Carotid Atherosclerosis in Adult Patients with Persistently Active Juvenile Idiopathic Arthritis Compared with Healthy Controls

Kristin Evensen, Hanne Aaserud Aulie, Ole Morten Rønning, Berit Flatø, and David Russell

ABSTRACT. ***Objective.*** Juvenile idiopathic arthritis (JIA) is the most common inflammatory rheumatic disease in childhood. It is regarded as a systemic inflammatory disease with possible increased risk of cardiovascular disease (CVD). The aim of this study was to assess carotid intima-media thickness (IMT) and carotid stenosis as surrogate measures for CVD in adults with longterm active JIA and healthy age- and sex-matched controls.

Methods. Seventy-five patients with JIA (age 28–45 yrs) with persistently active disease at least 15 years after disease onset were reexamined after a median of 29 years and compared with 75 matched controls. Patients and controls were examined by color duplex ultrasound of the carotid arteries to compare carotid IMT and carotid stenosis in the 2 groups.

Results. Patients with JIA did not have increased carotid IMT values compared with the controls (mean ± SD: 0.56 mm ± 0.09 vs 0.58 mm ± 0.07, p = 0.289). Patients with a higher disease activity indicated by the Juvenile Arthritis Disease Activity Score value above the median value had increased carotid IMT compared with the patients with a lower value, but not statistically different compared with controls. No carotid stenoses were detected in patients or controls.

Conclusion. We found similar carotid IMT values in adult patients with JIA and controls. (First Release February 15 2016; J Rheumatol 2016;43:810–15; doi:10.3899/jrheum.150499)

Key Indexing Terms:
ATHEROSCLEROSIS
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Juvenile idiopathic arthritis (JIA) is the most common inflammatory rheumatic disease in children, with an annual incidence of 15/100,000. Onset is before the age of 16, and about 50% still have active disease when they reach adulthood[1,2,3,4,5]. JIA has well-known associations with other autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), diseases known to have an increased risk of cardiovascular (CV) morbidity and mortality[6,7,8]. The longterm risk for CV disease (CVD) in patients with JIA is uncertain. However, given the potential of longterm disease duration and inflammation since childhood, patients with JIA may have an increased risk of CVD[9]. In 2006, the American Heart Association published guidelines endorsed by the American Academy of Pediatrics with a list of diseases in children with an increased risk of CVD where JIA was included[10].

Because CV events are rare in the young, surrogate markers of atherosclerosis such as carotid intima-media thickness (IMT) are valuable to detect early subclinical atherosclerosis. IMT of the carotid arteries is measured using B-mode ultrasonography (US), a noninvasive and well-recognized method for evaluating generalized atherosclerotic arterial disease[11,12].

A few studies have been conducted in children with JIA assessing carotid IMT[13,14,15,16,17]. No previous studies have assessed subclinical carotid atherosclerosis in adult patients with persistently active JIA.

The aim of our study was to assess subclinical atherosclerosis in an adult JIA population with persistently active JIA after at least 15 years of disease duration and compare results with those in a healthy control group.

MATERIALS AND METHODS

Patient population. Our study included 75 patients with persistently active JIA for at least 15 years after disease onset. These patients were all selected from a large JIA cohort closely followed up and described in detail elsewhere[3,18,19]. This cohort originally included 254 patients with JIA who

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were first-time referred to the Oslo University Hospital from 1980 to 1985, and later examined clinically after a median 15 years of disease duration, by mailed questionnaire after a median of 23 years and now clinically after a median of 29 years. Of the 134 patients in the original cohort still having active disease of at least 15 years after disease onset, 90 patients consented and were enrolled in our study. Fifteen patients were excluded because of practical reasons.

Seventy-five patients underwent color duplex examination of the carotid arteries. Retrospective analyses of data from the 134 eligible patients at the 15-year followup did not show any differences regarding sex, disease duration, or measures of disease activity and severity between the 75 included patients and the 59 eligible but not participating patients (data not shown). However, the nonparticipants were a median of 3.5 years younger.

Seventy-five age- and sex-matched controls were randomly selected from the Norwegian population register. Responders with a history of inflammatory arthritis were not included in our study.

The study was approved by the regional ethics committee. Subjects provided written informed consent.

Clinical examination and CV risk assessment. A rheumatologist carried out a clinical examination of patients and controls. Patients were categorized according to the International League of Associations for Rheumatology classification criteria[20].

