESR, mm/h	0.554*	0.376**
CRP, mg/dl	0.607*	0.546*

r=Spearman's correlation coefficients; *P< 0.001; **P< 0.05;
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index;
VAS: Visual analogue scale; ESR: Erythrocyte sedimantation rate;
CRP: C-reactive protein.

fully known. Studies have shown that chronic inflammation significantly contributes to accelerated atherogenesis in AS[17,18]. Arterial stiffness is regarded as a marker of CV risk and can be affected by chronic inflammation[19]. It is important to identify atherosclerosis in the early stages of AS by using biochemical markers and noninvasive assessments, such as YKL-40, CRP, PWV, and IMT-C. Thus, the current study was designed to examine if arterial stiffness measured by CF-PWV and serum YKL-40 levels predicted subclinical CVDs.

Atherosclerosis is caused by lipoprotein infiltration into the intima and is considered to be an inflammatory disease. Previous studies have demonstrated that increased common carotid artery IMT is a good indicator of subclinical stages of atherosclerosis[20,21]. A study by Peters et al., which evaluated subclinical atherosclerosis in AS patients by measuring the IMT-C, demonstrated higher IMT-C values in AS patients than in controls. Additionally, there was an association between IMT-C and CRP or BASDAI in AS patients[22]. Another
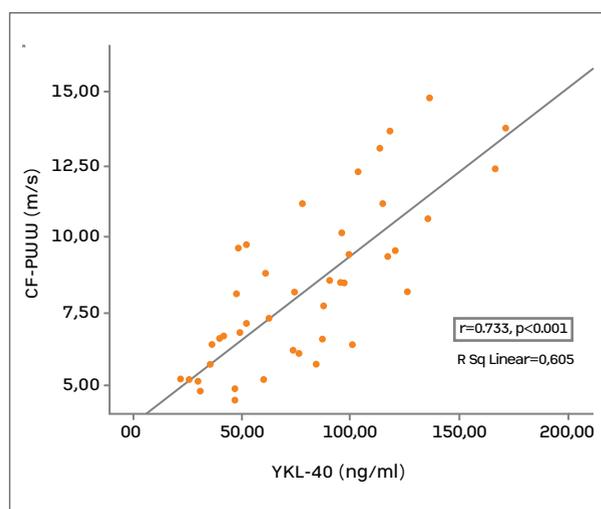
FIGURE 1. Correlation between carotid-femoral pulse wave velocity (CF-PWV) and serum YKL-40 level in patients with ankylosing spondylitis

study demonstrated higher carotid bulb IMT in AS patients than in controls. A correlation between carotid bulb IMT and ESR suggested the possible role of inflammation in accelerating the atherosclerotic process in AS patients. However, there was no correlation between IMT-C and disease activity in the AS patients in this study[23]. A study by Gonzales-Juanatey et al. demonstrated higher IMT-C values in AS patients with no associated cardiovascular risk factors than in controls[14]. However, a study by Capkin et al. revealed that AS patients have higher PWV values but no statistically significant differences in IMT-C levels compared to controls[13]. In another cross-sectional study, the authors demonstrated that IMT-C in young AS patients without clinically evident cardiovascular risk factors did not differ from that in healthy controls[24]. This is consistent with our findings, since we found no differences in IMT-C between AS patients and controls. In this study,

TABLE III. INFLUENCE OF DIFFERENT FACTORS ON CF-PWV IN PATIENTS WITH ANKYLOSING SPONDYLITIS

Dependent variable	Independent variable	B (SE)	Beta	P
CF-PWV, m/s				
Panova <0.001	YKL-40	0.028 (0.011)	0.382	0.013
R^2= 0.728, Adjusted R^2= 0.707	IMT-C	3.585 (1.007)	0.349	0.001

The multivariate backward linear regression model was used for AS patients. P value < 0.05 indicates the presence of regression; Independent variables are as follows: Age, Symptom duration, C-reactive protein, Bath Ankylosing Spondylitis Disease Activity Index, YKL-40, IMT-C;Intima-media thickness-carotid

