Subclinical heart failure in juvenile idiopathic arthritis: a consequence of chronic inflammation and subclinical atherosclerosis

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Introduction

Juvenile idiopathic arthritis (JIA) is the most frequent chronic rheumatic disease encountered in children before the age of 16 years [1]. JIA is a heterogeneous group of disorders with different degrees of disease progression and different prognoses. The most common subtypes are oligoarticular JIA (50–60%), polyarticular JIA (30–35%), and systemic JIA (10–20%) [2].

The atherosclerotic process starts in childhood [3]. For most children, the degree of vascular involvement is minor and the rate of progression is slow. By contrast, in chronic inflammatory diseases, including JIA, the chronic inflammatory process has been suggested to play an important role in the acceleration of atherosclerosis, which contributes to the development of cardiovascular diseases (CVDs) including heart failure [4,5].

CVD is more prevalent in patients with rheumatoid arthritis (RA), and is diagnosed at an earlier age than in the general population. Mortality among RA patients is also higher than in the general population and is largely as a result of CVD [6]. Studies had shown that RA patients have accelerated atherosclerosis, which is correlated with markers of inflammation and aortic inflammation without any clinical signs of CVD [7,8]. As chronic inflammation is the basis of JIA it is reasonable to expect that JIA may produce harmful effects on many organ systems, including the cardiovascular system.

The aim of this study was to explore the presence of subclinical atherosclerosis and subclinical heart failure in JIA patients without manifest cardiovascular disease and to examine the risk factors that may be associated with the subclinical heart failure.

Background and aim of work

Chronic inflammation is the basis of juvenile idiopathic arthritis (JIA). Hence, it is expected that JIA may produce harmful effects on the cardiovascular system. The aim of this study was to explore the presence of subclinical atherosclerosis and subclinical heart failure in JIA patients without manifest cardiovascular disease and to examine the risk factors that may be associated with the subclinical heart failure.

Patients and methods

Fifty JIA patients and 50 healthy matched controls were enrolled in this study. Inflammatory markers in the serum, together with intima-media thickness (IMT) and flow-mediated dilation (FMD) of brachial arteries as surrogate markers of subclinical atherosclerosis, were assessed and compared between patients and controls. Echocardiographic parameters of heart failure, including the Tei index and ejection fraction%, were also evaluated.

Results

JIA patients had significantly increased IMT and impaired endothelial dysfunction as measured by FMD% of the brachial artery in comparison with controls. JIA patients had significantly higher Tei index and significantly lower ejection fraction% in comparison with controls. In regression analysis only systemic JIA, FMD%, and IMT were significantly associated with the presence of subclinical heart failure among patients with JIA.

Conclusion

Our findings indicate the presence of subclinical heart failure in these patients. JIA patients with subclinical atherosclerosis, with systemic disease, and with active disease are at greatest risk of developing subclinical heart failure.

Keywords:
juvenile idiopathic arthritis, subclinical atherosclerosis, subclinical heart failure

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Patients and methods
Fifty consecutive children who fulfilled the criteria of the International League of Associations for Rheumatology for the diagnosis of JIA [9] were recruited into this study from the outpatient clinics of Rheumatology and Pediatric Departments, Aseer Central Hospital, Saudi Arabia, from May 2013 to June 2014. There were 30 female and 20 male patients and their ages ranged from 9 to 15 years. The duration of JIA ranged from 2.5 to 8 years. For the control group, 50 apparently healthy children (24 girls and 26 boys) were consecutively recruited, with their ages ranging from 9 to 15 years. To be eligible for enrollment in the study, patients should have had no history of previous CVD. Children with any medical conditions other than the current JIA that may predispose to CVD were excluded from the study. None of the patients had diabetes mellitus. A written consent was obtained from the parents of all children before inclusion in the study. The study was approved by local ethics committee.

Clinical assessment
Personal and clinical data were obtained from the eligible patients through interviews. The medical records of all patients were reviewed. Disease activity was evaluated according to the Ringold and Wallace criteria. An inactive disease was indicated by the following criteria: no joints with active arthritis, lack of fever, rash, serositis, splenomegaly, generalized lymphadenopathy associated with JIA, no signs of active uveitis, normal erythrocyte sedimentation rate or C-reactive protein, and no signs of active disease based on the physician global assessment of disease activity [10].

