

Is heart-type fatty acid binding protein (H-FABP) a valid marker of arterial stiffness in patients with systemic sclerosis?

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Ethics Committee Approval

Ethics approval was taken from the Selçuk University Non-Invasive Ethics Committee dated 06.01.2015 and meeting number 2015/1.

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest

No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Both micro- and macro-vascular involvement has been researched in systemic sclerosis (SSc) for many years. In this study, the relationship of arterial stiffness with heart-type fatty acid binding protein (h-FABP), which is well-accepted as a cardiac marker, was investigated for the first time.

Methods: In this case-control study, 40 patients diagnosed with SSc between the ages of 18 and 65 were included. Thirty healthy individuals of similar age and gender were included as the control group. Patients were excluded from the study if they had cardiovascular risk factors, active infections, and/or malignancies. Along with detecting biochemical markers in the blood, results from methods, such as 24-h blood pressure Holter recordings, pulse-wave velocities (PWV), and echocardiograms (ECHO) were obtained from patients.

Results: The homocysteine mean level was higher in the patient group than in the control group ($P < 0.001$). H-FABP and asymmetric dimethylarginine (ADMA) means were similar between the two groups ($P = 0.286$ and $P = 0.340$, respectively). Vascular parameters, including mean arterial pressure (MAP), augmentation index normalized to the 75 /min heart rate (AIx @ 75), and PWV were also similar between the two groups ($P = 0.498$, $P = 0.382$ and $P = 0.180$, respectively).

Conclusion: It can be concluded that no ongoing myocardial damage occurs based on normotensive Holter findings, normal h-FABP levels, and ECHO findings in our patients. It is suggested that vasodilatory treatments, such as pentoxifylline and calcium channel blockers, which the patients receive for SSc treatment due to Raynaud Syndrome, may protect them from hypertension and therefore offer protection from myocardial damage.

Keywords: Systemic sclerosis, Heart fatty acid binding protein, Arterial stiffness, Pulse wave velocity, Homocysteine

Introduction

Systemic sclerosis (SSc) is a chronic, autoimmune, multisystemic connective tissue disease of unknown etiology. SSc is characterized by functional and structural abnormalities in small blood vessels and progressive fibrosis in the skin and internal organs [1]. Other than microvascular involvement, SSc has also been recently associated with macrovascular disease [2], endothelial dysfunction, and increased arterial stiffness [3, 4]. Measurements of arterial tension and stiffness are the most important parameters in assessment of endothelial dysfunction and early atherosclerosis in patients with systemic autoimmune disease [5]. Asymmetric dimethylarginine (ADMA), a nitric oxide synthase inhibitor, is a specific marker of cardiovascular pathologies in chronic inflammatory diseases. Significantly elevated ADMA levels are considered to be an indicator of endothelial dysfunction and impaired coronary microcirculation. Heart-type fatty acid binding protein (h-FABP) is a cytoplasmic protein responsible for the intracellular transport of free fatty acids in cardiomyocytes. It has been observed that a significant relationship between carotid-femoral pulse-wave velocities (PWV) and h-FABP levels [6] exists, and this relationship has been shown to be a useful predictor for cardiovascular events in patients with stable coronary artery disease [7]. Furthermore, h-FABP appears to be a useful marker in deaths not only due to cardiovascular causes in the general population but also in deaths associated with all other causes [8]. Homocysteine is an amino acid containing a sulfhydryl group and is a component of the normal methionine and cysteine amino acid biosynthetic pathways. Homocysteine is known as an independent risk factor for atherosclerosis [9] and is associated with cardiovascular disease (CVD) [10].

Impaired coronary microcirculation, macrovascular involvement, and subclinical atherosclerosis have been demonstrated in some SSc patients who do not have CVD [11].

The aim of this study was to detect the early association of arterial stiffness in SSc patients with changes in biochemical markers, such as h-FABP, ADMA, and homocysteine in addition to methods, such as 24-h blood pressure values, Holter recordings, PWVs, and ECHO results.