TABLE IV. COMPARISON OF ANKYLOSING SPONDYLITIS (AS) PATIENTS ACCORDING TO DISEASE ACTIVITY

	AS group with BASDAI<4 (n=23)	AS group with BASDAI≥4 (n=20)	P
Age, years	36.9 ± 10.4	32.0 ± 9.4	0.114
Male/female, n (%)	13/10 (56.5/43.5)	15/5 (75/25)	0.205
Symptom duration, years	11.2 ± 7.6	7.1 ± 5.5	0.051
BMI, kg/m²	24.3 ± 1.8	25.2 ± 2.0	0.136
BASDAI score	2.2 ± 0.9	5.4 ± 1.1	<0.001
VAS, cm	2.9 ± 1.6	7.6 ± 1.4	<0.001
YKL-40, ng/ml	54.1 ± 21.8	107.4 ± 31.9	<0.001
CF-PWV, m/s	6.6 ± 1.6	10.1 ± 2.7	<0.001
IMT-C, mm	0.5 ± 0.3	0.7 ± 0.2	0.008
ESR, mm/h	17.8 ± 8.4	38.2 ± 10.3	<0.001
CRP, mg/dl	0.7 ± 0.5	2.7 ± 1.3	<0.001

BMI: Body mass index; VAS: Visual analogue scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CF-PWV: Carotid–femoral pulse wave velocity; IMT-C: Intima-media thickness-carotid; LDL: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; TGs: Triglycerides; TC: Total cholesterol; ESR: Erythrocyte sedimantation rate; CRP: C-reactive protein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

we also demonstrated that the IMT-C of AS patients was correlated to the indexes of disease activity, such as CRP, ESR, VAS, and BASDAI.

YKL-40 is a new potential biomarker of inflammation and vascular dysfunction in patients with coronary artery disease. It is expressed by local inflammatory cells (such as macrophages, neutrophils, and endothelial and vascular smooth muscle cells) during inflammation[25]. Unlike CRP, which is produced in the liver in response to systemic inflammation, YKL-40 is produced locally at the site of inflammation, suggesting that YKL-40 could be superior to CRP in predicting disease progression and could possibly be used for this purpose[26]. It plays an important role in angiogenesis and remodeling of the extracellular matrix[27,28]. YKL-40 expression has been detected in macrophages and vascular endothelial cells during the early development of atherosclerosis[29]. Recently, several clinical studies have described an association between increased YKL-40 levels and CVDs[30,31]. Previous studies support the idea that soluble biomarkers can predict CVDs in AS[10,32]. In our previous study, we found that YKL-40 levels were higher in patients with early rheumatoid arthritis than in healthy controls[33]. We also observed a strong relationship between YKL-40 levels and the severity of disease activity. In another study, biomarkers of endothelial damage and disease activity were evaluated in AS patients. Serum levels of YKL-40 were increased and weakly associated with radiographic progression[34]. In our study, YKL-40 was correlated with factors related to disease activity indicators such as CRP, ESR, VAS, and BASDAI. Furthermore, YKL-40 levels in AS patients also demonstrated a strong correlation with CF--PWV and IMT-C. Based on our results, we believe that YKL-40 may be a new biomarker of disease activity that can also be used to predict the development of atherosclerosis in patients with AS.

Arterial stiffness, which is assessed by PWV, is important for diagnosing the early stages of atherosclerosis[35]. Many studies have demonstrated higher aortic PWV in patients with inflammatory arthritis[16,36]. Demiralp et al. assessed aortic elasticity and the stiffness index in AS patients without cardiovascular involvement and reported decreased aortic elasticity and an increased aortic stiffness index[37]. In a cohort of AS patients, CVDs risk factors, including blood lipids, hypertension, smoking, diet, and physical inactivity, were evaluated. No differences were demonstrated between AS patients and the general population. The authors suggested that the increased presence of CVDs in AS

may be caused by other factors, such as NSAID use or chronic inflammation[38]. Furthermore, it has been reported that endothelial dysfunction was correlated with the degree of inflammation in AS[39]. In a study by Capkın, which investigated subclinical atherosclerosis by assessing the PWV and IMT-C in AS patients, AS patients were demonstrated to have higher PWV values. However, there were no differences at IMT-C levels between patients with AS and the controls[13]. Their findings are consistent with those in our own study. In the present study, CF-PWV was greater in AS patients than in healthy individuals. In addition, we found a correlation between CF-PWV and YKL-40, ESR, and CRP values, suggesting that inflammation may accelerate the atherosclerotic process in AS patients.

We also performed a multiple regression analysis using CF-PWV as the dependent variable, while the predictors were age, symptom duration, CRP, BASDAI, YKL-40, and IMT-C. The final sample size (43 AS patients) did not allow us to analyze certain predictors, such as traditional cardiovascular risk factors. The results showed that CF-PWV was explained by the model composed of YKL-40 levels and IMT-C. Thus, our results indicate that YKL-40 contributed to explaining subclinical atherosclerosis as assessed by CF-PWV.