Patients with clinically active disease and those with inactive disease with ongoing antirheumatic treatment were defined as having active disease[20] and included in our study.

The Juvenile Arthritis Disease Activity Score (JADAS)[21] was used to measure JIA disease activity. Each score is calculated using 4 JIA disease activity measurements: (1) number of joints with active disease (71 joints); (2) the physician's global assessment of disease activity measured on a 10-cm visual analog scale (VAS), where 0 = no activity and 10 = maximum activity; (3) the patient's global assessment of well-being measured on a 10-cm VAS, where 0 = doing very well and 10 = doing very poorly; and (4) standardized erythrocyte sedimentation rate.

The global score ranges between 0–101. JADAS from 1–4 corresponds to 1 = disease remission, 2–3.9 = minimal disease activity, and 4 = acceptable symptoms[22].

Patients and controls were interviewed about previous CVD, known CV risk factors [hypertension (HTN), hyperlipidemia, diabetes, and smoking], and a family history of CVD, defined as a first-degree relative having CVD before the age of 65 years in women and 55 years in men. Body mass index (BMI) and waist circumference were measured in all participants. Blood pressure was obtained in patients and controls after 5 min of rest in a supine position and the average of 3 measurements was used.

Laboratory assessments. Blood samples were collected after an overnight fast in patients and controls and analyzed for low-density lipoprotein (LDL), high-density lipoprotein, total cholesterol, triglycerides, high-sensitivity C-reactive protein (hsCRP), glucose, and glycosylated hemoglobin (HbA1c).

Carotid US. Patients and controls were examined with color duplex US of the carotid arteries by a neurologist with long experience in US of the carotid arteries. The neurologist was blinded regarding the patients' and controls' clinical and laboratory data.

The examination was carried out in the supine position with the head angled at about 45° toward the contralateral side. IMT measurements were synchronized with the QRS-complex on the echocardiogram and made in each carotid artery at the peak of the R wave where the lumen is widest. IMT was defined as the distance between the lumen-intima and media-adventitia borders of the vessel, identified as a double-line pattern in a longitudinal image[23]. IMT was measured in the carotid arteries on both sides of the neck in 3 segments: (1) in the far wall of the common carotid artery, 1 cm proximal to the bifurcation, over an area of 1 cm and in 3 different projections: lateral, posterior, and anterior; (2) in the far wall of the carotid bifurcations over an area of 1 cm in the lateral position; (3) in the far wall of the proximal internal carotid arteries (ICA) immediately distal to the bifurcation over an area of 1 cm in the lateral projection.

Plaques in the areas of interest were included in the IMT measurements and not defined separately. We used the averaged value of the 10 carotid IMT measurements in each subject for further analyses. The Consensus Panel-Greyscale and Doppler US criteria were used for the diagnosis of ICA stenosis[24]. Blood flow peak systolic velocities (PSV) in the ICA < 125 cm/s was defined as < 50% stenosis and PSV in the ICA > 125 cm/s as > 50% stenosis.

The carotid US examinations were carried out according to the American Society of Echocardiography guidelines[25] using a Vivid 7 US instrumentation with a linear M12L probe (14 MHZ; General Electric).

Statistical analyses. Statistical analyses were performed using the statistical software package of SPSS for Windows (version 18) for the one-to-one matching and paired analyses using the paired samples Student t test. A 1-way ANOVA was performed to detect differences between JIA categories.

A multivariable analysis using the linear regression model was performed to study the association between traditional CV risk factors for increased IMT in patients and controls separately, using a manual backward elimination procedure. Any variable with $p < 0.25$ from the univariable analysis was considered a candidate for the multivariable model. Multivariable analyses were preceded by estimation of correlations between variables.

To investigate whether a higher disease activity according to the JADAS had any influence on carotid IMT, patients were dichotomized to above and below the median JADAS value of the group. The independent sample Student t test was used to study the differences between groups. A significance level of 5% was used.

RESULTS

Seventy-five patients and 75 age- and sex-matched controls took part in our study. None of the patients or controls had previous CVD. Patient characteristics are shown in Table 1. A higher percentage of the patients with JIA than controls were smokers (27% vs 13%, $p = 0.041$; Table 2). Diastolic blood pressure and the plasma level of CRP were higher in patients than controls ($p = 0.043$ and $p = 0.003$, respectively; Table 2).

Table 1. Patient characteristics. Values are n (%) or median (range).

