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ORIGINAL ARTICLE PEDIATRICS

The relationship between *Brucella* infection and aortic stiffness in children

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ABSTRACT

OBJECTIVE: In this study, it was aimed to show whether *Brucella* infection, which causes various cardiovascular complications in children, can lead to an increase in aortic stiffness with a noninvasive method, echocardiography.

METHODS: Children who were diagnosed with *Brucella* infection and who had tachycardia, chest pain and murmur that were not related to body temperature increase during the treatment were evaluated cardiologically and had echocardiographic examination, were included in the study. Aortic strain, aortic distensibility measurement results and aortic stiffness index of the patients in the patient and control groups were calculated.

RESULTS: Our study included 53 cases with a mean age of 11.43±4.13 years in the patient group and 68 cases with a mean age of 10.16±3.61 years in the control group. We found that systolic blood pressure was lower in the patient group than in the control group (p=0.014). In the analysis of laboratory parameters, blood glucose level was found to be significantly higher in the patient group (p=0.001). In the statistical evaluation of aortic strain, aortic stiffness index and aortic distensibility measurement results between the patient and control groups, no statistically significant difference was found between the groups (p=0.287, p=0.784, p=0.208).

CONCLUSION: In our study, where we tried to show a new parameter that could contribute to the increase in aortic stiffness, the results showed that *Brucella* infection was not a factor that increased aortic stiffness in the pediatric age group.

Keywords: Aortic stiffness; brucellosis; children; infection.

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Brucellosis is one of the most common zoonotic diseases around the world. *Brucella* infection affects a large number of people every year and continues to be an important public health problem for Turkey, Mediterranean Basin, Asia, Africa, South America, Eastern Europe and Middle East countries. *Brucella* bacteria are small, nonmotile, gram-negative coccobacilli [1]. *Brucella* infection is mainly transmitted through contact with infected animals and their products, consumption of raw or unpasteurized foods of animal origin, and inhalation of aerosols. In the clinical course of *Brucella* infection, acute infection, subacute infection, and chronic infection can be seen [2]. *Brucella* infection is a multisystemic disease, and central nervous system and cardiovascular system involvement are among the most serious complications of *Brucella* infection. Childhood cases constitute 20–30% of Brucellosis cases [3, 4]. Cardiovascular system involvement is seen in 2% of *Brucella* infections. It

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most commonly causes endocarditis [5]. Like other infections, *Brucella* infection leads to endothelial dysfunction. The cause of cardiovascular complications in *Brucella* infection may be dysfunction of endothelial cells and increased inflammatory response [6].

Studies have shown that an increase in aortic stiffness, which means a decrease in the elasticity of the aorta or loss in its ability to respond to pressure changes, is associated with diffuse atherosclerosis. In addition, studies have shown that many different vascular diseases are associated with increased aortic stiffness, and it has been stated that increased aortic stiffness is a risk factor for cardiovascular diseases [7–9]. Atherosclerosis, one of the most important causes of cardiovascular diseases, begins to develop in the pediatric age group. Studies have reported that many acute and chronic infectious agents may be responsible for the pathophysiology of atherosclerosis [10].

Although it is stated that cardiovascular disease risk factors are associated with increased aortic stiffness in the pediatric age group, the possible mechanisms contributing to the increase in aortic stiffness have not been fully understood today. It has been reported in studies that endothelial dysfunction, which may result from bacterial infection, mechanical damage, hyperinflammation, and autoantibodies, is associated with arterial stiffness and atherosclerosis [11, 12]. Many studies have investigated the relationship between human immunodeficiency virus (HIV) infection, *cytomegalovirus* (CMV) infection, Chagas disease, coronavirus 2019 disease (COVID-19) and aortic stiffness [13–16]. Except for the study conducted by Togan et al. [6] on adults investigating the relationship between *Brucella* infection and arterial stiffness, no study was found.

Our aim in this study is to contribute to the literature by investigating whether *Brucella* infection, which is endemic in our region and can cause serious complications in the cardiovascular system, affects aortic stiffness, a new parameter with high predictive value for the development of cardiovascular diseases, in children.

Highlight key points

- *Brucella* infection is a multisystemic disease and cardiovascular system involvement is among the life-threatening complications of *Brucella* infection.
- Aortic stiffness is associated with diffuse atherosclerosis.
- Although the relationship between the development of atherosclerosis and *Brucella* infection in adults has been determined, this relationship has not been shown in children.
- It is not known whether *Brucella* infection affects aortic stiffness in children or not.

MATERIALS AND METHODS

Study Population

In our study, 162 cases who were followed up and treated for *Brucella* infection by the Pediatric Infection Clinic of a 3rd Stage Training and Research Hospital between 01 July 2020-01 July 2021 were included. The clinical findings, laboratory and echocardiographic parameters of the cases were obtained by retrospective analysis of the files.