Materials and methods

This study was performed as a case-control study in patients who presented to our Internal Medicine/Rheumatology outpatient clinic. Patients were evaluated by the cardiology department of our facility for cardiovascular involvement based on 24-h Holter and transthoracic ECHO results. The study was initiated after the approval of Selçuk University Non-Invasive Ethics Committee dated 06.01.2015 and meeting number 2015/1.

Inclusion criteria

Thirty-eight females and two male patients who were diagnosed with SSc between the ages of 18 and 65 and met the disease diagnosis requirement of a total score of 9 and above according to the 2013 ACR/EULAR Scleroderma Classification Criteria were included in the study. Forty patients met the study inclusion criteria. Thirty healthy individuals with similar ages and genders were included as the control group.

Exclusion criteria

Patients were excluded from the study if they had one or more of several conditions: (1) cardiovascular risk factors (coronary artery, cerebrovascular and/or peripheral arterial disease history, diabetes mellitus, hypertension, and/or obesity), active infections, and/or malignancies. Healthy controls also had no systemic disease and no signs of an acute or chronic infection.

Clinical and laboratory investigations

H-FABP, ADMA, and homocysteine levels were obtained in the biochemistry laboratory from the remaining 2 cc of the biochemistry blood taken during routine blood sampling.

MyBioSource (Lot06/2015; Cat no: MBS020502) enzyme-linked immunosorbent assay (ELISA) kit was used for the h-FABP test.

For ADMA, symmetrical dimethylarginine (SDMA), L-monomethylarginine (LMMA), arginine, and citrulline analyses, pre-prepared plasma samples were dissolved at room temperature. The ABSCIEX API 3200 High Performance Liquid Chromatography (HPLC) device in the Medicine Biochemistry Laboratory of our faculty was used in a positive mode based on electrospray ion source (ESI) using PhenomenexLuna 50x4.6,5µ C18 HPLC column to analyze the samples.

For homocysteine, after dissolving pre-prepared plasma samples at room temperature, the samples were analyzed in positive mode using ESI at ABSCIEX API 3200 triple quadrupole mass spectrometer (Canada) device at our faculty hospital.

Ambulatory blood pressure monitoring and arterial stiffness monitoring were performed using an oscillometric type Mobile O Graph NG (IEM GmbHStolberg, Germany) device that measures blood pressure within desired intervals as number of pulses per minute in addition to measuring arterial stiffness parameters, including augmentation pressure, augmentation index, pulse pressure, and PWV. Blood pressure measurements were obtained from both arms. If the difference of the measurements between the two arms was not more than 10 mmHg, the cuff was placed on the non-dominant arm. If the difference was more than 10 mmHg, the cuff was placed on the arm that yielded the higher value. The patients were informed about the procedure and the device, and they were told to perform their daily activities while keeping the arm with the cuff at the level of the heart during the measurements. The sleep period was determined as between 24:00 at night and 8:00 in the morning.

ECHO examination was performed using the Vivid E9 ultrasound system (General Electric, Ultrasound AS, Horten, Norway) possessing a 1.5-4.6 MHz transducer system. Measurements were obtained from the left lateral decubitus position from the standard parasternal long axis, short axis, and apical two and four chamber windows. All patients underwent standard two-dimensional (2D) and colored Doppler ECHO examinations. Septum and posterior wall thickness of the left ventricle, diastolic and end-diastolic diameters, and left atrium and aorta diameters were measured from the parasternal long-axis window. The left ventricular injection fraction was calculated from the apical four chamber and two chamber images by averaging the ejection fractions obtained by the modified Simpson method.

Statistical analysis

The statistical analysis of the data was performed by using SPSS version 22.0 (SPSS Inc. Chicago, IL, USA) and Microsoft Office Excel version 2010. One sample Kolmogorov–Smirnov Test was used for the compatibility of the data to normal distribution. A Student's t-, Mann–Whitney U, chi-squared, Fisher's exact, and Spearman's and Pearson's correlation tests were used for comparison of the data. A *P*-value of < 0.05 was accepted as statistically significant. Epi Info software was used to calculate the sample size. The minimum sample size was 15 participants at the level of $\alpha = 0.05$ with 95% power.