BMI was calculated for each child to determine childhood overweight and obesity. For children and teens, BMI is age and sex specific and is often referred to as BMI for age. A child's weight status is determined using an age–specific and sex–specific percentile for BMI rather than the BMI categories used for adults [11,12]. Systolic (SBP) and diastolic (DBP) blood pressures were measured twice at the right arm after a 10 min rest using a calibrated sphygmomanometer with appropriate cuff size and were averaged.

Laboratory investigations
Blood samples of 10 ml were drawn from all participants early in the morning after an overnight fast. To assess inflammatory markers, serum samples were collected, frozen, and stored at a temperature of −80 °C until analyses were performed. The concentrations of interleukin (IL)–6 and tumor necrosis factor α (TNF-α) were determined immune-enzymatically using commercially available ELISA kits (Parameter Human Immunoassays; R&D Systems Inc., Minneapolis, Minnesota, USA) with the use of an ELX 800 Automated Microplate Reader (Bio-Tek Instruments, Winooski, Vermont, USA). High sensitivity-CRP (hs-CRP) was determined by means of the immune-turbid metric method [Tina-quant hs-CRP (Latex) HS, Roche, Hitachi 912; La Roche, Tokyo, Japan]. Lipid profiles were determined using dry chemistry methods with the Vitros S 350 analyzers by Ortho Clinical Diagnostics (Ortho Clinical Diagnostics Vitros S 350 Chemistry Analyzer, Auckland, New Zealand), according to the manufacturer’s instructions.

Assessment of the cardiovascular parameters
Brachial artery flow-mediated dilatation
The flow-mediated dilatation (FMD) of the brachial artery was measured to assess the vascular endothelial function. Participants rested for 10 min on a plain surface to reach a stable status for heart rate and blood pressure. Brachial artery diameter was assessed using a high-resolution B-mode sonogram (Vivid 3, 7.5 MHz transducer; General Electric) by placing the probe at 5 cm above the anterior cubital cavity of the nondominant arm. Forearm ischemia was induced by inflating a sphygmomanometer cuff to 50 mmHg more than SBP for 5 min. Brachial artery diameter, measured in millimeters before ischemia, was assessed as baseline brachial artery diameter. Sixty seconds after deflation the same assessment was done to measure the brachial artery diameter after ischemia. Measurement of arteries was performed during the diastolic phase, measuring the distance between the outermost limit of one side of the artery to the other. The FMD% was calculated according to the following formula: FMD% = [(maximum diameter−baseline diameter)/baseline diameter]×100 [13].

Carotid ultrasound scanning
JIA patients were examined in the supine position with their neck in extension and head turned contralaterally 45° with a high-resolution B-mode ultrasonography equipped with a 5–12 MHz linear array transducer using a PHILIPS HQ 8250 Ultrasound device. All ultrasound examinations were performed by the same operator who was blinded to clinical and laboratory findings of the participants. The right and left common carotid arteries were evaluated. Measurements included end-diastolic (minimum diameter) intima-media thickness (IMT) of the far walls (the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line) [14]. Average IMT calculation in millimeters was obtained from three measurements taken 1 cm below the common carotid bifurcation.
Echocardiographic Doppler examination

Two-dimensional, motion mode, and Doppler studies were performed with transthoracic echocardiography using a Siemens Sonoline G60S ultrasound imaging system with a P4–2 transducer. Measurements were taken in accordance with the recommendations of the American Society of Echocardiography [15]. Calculations were made using the internal analysis software of the echocardiographic device. The motion mode measurement of left ventricular (LV) functions was performed using the Teichholz formula. In the current study we determined the ejection fraction (EF%) and the Tei index of all participants. The Tei index was calculated from the ratio of time intervals expressed by the formula: Tei index = (a−b)/b [16]. Measurements were taken from three consecutive beats and averaged. The parameters for the formula were determined by first locating the sample volume at the tips of the mitral valve leaflets in the apical four-chamber view, which enabled the measurement of ‘a’ (the time interval between the end and the start of the transmitral flow). The sample volume was then located in the LV outflow tract, just below the aortic valve (apical five-chamber view), for the measurement of ‘b’ (LV ejection time). All the echocardiographic examinations were carried out and analyzed by one experienced cardiologist physician, who was blinded to the participants’ cardiovascular risk factor status.