Characteristics	Patients with JIA, n = 75
Age, yrs	38 (28–45)
Male	18 (24)
Disease duration, yrs	29 (26–40)
Onset age, yrs	9 (5–11)
JADAS	4.75 (0.2–27.1)
JIA categories distribution	
Systemic arthritis	4 (5)
RF-negative polyarthritis	10 (13)
RF-positive polyarthritis	5 (7)
Persistent oligoarthritis	12 (16)
Extended oligoarthritis	13 (17)
Enthesitis-related arthritis	16 (21)
Psoriatic arthritis	12 (16)
Unclassified	3 (4)
Current medication at 29-yr followup	
Anti-TNF	20 (27)
Methotrexate	15 (20)
NSAID daily	21 (28)
Prednisolone	5 (7)

JIA: juvenile idiopathic arthritis; JADAS: Juvenile Arthritis Disease Activity Score; RF: rheumatoid factor; anti-TNF: antitumor necrosis factor; NSAID: nonsteroidal antiinflammatory drug.

Table 2. Traditional cardiovascular risk factors in patients with JIA and controls. Values are mean ± SD unless otherwise specified.

Variables	Patients, n = 75	Controls, n = 75	p
Diabetes, n (%)	1 (1.3)	0	
Hypertension, n (%)	4 (5.3)	0	
Systolic blood pressure, mmHg	119.0 ± 13.8	115.6 ± 10.2	0.081
Diastolic blood pressure, mmHg	75.2 ± 9.7	72.2 ± 8.5	0.043
Daily smoking, n (%)	19/71 (26.8)	9/71 (12.7)	0.041
BMI, kg/m^2	25.4 ± 5.3	25.8 ± 4.8	0.674
Total cholesterol, mmol/l	4.8 ± 1.0	5.0 ± 0.9	0.213
HDL, mmol/l	1.5 ± 0.4	1.5 ± 0.4	0.522
LDL, mmol/l	2.97 ± 0.99	3.0 ± 0.89	0.599
Triglycerides, mmol/l	0.92 ± 0.52	0.98 ± 0.62	0.542
Glucose, mmol/l	5.2 ± 0.5	5.1 ± 0.5	0.663
HbA1c	5.4 ± 0.3	5.4 ± 0.4	0.215
CRP, mg/l, median (range)	1.8 (0–38)	0.94 (0–23)	0.003
Average carotid IMT, mm	0.56 ± 0.09	0.58 ± 0.07	0.289
Carotid stenosis, n	0	0	

JIA: juvenile idiopathic arthritis; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1c: glycosylated hemoglobin; CRP: C-reactive protein; IMT: intima-media thickness.

The carotid US findings are shown in Table 2. We did not study intraobserver variability, but the same neurologist had an ICC = 0.93 in a previous carotid IMT study[26]. There was no difference in average carotid IMT between patients with JIA and controls (mean ± SD: 0.56 mm ± 0.09 vs 0.58 mm ± 0.07, p = 0.289, respectively). No carotid stenoses were detected in patients or controls.

A multivariable linear regression analysis was carried out to identify possible risk factors for increased IMT in patients and controls separately. In patients, all the risk factors except CRP were associated with IMT in the univariable analysis (p < 0.25; Table 3). Because LDL and total cholesterol were strongly correlated (r = 0.94), only LDL was included in the multivariable analysis to avoid colinearity. A multiple linear regression analysis with a backward elimination procedure showed that glucose, HTN, and daily smokers were the only independent risk factors for increased IMT in the patients, explaining 30% of the variance (r^2 = 0.30; Table 4).

In controls, total cholesterol, glucose, HbA1c, BMI, and LDL were identified as possible risk factors of increased IMT in the univariable analysis (Table 3). Because total cholesterol and LDL were strongly correlated (r = 0.94), total cholesterol was included in the multivariable analysis. In the multiple linear regression analysis, HbA1c and BMI were identified as independent risk factors of IMT in the controls, explaining 15% of the variance (r^2 = 0.15; Table 4).

Carotid IMT values for patients in different JIA categories are shown in Table 5. We did not find any difference in carotid IMT values when patients were compared according to their JIA categories (p = 0.268). Few patients in each category may explain these findings.

Thirty-four patients had a JADAS score above the median value of 4.75 and these patients had higher IMT values than the patients with a score below the median value (mean ± SD: 0.56 ± 0.08 vs 0.60 ± 0.06, p = 0.03), but still not significantly different from the controls (p = 0.091).

Table 3. Associations between traditional cardiovascular risk factors and carotid IMT in patients with JIA and controls.