Results

A total of 70 participants, including 40 (38 women, two men) patients and 30 (29 women, one man) control subjects, were enrolled in our study. The mean age of the patient group was 47.40 (9.91), and the mean age of the control group was 44.83 (9.53).

Evaluating the disease duration of the patients, the average duration of the disease was 6.03 (5.118). The shortest disease duration was one year, and the longest was 20 years.

The mean homocysteine level was 12.43 $\mu\text{mol/L}$ (8.94) in the patient group and 7.01 $\mu\text{mol/L}$ (3.99) in the control group. Homocysteine and C-reactive protein (CRP) levels were higher in the patient group than the control group ($P < 0.001$ and $P < 0.001$ respectively). The mean h-FABP in the patient group was 8.68 ng/ml (5.77) and 7.15 ng/ml (5.98) in the control group. The mean h-FABP and ADMA levels were similar between two groups ($P = 0.286$ and $P = 0.340$ respectively). Biochemistry data of the patient and control groups are summarized in Table 1.

Table 1: Comparison of biochemistry data in patient and control groups

Parameters	Patient		Control		<i>P</i> -value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
WBC (K/uL)	7.27 (2.77)	7.00 (1.52)	7.00 (1.52)	0.632	
NE (K/uL)	4.65 (2.26)	3.78 (1.09)	3.78 (1.09)	0.038	
LY (K/uL)	1.80 (0.77)	2.46 (0.69)	2.46 (0.69)	0.001	
Hg (g/dL)	12.59 (1.34)	13.23 (1.12)	13.23 (1.12)	0.036	
PLT (K/uL)	264.73 (59.61)	267.33 (69.68)	267.33 (69.68)	0.867	
UT LC (HPF)	5.95 (20.84)	1.57 (5.34)	1.57 (5.34)	0.088*	
ESR (m/h)	28.05 (18.98)	17.10 (9.94)	17.10 (9.94)	0.003	
Creatinine (mg/dL)	0.70 (0.12)	0.68 (0.07)	0.68 (0.07)	0.479	
ALT (u/L)	14.80 (6.97)	21.43 (14.18)	21.43 (14.18)	0.023	
Uric Acid (mg/dL)	4.73 (1.56)	4.43 (0.91)	4.43 (0.91)	0.363	
Hcy (umol/L)	12.43 (8.94)	7.01 (3.99)	7.01 (3.99)	<0.001*	
CRP (mg/L)	8.33 (10.83)	3.42 (0.74)	3.42 (0.74)	<0.001*	
Glucose (mg/dL)	97.30 (17.96)	96.57 (12.22)	96.57 (12.22)	0.848	
h-FABP (ng/ml)	8.68 (5.77)	7.15 (5.98)	7.15 (5.98)	0.286	
ADMA ($\mu\text{mol/L}$)	0.37 (0.18)	0.33 (0.15)	0.33 (0.15)	0.340	
Arginine ($\mu\text{mol/L}$)	246.18 (76.53)	233.95 (81.01)	233.95 (81.01)	0.521	
Arginine /ADMA ratio	736.17 (263.83)	761.44 (224.04)	761.44 (224.04)	0.674	
Citrulline ($\mu\text{mol/L}$)	11.49 (5.16)	16.88 (8.83)	16.88 (8.83)	0.001*	
Citrulline/Arginine ratio	0.05 (0.03)	0.07 (0.03)	0.07 (0.03)	0.001	
SDMA ($\mu\text{mol/L}$)	0.41 (0.16)	0.32 (0.14)	0.32 (0.14)	0.029	
L-NMMA ($\mu\text{mol/L}$)	0.54 (0.29)	0.44 (0.20)	0.44 (0.20)	0.102	