53 Brucellosis cases who were followed up by the pediatric infection clinic due to *Brucella* infection, but who had tachycardia, chest pain and murmur that were not related to body temperature increase during the treatment, were evaluated cardiologically and had echocardiography, were included in the study. 109 cases were excluded from the study. Due to the lack of cardiological evaluation. Children with any concomitant chronic inflammatory disease, endocrinological disease (including familial hyperlipidemia, diabetes), rheumatic disease, chronic renal failure or any other infectious disease were not included in the study.

As the control group, 68 patients who applied to the pediatric cardiology outpatient clinic of our hospital, whose laboratory and echocardiographic results could be accessed, and who did not have any cardiological disease as a result of the evaluation, were included. Body weights, heights, body mass indexes (BMI), systolic and diastolic blood pressures of the patient and control groups were recorded.

Laboratory Analysis

Blood culture and/or standard tube agglutination test were performed in cases with symptoms and signs suggestive of *Brucella* infection. Sero positivity in the standard tube agglutination test was defined as a standard tube agglutination titer of 1/160 or higher. Agglutination at a titer of 1/160 and above, together with clinical findings, was considered positive for *Brucella* infection. Glucose, leukocyte count, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP) level, total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride (TG), low-density lipoprotein (LDL)-cholesterol were saved in the patient and control groups.

Echocardiographic Measurement

Echocardiographic Evaluation of Aortic Stiffness

Echocardiographic measurements were performed in 53 cases diagnosed with acute bucella infection and undergone cardiological evaluation, during the acute infection period and in 68 cases included in the control group, under the control of the pediatric cardiology outpatient clinic. All echocardiographic measurements were made by a single physician with the Vivid 5S (General Electric Medical Systems) device. In addition to standard measurements, aortic distensibility was also measured to show the increase in aortic stiffness. In transthoracic echocardiography, M-mode measurements were made 3 cm distal to the aortic valve in parasternal long-axis view (Fig. 1). Simultaneously, the patient's brachial blood pressure arterial measurements were recorded. Pulse pressure was calculated by subtracting blood pressure. Aortic strain, aortic distensibility and aortic stiffness index were used as aortic stiffness parameters.

Calculation of Aortic Strain, Aortic Stiffness, and Aortic Distensibility

Aortic stiffness parameters were calculated according to the following formulas [7].

Aortic Strain (%)=100x(Systolic Diameter- Diastolic Diameter)/ Diastolic Diameter

Aortic Distensibility (cm^2/dyn2)=2x(Aortic Strain)/(Systolic Blood Pressure-Diastolic Blood Pressure)

Aortic Stiffness Index=Ln(Systolic Blood Pressure/Diastolic Blood Pressure)/(Aortic Strain)

(Ln=natural logarithm)

Statistical Analysis

The data obtained in the study were evaluated with the SPSS (IBM, Version 21.0, Chicago, IL) package program. Categorical data were expressed as numbers (%) and compared with the chi-square test. The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Continuous data that did not show a normal distribution were shown as median (minimum and maximum) and compared with the Mann-Whitney U test. For the statistical significance level, $p<0.05$ was accepted.

Ethics

Ethics approval for the conduct of the study was obtained from the Adiyaman University Clinical Research Ethics Committee (date: 16.11.2021, number: 2021/09-08).

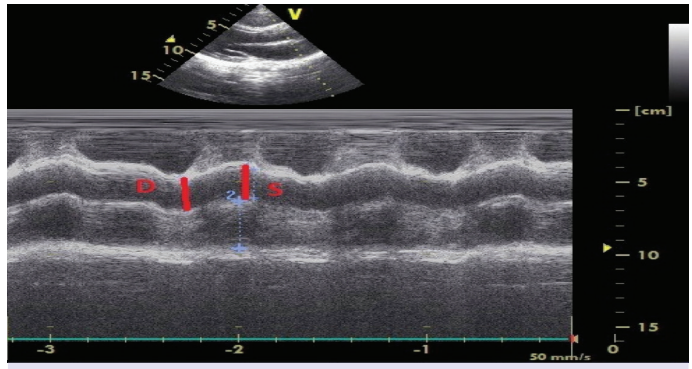

Figure 1. M mode transthoracic echocardiography view of systolic-diastolic diameters of the ascending aorta.