Variables	Patients, n = 75			Controls, n = 75		
	ß	95% CI	p	ß	95% CI	p
Triglycerides	0.038	–0.001 to 0.077	0.057	0.001	–0.028 to 0.027	0.981
LDL	0.034	0.014–0.053	0.001	0.012	–0.007 to 0.031	0.198
HDL	–0.077	–0.124 to –0.030	0.002	0.002	–0.040 to 0.045	0.915
Total cholesterol	0.023	0.004–0.042	0.018	0.012	–0.006 to 0.030	0.187
Glucose	0.068	0.032–0.104	< 0.001	0.033	–0.001 to 0.067	0.060
HbA1c	0.081	0.019–0.143	0.011	0.037	–0.008 to 0.083	0.105
CRP	-5.63×10^{-5}	–0.03 to 0.003	0.973	–0.001	–0.006 to 0.004	0.695
BMI	0.006	0.003–0.010	0.001	0.004	0.001–0.008	0.013
Hypertension	0.091	0.002–0.179	0.044	–0.025	–0.130 to 0.079	0.634
Daily smoking	0.054	0.009–0.098	0.019	–0.002	–0.054 to 0.049	0.927

IMT: intima-media thickness; JIA: juvenile idiopathic arthritis; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HbA1c: glycosylated hemoglobin; CRP: C-reactive protein; BMI: body mass index.

Table 4. Independent risk factors of increased IMT using linear regression analysis (n = 75).

Characteristics	β	95% CI	p
Patients, $r^2 = 0.30$			
Glucose	0.066	0.031–0.100	< 0.001
Hypertension	0.090	0.012–0.169	0.025
Daily smokers	0.047	0.005–0.089	0.027
Controls, $r^2 = 0.15$			
HbA1c	0.051	0.008–0.094	0.020
BMI	0.005	0.001–0.008	0.006

IMT: intima-media thickness; HbA1c: glycosylated hemoglobin; BMI: body mass index.

Table 5. JIA categories and carotid IMT measurements.

Variables	n = 75, n (%)	Average Carotid IMT, mm, mean ± SD
Systemic arthritis	4 (5)	0.485 ± 0.02
RF-negative polyarthritis	10 (13)	0.564 ± 0.04
RF-positive polyarthritis	5 (7)	0.603 ± 0.10
Persistent oligoarthritis	12 (16)	0.563 ± 0.05
Extended oligoarthritis	13 (17)	0.587 ± 0.08
Enthesitis-related arthritis	16 (21)	0.601 ± 0.09
Psoriatic arthritis	12 (16)	0.577 ± 0.05
Unclassified	3 (4)	0.639 ± 0.06

JIA: juvenile idiopathic arthritis; IMT: intima-media thickness; RF: rheumatoid factor.

DISCUSSION

In our study, we found no difference in carotid IMT values in patients with JIA compared with healthy controls. Carotid IMT values were comparable between JIA categories. Patients with a higher disease activity indicated by a JADAS value above the median value had increased carotid IMT compared with patients with a lower value, but values were not statistically different compared with controls.

There are, to our knowledge, no similar studies in adult patients with JIA. Five case-control studies have been made in children with JIA[13,14,15,16,17]. Three of these studies found an increased carotid IMT in children with JIA compared with controls[13,14,16]. Two studies[15,17] could not confirm these findings, similar to the results in our study.

Accelerated atherosclerosis is common in patients with rheumatic diseases. This is because of autoimmune and inflammatory mechanisms that eventually lead to endothelial dysfunction and atherosclerosis development[27]. A few studies have indicated that JIA and atherosclerosis share common inflammatory cytokine profiles[9,28,29]. It is therefore possible that this pathophysiological process leads to accelerated atherosclerosis in patients with JIA. With this background, we expected to find increased carotid IMT values in adult patients with JIA who had longterm disease duration. We found, however, comparable carotid IMT values in patients and controls. The carotid IMT values were also comparable to values in a healthy population described by Lim, *et al*[30].