Statistical analysis

Continuous data were expressed as mean ± SD and categorical data were expressed as number and percentage. All continuous data were tested for skewness and kurtosis before any analyses. Comparisons between continuous data were made using the independent-sample Student’s t-test and comparisons between categorical data were made using the χ2-test. The regression analysis model was used to reveal the variables that could predict subclinical heart failure among patients who had JIA. In the current study, on the basis of the cutoff points of Tei index and EF%, the JIA patients were dichotomized into two groups: JIA patients with subclinical heart failure (with Tei index>0.49 and/or EF%<45) and JIA patients without subclinical heart failure. Subclinical statistical significance was determined at P value less than 0.05. All calculations were made using SPSS, version 20.0.

Results

This study included 50 JIA patients (30 girls and 20 boys) and 50 healthy controls (24 girls and 26 boys). The average age of the JIA patients was 12.1 ± 2 years, and the average age of the controls was 11.9 ± 2.2. The two groups were similar as regards age and sex. BMI did not differ significantly between the JIA patients and the controls (20.2 ± 1.4 vs. 19.9 ± 1.8 kg/m², respectively; P = 0.554) (Table 1).

The JIA features of the patients are shown in Table 1. The average duration of JIA among the patients was 4.7 ± 1.4 years. The criteria for active disease were met by 56% (n = 28) of the patients (52.4%). Of them, 42% (n = 21) had oligoarticular type, 34% (n = 17) had polyarticular type, and 24% (n = 12) had systemic type of JIA. Among the patients who participated in the study 70% (n = 35) were currently using corticosteroids, 40% (n = 20) were on methotrexate, and 8% (n = 4) were on biological therapy.

JIA patients and controls

IL-6, hs-CRP, and TNF-α were significantly higher in the JIA patients in comparison with the controls (P < 0.001).

Indicators of subclinical atherosclerosis

Before the induction of ischemia, ultrasonographic examination of the participants revealed that the brachial artery diameter did not differ significantly between the JIA patients and controls; however, FMD% was lower in the JIA patients in comparison...
with controls (6.9 ± 1.1 vs. 10.1 ± 1, respectively). This difference was significant (95% confidence interval: −3.67 to −2.83, P < 0.001). The carotid IMT of the JIA patients was 0.49 ± 0.03 mm compared with 0.43 ± 0.03 mm in the controls. This difference was significant (95% confidence interval: 0.05–0.07, P < 0.001).

**Indicators of subclinical heart failure**

Echocardiographic examination showed that Tei index was significantly higher in the JIA patients than in controls (0.44 ± 0.06 vs. 0.39 ± 0.07, P < 0.001). JIA patients had significantly lower EF% than controls (51.4 ± 11.5 vs. 66.5 ± 10.3, P < 0.001) (Table 1). Of the patients with JIA, 26% (n = 13) had EF% less than 45 and Tei index more than 0.49, indicating that these patients had subclinical heart failure.

**Variables associated with markers of subclinical heart failure in JIA patients**

JIA patients with subclinical heart failure had significantly higher BMI, SBP, and DBP compared with patients without subclinical heart failure, whereas age, sex, and presence of dyslipidemia did not differ significantly between patients with and those without subclinical heart failure. As regards the type of JIA, 53.8% of the JIA patients with evidence of subclinical heart failure had systemic disease, whereas only 23.1% the patients had oligoarticular and another 23.1% had polyarticular JIA. Patients with heart failure more frequently had active disease compared with patients without subclinical heart failure (84.6% vs. 45.9%, respectively). However, disease duration was not statistically different between patients with and those without subclinical heart failure. Serum levels of the inflammatory markers (hs-CRP, IL-6, and TNF-α) were all significantly higher in the JIA patients with subclinical heart failure than in those without subclinical heart failure. Indicators of subclinical atherosclerosis also differed significantly between the two groups; that is, JIA patients with subclinical heart failure had significantly lower FMD% and significantly higher IMT than did patients without subclinical heart failure (Table 2).