Table 1. Laboratory parameters by groups

Laboratory parameters	Patient group (n=53)	Control group (n=68)	p
Leukocyte ccount (10^3/uL)	7336±2494	6523±2674	0.090
Glucose (mg/dL)	95.21±11.78	86.7±15.1	**0.001**
ESR	6.00 (2-43)	7.00 (1-25)	0.393
CRP (mg/dL)	0.00 (0-24)	0.00 (0-9)	0.195
Total cholesterol (mg/dL)	157.74±30.11	160.10±31.32	0.677
LDL (mg/dL)	89.58±28.11	91.14±26.07	0.753
HDL (mg/dL)	48.81±13.93	49.13±17.07	0.912
TG (mg/dL)	96.75±27.28	99.13±33.41	0.675

ESR: Erythrocyte sedimentation rate; CRP: C-Reactive protein level; LDL: Low density lipoprotein; HDL: High density lipoprotein; TG: Triglyceride.

RESULTS

In our study, there were 53 cases, 62.3% (33) male, 37.7% (20) female, with a mean age of 11.43±4.13 years in the patient group, and 68 cases 60.2% (41) male, 39.8% (27) female, with a mean age of 10.16±3.61 years in the control group were included. No statistically significant difference was found between the patient and control groups in terms of age and gender (p=0.075, p=0.825).

Mean height was 144.28±21.39 cm, mean weight was 38.28 ±13.60 kg in the patient group, mean height was 138.45±21.54 cm, mean weight was 37.68 ±16.23 kg in the control group, BMI was 17.67±2.78 in the patient group and 18.61±3.49 in the control group. In the statistical evaluation made between the patient and control groups in terms of height, mean weight and BMI, no statistically significant difference was found between the groups (p=0.141, p=0.830, p=0.112).

TABLE 2. Echocardiographic measurement results and blood pressures by groups

Echocardiographic measurements	Patient group (n=53)	Control group (n=68)	p
Left ventricular diastole diameter	39.64±5.76	39.38±6.62	0.822
Left ventricular systole diameter	24.52±4.24	24.45±5.07	0.934
Ejection fraction	69.11±8.63	68.76±7.91	0.818
Aortic systole diameter	20.98±4.35	19.66±3.61	0.071
Aortic diastole diameter	17.92±4.45	17.07±3.47	0.240
Systolic blood pressure	108.12±9.81	112.72±10.18	**0.014**
Diastolic blood pressure	63.03±8.55	65.00±8.35	0.207
Pulse pressure	45.09±7.04	47.72±9.75	0.101
Aortic strain	12.50 (3.70–58.82)	14.60 (3.70–50.0)	0.794
Aortic stiffness index	2.60±0.84	2.55±0.75	0.784
Aortic distensibility	0.45 (0.15–2.60)	0.65 (0.14–2.70)	0.640

The laboratory parameters of the patient and control groups are given in Table 1. When the laboratory parameters of the patient group were compared with the control group, blood glucose levels were higher in the patient group. A statistically significant difference was found between the groups in the statistical evaluation (p=0.001).

Aortic stiffness parameters of the patient and control groups and other echocardiographic parameters are given in Table 2. A statistically significant difference was not found between the groups in terms of aortic strain, aortic stiffness index and aortic distensibility (p=0.794, p=0.784, p=0.640). When the patient group was compared with the control group in terms of analysis results of aortic parameters and other echocardiographic parameters, systolic blood pressure was found to be lower in the patient group. A statistically significant difference was found between the groups in the statistical evaluation (p=0.014).

DISCUSSION

Brucellosis remains a significant health threat in many countries. The most important way to transmission of *Brucella* infection is the consumption of raw or unpasteurized animal products [17]. In our study, all of the cases had consumption of unpasteurized animal products. Brucellosis is more common in males, and 60% of cases are between the ages of 13–40 years [18]. Ciftdogan and Aslan [19] and Lu et al. [20] reported that *Brucella* infection is more common in males, Dean et al. [2] and Colmenero et al. [4] reported that cardiovascular complications of *Brucella* infection were more common in males. In our study, 37.7% (20) of the cases were girls and 62.3% (33) of the cases were boys in the patient group, 60.2% (41) were boys and 39.8% (27) were girls in the control group, which was consistent with the literature.

In *Brucella* infection, chronic disease is rare in the pediatric age group [2, 21]. In our study, all of the cases were followed up in terms of acute *Brucella* infection. There was no case diagnosed as chronic *Brucella* infection.

Brucella infection can lead to multiple systems involvement and the clinical picture may be variable in children. It is known that the activation of the endothelial system due to inflammatory changes in *Brucella* infection is effective in the formation of complications related to the cardiovascular system. In the pathogenesis of the changes in the cardiovascular system, both this increased inflammatory response and the immunological reactions secondary to the infection in the vessel wall lie [22, 23]. In the cardiovascular system most commonly causes endocarditis and the aortic valve is affected. In addition, myocarditis, pericarditis, endarteritis, arterial and venous thrombosis, cutaneous vasculitis and peripheral and cerebral aneurysms are cardiovascular complications that may develop due to *Brucella* infection [5, 24, 25].