A limitation of this study is that there we lacked data regarding prior medication use, such as use of NSAIDs, DMARDs, and anti-TNF. We also cannot fully exclude the possible confounding effects of active disease, such as elevated ESR, CRP, and BASDAI score. Another limitation of our study was the relatively small patient number. Therefore, further research is needed in larger patient populations to confirm our findings.

Since the development of coronary atherosclerosis in patients with AS can occur independently of traditional risk factors, additional markers of coronary artery disease are required. This study showed that serum YKL-40 levels were increased in patients with AS. In addition, we found increased arterial stiffness, as indicated by increased CF-PWV, in AS patients compared to that in controls. Moreover, CF-PWV correlated with IMT-C, which is a reliable indicator of subclinical atherosclerosis. Hence, our results demonstrate that the development of atherosclerosis in AS may be shown by increased arterial stiffness. Additionally, YKL-40 might be used as a screening marker for coronary atherosclerosis in patients with AS because of its correlation with CF-PWV and IMT-C. As a result, we suggest that serum YKL-40 level and CF-PWV may predict early and subclinical atherosclerosis in patients with AS.

CORRESPONDENCE TO

Aysegul Kucukali Turkyilmaz
Recep Tayyip Erdogan University Education and Research Hospital,
Physical Medicine and Rehabilitation Department
E-mail: aysegulkemal@gmail.com

REFERENCES

1. Mathieu S, Joly H, Baron G, et al. Trend towards increased arterial stiffness or intima-media thickness in ankylosing spondylitis patients without clinically evident cardiovascular disease. Rheumatology 2008;47:1203-1207.

2. Lehtinen K. Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. Ann Rheum Dis 1993;52:174-176.

3. Nurmohamed MT, van der Horst-Bruinsma I, Maksymowych WP. Cardiovascular and cerebrovascular disease in ankylosing spondylitis:current insights. Curr Rheumatol Rep 2012;14:415--421.

4. Kullo IJ, Ballantyne CM. Conditional risk factors for atherosclerosis. Mayo Clin Proc 2005;80:219-230.

5. Hahn BH, Grossman J, Chen W, McMahon M. The pathogenesis of atherosclerosis in autoimmune rheumatic disease:roles of inflammation and dyslipidemia. J Autoimmun 2007;28:69-75.

6. Maksimowicz-McKinnon K, Bhatt DL, Calabrese LH. Recent advances in vascular inflammation:C-reactive protein and other inflammatory biomarkers. Curr Opin Rheumatol 2004; 16(1):18-24.

7. Rathcke CN, Vestergaard H. YKL-40, a new inflammatory marker with relation to insülin resistance and with a role in endothelial dysfunction and atherosclerosis. Inflamm Res 2006;55:221-227.

8. Kucur M, Isman FK, Karadag B, et al. Serum YKL-40 levels in patients with coronary artery disease. Coron Artery Dis 2007;18:391-396.

9. Rathcke CN, Vestergaard H. YKL-40 an emerging biomarker in cardiovascular disease and diabetes.Cardiovasc Diabetol 2009;8:61.

10. Pedersen SJ, Hetland ML, Sørensen IJ, et al. Circulating levels of interleukin-6, vascular endothelial growth factor, YKL-40, matrix metalloproteinase-3, and total aggrecan in spondyloarthritis patients during 3 years of treatment with TNFα inhibitors.Clin Rheumatol 2010;29(11):1301-1309.

11. Simon A, Megnien JL, Chironi G. The value of carotid intima-media thickness for predicting cardiovascular risk. Arterioscler Thromb Vasc Biol 2010;30(2):182-185.

12. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27(21):2588-2605.

13. Capkin E, Kiris A, Karkucak M, et al. Investigation of effects of different treatment modalities on structural and functional vessel wall properties in patients with ankylosing spondylitis.Joint Bone Spine 2011;78(4):378-382.

14. Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, et al. The high prevalence of subclinical atherosclerosis in patients with ankylosing spondylitis without clinically evident cardiovascular disease. Medicine (Baltimore) 2009;88(6):358-365.

15. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria.Arthritis Rheum 1984;27 (4):361-368.