In our study, we matched 1 control to 1 patient with JIA of the same age and sex. This matching is useful because age and sex are variables that are strongly related to both the exposure and outcome of interest. It is well known that IMT increases with age and that this increase seems to be greater in men than in women[31]. The mean age of the JIA group and controls was 38 years; hence they have not been exposed to traditional CV risk factors for a very long duration, and 76% were women. However, increased carotid IMT values have been found in children with JIA compared with age- and sex-matched controls with a much shorter disease duration than in our study[13,16]. This finding may be due to the differences in the inflammatory atherosclerotic process in children with JIA and adults with JIA. In younger individuals, the inflammatory atherosclerotic process can form fatty streaks in the endothelium. These fatty streaks may progress into atherosclerotic plaques, but can also disappear with time[32]. Hence, a possible explanation for the atherosclerosis found in children with JIA, but not in adult patients with JIA, may be a reversal of early subclinical atherosclerosis.

Chronic inflammatory diseases such as RA and SLE are associated with an increased risk of CVD[7,8]. This risk is still uncertain for patients with JIA. CVD in adults with RA has also been associated with an increased prevalence of CV risk factors such as smoking, diabetes mellitus, and HTN[33,34,35,36]. In our study, we found increased daily smoking, diastolic blood pressure, and increased CRP in patients compared with controls. The children with JIA in the studies by Breda, *et al*[13] and Vlahos, *el al*[16] all had increased CV risk factors compared with controls. In 1 study of children with known CV risk factors (HTN, diabetes, hyperlipidemia, and obesity), increased carotid IMT has been described[37].

JIA is a heterogeneous disease with differences in the degree of inflammation between categories. Systemic inflammation is more marked in the polyarticular and systemic categories[38]. In our study, 20% of the patients were in the polyarticular category and 5% in the systemic category. We did not, however, find any differences in carotid IMT values between the 2 categories. This is in contrast to results presented by 3 other studies of children with JIA[13,14,16] in which 1 study[16] found increased carotid IMT in the systemic category and 2 others[13,14] showed increased carotid IMT in the oligoarticular and polyarticular categories. A direct comparison of atherosclerotic changes is difficult between the studies of children with JIA because of the diversity in category presentation and because these studies have few participants. In our study, there were also few patients in each category and this may be the reason we did not find differences in carotid IMT between the different JIA categories.

We found that patients with a JADAS value over the median value had higher carotid IMT values compared to patients with a JADAS value under the median value. This

may suggest more subclinical atherosclerosis in patients with a more active JIA disease. This is in concordance with a recent study of some of the same patients with JIA as included in our study having increased arterial stiffness compared with healthy controls[39]. It is, however, important to stress that in our study, IMT measurements in patients with a JADAS value over the median value were similar to those in the controls.

In 1 study of children with JIA[13], all patients were treated with nonsteroidal antiinflammatory drugs (NSAID) and/or disease-modifying antirheumatic drugs (DMARD), mainly methotrexate (MTX) before inclusion. Antitumor necrosis factor (anti-TNF) medication has been shown to be effective in the treatment of JIA[40], and in the systemic JIA type, interleukin 6 (IL-6) and IL-1 blockades have been shown to be effective[41,42]. In our study, 20 patients (27%) were currently being treated with anti-TNF and 15 (20%) with MTX. In patients with RA, early treatment with anti-TNF-α and MTX has been associated with lower CV risk[43,44]. DMARD has been shown to reduce progression of atherosclerosis in patients with RA in several studies[45,46,47]. This suggests that early initiation of DMARD may reduce CV risk in these patients[45]. In 1 study of patients with RA, carotid IMT values were reduced after a 1-year treatment with DMARD[46]. In 1 study of children with JIA[13], 16 of the 38 patients had a more aggressive disease and needed treatment with an anti-TNF medication. After 12 months, all patients with JIA were reexamined with carotid US and they found a reduction in carotid IMT of 0.06 mm in the anti-TNF group and 0.03 mm in the group receiving NSAID and/or MTX. These findings may indicate that early and optimal medical treatment of patients with JIA could reduce the acceleration of atherosclerosis. The patients with JIA in our study have been closely followed up at the national hospital for rheumatic diseases (Oslo University Hospital), thus receiving optimal treatment; that may have delayed the atherosclerotic process in these patients.

The limitation of our study is the low number of patients included. However, our present study remains the largest on carotid IMT in patients with JIA. Few of the patients in the study had the JIA subtypes associated with a higher degree of inflammation. However, the strengths of our study are the longterm followup of a well-defined cohort of patients with JIA and the presentation of novel data on carotid IMT in adult patients with JIA.

In our study, we found carotid IMT values in adult patients with JIA similar to those in age- and sex-matched controls. We could not confirm findings in previous studies of children with JIA that suggest an increased CV risk. The limited number of patients challenges the generalization of the findings of our present study.

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