The studies reported that the increase in aortic stiffness is associated with diffuse atherosclerosis, and it has been shown in studies that chronologically, there is an increase in aortic stiffness first, followed by hypertension, and that hypertension causes atherosclerosis [13, 14, 26, 27]. Atherosclerosis, one of the most important causes of cardiovascular diseases, begins to develop in

the pediatric age group. Risk factors for the development of atherosclerosis such as advanced age, sex and heredity, lipid metabolism disorders, high blood pressure, sedentary lifestyle and high blood sugar have been defined. In addition to these risk factors, some viral infections such as CMV, *Epstein-Barr virus* (EBV), *HIV*, *herpes simplex viruses* (HSV-1 and HSV-2), *Helicobacter pylori* (*H. pylori*) and *hepatitis viruses* have also been shown to be associated with atherosclerosis [13, 14, 26–30]. Chukkapalli et al. [31] and Velsko et al. [32] demonstrated the presence of bacterial or viral pathogens in atherosclerotic plaques. The relationship between *Brucella* infection and the development of atherosclerosis was reported by Togan et al. [33] and Karahocagil et al. [34]. It has been shown that infections constitute a risk factor for atherosclerosis and contribute to the chronic inflammatory process through direct or indirect effects [13, 14, 26–30]. In addition, in the study of Gursoy et al. [35], it was shown that endothelial functions are impaired in patients with Brucellosis.

Aortic stiffness in adulthood is partially predicted by risk factors for cardiovascular diseases such as metabolic syndrome in childhood, physical activity, diet, and smoking. However, the relationship of childhood aortic stiffness to adult aortic stiffness is unknown [36, 37]. It has been reported in studies that endothelial dysfunction, which may result from bacterial infections, mechanical damage, hyperinflammation, and autoantibodies, is associated with arterial stiffness and atherosclerosis [10, 11]. When the literature is examined, there are many studies showing the relationship between arterial stiffness and human immunodeficiency virus (HIV) infection, *cytomegalovirus* (CMV) infection, Chagas infection and COVID-19. However, there was no study other than the study by Togan et al. [6], which showed the relationship between *Brucella* infection and aortic stiffness [13–16].

As the parameters affecting aortic stiffness; body mass index, gender, height, race, diabetes mellitus, chronic inflammatory diseases, high blood pressure, and dyslipidemia were stated [36, 37]. In our study, patients with a history of chronic disease and/or different races were not included in order to exclude other parameters that may affect aortic stiffness. In addition, there was also no statistically significant difference between the groups in terms of height, gender or BMI. In the literature review, it is reported that high blood pressure is one of the factors that increases aortic stiffness [38]. When the blood pressures of the patient and control groups were evaluated in our study, systolic blood pressure was found to be lower in the patient group compared to the control group, but none of the patients from both groups had hyper or hypotension.

The laboratory parameters of the patient and control groups are given in Table 1. When the literature is reviewed, it has been reported that insulin resistance and/or diabetes mellitus, high blood cholesterol level, and systemic inflammation are important factors associated with or increasing aortic stiffness [39, 40]. In our study, blood sugar was found to be higher in the patient group than in the control group. However, none of our patients had diabetes mellitus and/or insulin resistance that would affect aortic stiffness parameters. There was no statistically significant difference between the groups in the comparison of the results of aortic stiffness parameters.

In the study of Togan et al. [6], in which they evaluated aortic stiffness in adults with Brucellosis, it was shown that aortic stiffness was impaired in patients with Brucellosis. In addition, it was stated that the chronic inflammation that develops in Brucellosis plays an important role in the development of atherosclerotic disease and Brucellosis can be considered as a predisposing factor for the development of atherosclerosis. As a suggestion, it has been stated that measuring aortic stiffness may be a reasonable method for identifying individuals with Brucellosis who are at risk of developing atherosclerosis [6].

Conclusion

In our study, where we tried to show a new parameter that could contribute to the increase in aortic stiffness, the results showed that *Brucella* infection was not a factor that increased aortic stiffness in the pediatric age group.

Ethics Committee Approval: The Adiyaman University Clinical Research Ethics Committee granted approval for this study (date: 16.11.2021, number: 2021/09-08).

Authorship Contributions: Concept – HU, CV; Design – HU, MT; Supervision – HU, NE; Fundings – HU, CV; Materials – HU, MT; Data collection and/or processing – HU, CV; Analysis and/or interpretation – HU, NE; Literature review – HU, MT; Writing – HU, SY; Critical review – HU, SY.

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