**Factors that predict the presence of subclinical heart failure in regression analysis**

In regression analysis only systemic JIA, FMD%, and IMT were significantly associated with the presence of subclinical heart failure among patients with JIA (Table 3).

**Discussion**

The main finding of the current study is that JIA patients had significantly increased IMT and impaired endothelial function as measured by FMD% of the brachial artery in comparison with controls. This finding strongly supports the presence of early cardiovascular changes that predispose to the development of atherosclerosis. Another major finding of the current study is that JIA patients had significantly higher Tei index and significantly lower EF% in comparison

### Table 2 Characteristics of patients with JIA with and without subclinical heart failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>JIA patients with subclinical heart failure</th>
<th>JIA patients without subclinical heart failure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12.3 ± 1.9</td>
<td>11.5 ± 2.1</td>
<td>0.223</td>
</tr>
<tr>
<td>Females [n (%)]</td>
<td>23 (62.2)</td>
<td>7 (53.8)</td>
<td>0.599</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.9 ± 1.5</td>
<td>20.8 ± 1</td>
<td>0.066</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>111.7 ± 8.5</td>
<td>117.2 ± 7.1</td>
<td>0.042</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74.6 ± 10.6</td>
<td>81.7 ± 9.8</td>
<td>0.040</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5 (13.5)</td>
<td>2 (15.4)</td>
<td>0.867</td>
</tr>
<tr>
<td>JIA disease characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>4.8 ± 1.5</td>
<td>4.3 ± 1.2</td>
<td>0.320</td>
</tr>
<tr>
<td>Active disease</td>
<td>17 (45.9)</td>
<td>11 (84.6)</td>
<td>0.016</td>
</tr>
<tr>
<td>JIA type [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligoarticular</td>
<td>18 (48.6)</td>
<td>3 (23.1)</td>
<td>0.013</td>
</tr>
<tr>
<td>Polyarticular</td>
<td>14 (37.8)</td>
<td>3 (23.1)</td>
<td>0.037</td>
</tr>
<tr>
<td>Systemic</td>
<td>5 (13.5)</td>
<td>7 (53.8)</td>
<td>0.627</td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hs-CRP</td>
<td>1.5 ± 0.9</td>
<td>2.2 ± 1.2</td>
<td>0.032</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.9 ± 0.9</td>
<td>2.6 ± 0.9</td>
<td>0.019</td>
</tr>
<tr>
<td>TNF-α</td>
<td>2.1 ± 0.8</td>
<td>2.5 ± 0.5</td>
<td>0.037</td>
</tr>
<tr>
<td>Atherosclerosis markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial artery</td>
<td>3.8 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>0.289</td>
</tr>
<tr>
<td>FMD%</td>
<td>7.2 ± 1.1</td>
<td>6.3 ± 1.1</td>
<td>0.009</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>0.48 ± 0.03</td>
<td>0.51 ± 0.03</td>
<td>0.003</td>
</tr>
<tr>
<td>Drugs used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>26 (70.2)</td>
<td>9 (69.2)</td>
<td>0.944</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>13 (35.1%)</td>
<td>7 (53.8)</td>
<td>0.236</td>
</tr>
<tr>
<td>Biologics</td>
<td>3 (8.1%)</td>
<td>1 (7.8%)</td>
<td>0.964</td>
</tr>
</tbody>
</table>