* Mann–Whitney U Test, in comparison of other tests, Student's t-test was used. WBC: White blood cell, NE: Neutrophil, LY: Lymphocyte, Hg: Hemoglobin, Plt: Platelet, UT LC: Leukocyte count in urine test, ALT: Alanine aminotransferase, ESR: Erythrocyte sedimentation rate, Hcy: Homocysteine, CRP: C-reactive protein, h-FABP: Heart type fatty acid binding protein, ADMA: Asymmetric dimethylarginine, SDMA: Symmetric dimethylarginine, L-NMMA: L-monomethylarginine

The mean arterial pressure (MAP) in the patient group was 88.68 mmHg (12.04) and 90.40 mmHg (7.95) in the control group. AIx@75 was detected as 28.52% (6.50%) in the patient group and 26.96% (6.59%) in the control group. PWV was determined as 6.75 (1.26) m/s in the patient group and 6.37 (1.00) m/s in the control group. No differences between the patient and control groups in terms of MAP, augmentation index normalized to 75 /min heart rate (AIx@75), and PWV ($P = 0.498$, $P = 0.328$, and $P = 0.180$ respectively) were detected. Twenty-four hour blood pressure Holter and ECHO data for

patient and control groups are summarized in Table 2. Table 3 summarizes the medications used by patients in our study.

Table 2: Comparison of echocardiography and 24-h Holter data from the patient and control groups

Parameters	Patient		Control		<i>P</i> -value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
EDD (mm)	45.53 (3.22)	44.63 (3.38)	44.63 (3.38)	0.265	
ESD (mm)	28.98 (2.84)	28.43 (3.60)	28.43 (3.60)	0.484	
PWDT (mm)	8.60 (1.78)	8.67 (1.32)	8.67 (1.32)	0.864	
IVSDT (mm)	8.70 (1.91)	9.03 (1.22)	9.03 (1.22)	0.406	
EF (%)	65.48 (3.45)	67.37 (5.37)	67.37 (5.37)	0.078	
LAD (cm)	3.24 (0.43)	3.20 (0.38)	3.20 (0.38)	0.748	
PAP (mmHg)	24.23 (4.90)	23.60 (3.78)	23.60 (3.78)	0.564	
SIS (mmHg)	113.58 (14.65)	113.30 (9.21)	113.30 (9.21)	0.348*	
DIA (mmHg)	68.28 (10.49)	71.47 (7.34)	71.47 (7.34)	0.159	
MAP (mmHg)	88.68 (12.04)	90.40 (7.95)	90.40 (7.95)	0.498	
PR (1/min)	80.13 (11.32)	76.17 (14.33)	76.17 (14.33)	0.201	
PP (mmHg)	44.83 (7.85)	41.90 (5.86)	41.90 (5.86)	0.091	
MSBP (mmHg)	103.95 (14.10)	105.87 (9.11)	105.87 (9.11)	0.518	
MDBP (mmHg)	69.80 (10.92)	72.40 (7.34)	72.40 (7.34)	0.264	
AIx@75 (%)	28.52 (6.50)	26.96 (6.59)	26.96 (6.59)	0.328	
PWV (m/s)	6.75 (1.26)	6.37 (1.00)	6.37 (1.00)	0.180	

* Mann–Whitney U Test, in comparison of other tests, Student's t-test was used. EDD: End-diastolic diameter, ESD: End-systolic diameter, PWDT: Posterior wall diastolic thickness, IVSDT: Interventricular septum diastolic thickness, EF: Ejection fraction, LAD: Left atrium diameter, PAP: Pulmonary artery pressure, SIS: Systolic pressure, DIA: Diastolic pressure, MAP: Mean arterial pressure, PR: Pulse rate, PP: Pulse Pressure, MSBP: Mid-systolic blood pressure, MDBP: Mid-diastolic blood pressure, AIx@75: Aortic augmentation index corrected for a heart rate of 75 bpm, PWV: Pulse wave velocity