16. Capkin E, Karkucak M, Kiris A, et al. Anti-TNF-α therapy may

17. not improve arterial stiffness in patients with AS: a 24-week follow-up. Rheumatology (Oxford) 2012;51(5):910-4.

17. Moyssakis I, Gialafos E, Vassiliou VA, et al. Myocardial performance and aortic elasticity are impaired in patients with ankylosing spondylitis. Scand J Rheumatol 2009;38(3):216-221.

18. Heeneman S, Daeman MJ. Cardiovascular risks in spondyloarthritis. Curr Opin Rheumatol 2007;19:358-362.

19. McEniery CM, Spratt M, Munnery M, et al. An analysis of prospective risk factors for aortic stiffness in men:20-year follow up from the Caerphilly prospective study. Hypertension 2010;56:36-43.

20. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis.Circulation 2007;115(4):459-467.

21. Simons PC, Algra A, Bots ML, et al. Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. The SMART Study (Second Manifestations of ARTerial disease).Circulation 1999;100(9):951-957.

22. Peters MJ, van Eijk IC, Smulders YM, et al. Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis.J Rheumatol 2010;37(1):161-166.

23. Perrotta FM, Scarno A, Carboni A, et al. Assessment of subclinical atherosclerosis in ankylosing spondylitis: correlations with disease activity indices. Reumatismo 2013;65(3):105-112.

24. Choe JY, Lee MY, Rheem I, et al. No differences of carotid intima-media thickness between young patients with ankylosing spondylitis and healthy controls. Joint Bone Spine 2008;75 (5):548-553.

25. Kushner I. The phenomenon of the acute phase response. Ann N Y Acad Sci 1982;389:39-48.

26. Kjaergaard AD, Johansen JS, Bojesen SE, et al. Role of inflammatory marker YKL-40 in the diagnosis, prognosis and cause of cardiovascular and liver diseases. Crit Rev Clin Lab Sci 2016; DOİ:10.1080/10408363.2016.1190683

27. Lee CG, Da Silva CA, Dela Cruz CS, et al. Role of chitin and chitinase/chitinase-like proteins in inflammation, tissue remodeling, and injury. Annu Rev Physiol 2011;73:479-501.

28. Shao R. YKL-40 acts as an angiogenic factor to promote tumor angiogenesis. Front Physiol 2013;4:122.

29. Michelsen AE, Rathcke CN, Skjelland M, et al. Increased YKL-40 expression in patients with carotid atherosclerosis.Atherosclerosis 2010;211(2):589-595.

30. Kastrup J, Johansen JS, Winkel P, et al. High serum YKL-40 concentration is associated with cardiovascular and all-cause mortality in patients with stable coronary artery disease. Eur Heart J 2009;30:1066-1072.

31. Wang Y, Ripa RS, Johansen JS, et al. YKL-40 a new biomarker in patients with acute coronary syndrome or stable coronary artery disease. Scand Cardiovasc J 2008;42:295-302.

32. Azevedo VF, Faria-Neto JR, Stinghen A, et al. IL-8 but not other biomarkers of endothelial damage is associated with disease activity in patients with ankylosing spondylitis without treatment with anti-TNF agents.Rheumatol Int 2013;33(7):1779-1883.

33. Turkyilmaz AK, Devrimsel G, Kirbas A, et al. Relationship between pulse wave velocity and serum YKL-40 level in patients with early rheumatoid arthritis.Rheumatol Int 2013;33(11): 2751-2756.

34. Maksymowych WP, Landewé R, Conner-Spady B, et al. Serum matrix metalloproteinase 3 is an independent predictor of structural damage progression in patients with ankylosing spondyli-

tis. Arthritis Rheum 2007;56:1846-1853.

35. Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor?Am J Epidemiol 1994;140(8):669-682.

36. Maki-Petaja KM, Hall FC, Booth AD, et al. Rheumatoid arthritis is associated with increased aortic pulse wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. Circulation 2006;12;1185-1192.

37. Demiralp E, Kardesoglu E, Kiralp MZ, et al. Aortic elasticity in patients with ankylosing spondylitis.Acta Cardiol 2004;59(6):630-634.

38. Sundström B, Johansson G, Johansson I, et al.Modifiable cardiovascular risk factors in patients with ankylosing spondylitis. Clin Rheumatol 2014;33(1):111-117.

39. Peters MJ, Visman I, Nielen MM, et al. Ankylosing spondylitis: a risk factor for myocardial infarction?Ann Rheum Dis 2010;69(3):579-581.