### Table 3 Regression analysis for the factors associated with subclinical heart failure

<table>
<thead>
<tr>
<th>Factors</th>
<th>Standardized coefficient β</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP, systolic blood pressure</td>
<td>0.057</td>
<td>0.099</td>
<td>0.922</td>
</tr>
<tr>
<td>DBP</td>
<td>0.289</td>
<td>0.504</td>
<td>0.617</td>
</tr>
<tr>
<td>Systemic JIA</td>
<td>0.333</td>
<td>2.183</td>
<td>0.043</td>
</tr>
<tr>
<td>Disease activity</td>
<td>0.304</td>
<td>1.840</td>
<td>0.082</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.271</td>
<td>1.738</td>
<td>0.099</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.261</td>
<td>1.743</td>
<td>0.098</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.291</td>
<td>1.917</td>
<td>0.071</td>
</tr>
<tr>
<td>FMD%</td>
<td>1.452</td>
<td>2.419</td>
<td>0.023</td>
</tr>
<tr>
<td>IMT</td>
<td>2.065</td>
<td>3.368</td>
<td>0.004</td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; FMD, flow-mediated dilatation; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6; IMT, intima-media thickness; JIA, juvenile idiopathic arthritis; SBP, systolic blood pressure; TNF-α, tumor necrosis factor α.
with controls. These findings indicate the presence of subclinical heart failure in these patients.

In agreement with our results, presence of subclinical atherosclerosis in patients with JIA as indicated by the increased IMT and the decreased FMD% in comparison with controls was also reported in the study by Głowińska-Olszewska et al. [17]. Many studies reported that subclinical atherosclerosis, vascular stiffness, and endothelial function impairment were more frequent among RA patients than among controls [18–20].

Chronic inflammation had been currently recognized as a risk factor for the development of atherosclerosis among patients with RA [21,22]. Chronic inflammation is also the basic feature of JIA, and it is reasonable to assume that the chronic inflammatory mediators play a major role in accelerated atherosclerosis in patients with JIA. Consistent with this concept, our results revealed that patients with JIA had significantly higher hs-CRP, TNF-α, and IL-6 in comparison with controls. Elevated serum proinflammatory cytokine levels are a well-identified feature in RA patients [23,24], and also in children with idiopathic arthritis [25,26]. Another important observation in the current study is that JIA patients who had subclinical heart failure more frequently had an active disease than did JIA patients without subclinical heart failure. This observation appears reasonable because JIA patients who had active disease had elevated inflammatory mediators in their sera, which is itself a risk factor for the accelerated atherosclerosis, which by its turn is a factor for the development of heart failure.

At present, FMD measurement is increasingly used to estimate the juvenile cardiovascular risk [17]. Notably, Aggoun et al. [27] observed that obese children had significantly impaired endothelial function in comparison with nonobese children despite the fact that IMT did not differ significantly between obese and nonobese children. This finding was associated with elevated ambulatory blood pressure. This observation indicated that impaired endothelial function seems to be the earliest marker of subclinical atherosclerosis. IL–6 and other proinflammatory cytokines are involved in the process of endothelial dysfunction, and these cytokines induce ICAM-1 expression and C-reactive protein synthesis [28]. Jednacz and Rutkowska-Sak [29] demonstrated significantly higher IL-6 levels in children with JIA compared with the control group; this finding is consistent with our findings.

IMT is a factor predicting the stage of atherosclerosis and it may help assess the cardiovascular risk in asymptomatic patients with a moderate cardiovascular risk [30]. In the current study, IMT was significantly higher among patients with JIA as compared with controls. The increased IMT in children with JIA compared with healthy children was also demonstrated by the study of Breda et al. [31]. In our study regression analysis, only systemic JIA, FMD%, and IMT were significantly associated with the presence of subclinical heart failure among patients with JIA. This finding indicates that systemic JIA and subclinical atherosclerosis are the principle mediators for the development of subclinical heart failure among patients with JIA.

However, the study by Jednacz and Rutkowska-Sak [29] did not demonstrate differences in IMT between healthy children and children with JIA. The study by Jednacz and Rutkowska-Sak [29] did not include children with a systemic disease in which the intensity of the inflammatory process was particularly high. In the study by Vlahos et al. [32] that enrolled and assessed CV risk in children with JIA, increased IMT was observed only in children with a systemic disease, and this difference was not observed for oligoarticular or polyarticular diseases. These observations strongly support the hypothesis that systemic JIA is a risk factor for development of subclinical heart failure.

Conclusion
Our findings indicate the presence of subclinical heart failure in JIA patients. JIA patients with subclinical atherosclerosis, with systemic disease, and with active disease are at greatest risk of developing subclinical heart failure.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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