Table 3: Percentages and types of drugs used in the patient group

Parameters	Drugs	
	Non-Users n (%)	Users n (%)
Pentoxifylline	5 (12.5)	35 (87.5)
Calcium channel blocker	18 (45)	22 (55)
Methotrexate	37 (92.5)	3 (7.5)
Hydroxychloroquine	10 (25)	30 (75)
NSAID	38 (95)	2 (5)
Cyc C	35 (87.5)	5 (12.5)
Cyc P	21 (52.5)	19 (47.5)
Azathioprine	25 (62.5)	15 (37.5)
Corticosteroids	26 (65)	14 (35)
Acetylsalicylic acid	6 (15)	34 (85)
IV PG C	38 (95)	2 (5)
IV PG P	38 (95)	2 (5)

NSAID: Non-steroidal anti-inflammatory drug, Cyc C: Receiving cyclophosphamide treatment currently, Cyc P: Cyclophosphamide treatment in the past, IV PG C: Receiving intravenous prostaglandin treatment currently, IV PG P: Intravenous prostaglandin treatment in the past

Discussion

In this study, we examined arterial stiffness in SSC patients without cardiovascular risk factors by obtaining measurements of ADMA, homocysteine, and h-FABP levels, which are considered to be associated with arterial stiffness. We aimed to determine the association of the PWV and AIx@75 values used to evaluate arterial stiffness with these parameters.

No differences between the patient and control groups in terms of AIx and PWV were found. Some miscellaneous studies in the literature state PWV, AIx and other arterial stiffness methods and markers did not differ between patients and control groups in different rheumatological conditions, including SSC, in addition to studies reporting that these differs significantly [12–14]. These conflicting data in the literature may have different causes. In our study, most patients were receiving vasodilator treatments, such as pentoxifylline (87.5%) and calcium channel blockers (55%), which cause an increase in aortic distensibility [15]. In addition, differences in methods used for arterial stiffness measurements can occur for other reasons. Our Holter device only had the capability of obtaining measurements from the upper arm. In various studies, it has been shown that SSC may only affect distal small vessels rather than large vessels [16], at least during the early course of the disease [17]. Hydroxychloroquine was being taken by 75% of our patients, and this drug may have positive effects on atherosclerosis, arterial stiffness, and lipid profiles in different patient groups [18]. Besides, functional and structural vascular

abnormalities in different rheumatological diseases may respond differently to vasodilator treatments, such as calcium channel blockers [19].

Homocysteine, which is known to have a strong relationship with arterial stiffness [20, 21], was found to be significantly higher in SSc patients compared to the control group in our study.

H-FABP values, which are accepted as a sensitive marker of myocardial injury [22], did not differ between SSc patients and the control group in our study. The main reason for this result may be related to an increase in h-FABP under conditions that cause damage to the vascular endothelium rather than conditions that cause functional effects to the vascular endothelium [6, 23]. Although molecular markers in our patients that prove the presence of arterial stiffness were found, it can be concluded that no ongoing myocardial damage was occurring based on normotensive Holter findings, normal h-FABP levels, and ECHO findings. Consequently, it can be thought that vasodilator treatments, such as pentoxifylline and calcium channel blockers, which the patients take as part of their SSc treatment due to Raynaud Syndrome, may protect them from hypertension and therefore offer protection from myocardial damage. However, the available data on this issue are insufficient and further studies are needed.

Limitations

The most important limitation of our study was the lack of measurements from other non-invasive and invasive methods (such as carotid intima-media thickness, flow- and nitrate-mediated vasodilation, and angiography), which are useful methods for demonstrating arterial stiffness.

Conclusion

SSc shows an increased risk of atherosclerosis, independent of traditional cardiovascular risk factors. Therefore, careful follow-up of SSc patients is also required with regard to CVD.

Therapeutic agents, such as calcium channel blockers, pentoxifylline, and hydroxychloroquine, which SSc patients use for their SSc treatment due to Raynaud Syndrome, may also have a positive effect on arterial stiffness due to their positive effects on blood pressure and lipid profiles.

More studies are needed to demonstrate both the relationship of H-FABP with arterial stiffness and its importance as a marker of myocardial damage in SSc patients.

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