ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/pediatr.2022-91466

Risk Factors to Pre-Clinical Atherosclerosis Evaluated by Carotid Intima-Media Thickness in Juvenile Idiopathic Arthritis: Descriptive Research

Juvenil İdiyopatik Artiritte Karotis İntima Media Kalınlığı ve Preklinik Ateroskleroz için Risk Faktörleri: Tanımlayıcı Araştırma

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ABSTRACT Objective: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood. Cardiovascular morbidity and mortality are becoming important health problems for children with inflammatory rheumatic diseases. The aim of this study was to evaluate carotid intima-media thickness (CIMT) in children with JIA and to examine its association with JIA subtype, markers of inflammation, and early atherosclerosis. **Material and Methods:** We included 112 (50 boys and 62 girls) patients who have been followed by a diagnosis of JIA for at least 6 months and 54 healthy control subjects (32 girls and 22 males) who were matched with the patients age and gender. All children underwent a carotid artery. Inflammation markers were evaluated in the patient group. Cumulative drug doses, total disease duration (TDD), active disease duration (ADD) were calculated. All CIMT values were compared in patients, subgroups, and control groups, and their relationship with inflammation markers was investigated. **Results:** CIMT values in found that children with JIA were significantly higher than in healthy children. There was no difference between the disease subgroups in terms of CIMT. No relationship was found between CIMT measurements and atherosclerosis risk factors, drugs, erythrocyte sedimentation rate, white blood cell and C-reactive protein. A negative correlation was found between mean platelet volume (MPV) and right CIMT. A statistically significant positive correlation was detected between the right CIMT and TDD (r=0.221, p=0.022), and ADD (r=0.248, p=0.010). **Conclusion:** The study showed that the patients with JIA had more risks than healthy controls for cardiovascular disease (CVD) regardless of subgroup. We concluded early and aggressive therapies may be protective for CVD. Negative correlation was found between MPV and CIMT that is consistent with recently published literature, but there is need for further studies with a larger patient population.

Keywords: Mean platelet volume;
carotid intima-media thickness;
juvenile idiopathic arthritis; atherosclerosis

ÖZET Amaç: Juvenil idiyopatik artrit [juvenile idiopathic arthritis (JIA)] çocukluk çağının en sık görülen kronik romatizmal hastalığıdır. Kardiyovasküler morbidite ve mortalite inflamatuar romatizmal hastalıkları olan çocuklar için önemli sağlık sorunları hâline gelmektedir. Bu çalışmanın amacı, JIA'lı çocuklarda karotis intima-media kalınlığını (KİMK) değerlendirmek ve JIA alt tipi, inflamasyon belirteçleri ve erken ateroskleroz ile ilişkisini incelemektir. **Gereç ve Yöntemler:** Çalışmaya en az 6 aydır JIA tanısı ile takip edilen 112 (62 kız, 50 erkek) hasta ile yaş ve cinsiyet açısından hasta gruplarına benzer 54 (32 kız, 22 erkek) çocuk sağlıklı kontrol grubu olarak alındı. Tüm çocuklara, karotis arter ultrasonografi yapıldı, inflamasyon belirteçlerine bakıldı. İlaç kümülatif dozları, aktif hastalık süreleri [active disease duration (ADD)], toplam hastalık süreleri [total disease duration (TDD)] hesaplandı. Tüm KİMK değerleri hastalar, alt gruplar ve kontrol grubunda karşılaştırıldı ve inflamasyon belirteçleri ile ilişkisi araştırıldı. **Bulgular:** JIA'lı çocuklarda KİMK değerleri sağlıklı çocuklardan anlamlı yüksek saptandı. JIA alt grupları arasında KİMK değerleri açısından fark saptanmadı. Ateroskleroz risk faktörleri, ilaçlar, eritrosit sedimantasyon hızı, beyaz küre sayısı ve C-reaktif protein ile KİMK değerleri arasında ilişki saptanmadı. Ortalama trombosit hacmi (OTH) ile sağ KİMK arasında negatif korelasyon bulundu. Sağ KİMK ile TDD (r=0,221, p=0,022) ve ADD (r=0,248, p=0,010) arasında istatistiksel olarak anlamlı pozitif korelasyon saptandı. **Sonuç:** Çalışmamızda, alt gruptan bağımsız olarak JIA'lı hastaların kardiyovasküler hastalık (KVH) açısından sağlıklı kontrollere göre daha fazla risk taşıdığını gösterdik. Erken ve agresif tedavilerin KVH için koruyucu olabileceği sonucuna vardık. OTH ve KİMK arasında yakın zamanda yayımlanmış literatürle uyumlu negatif korelasyon bulundu ancak daha geniş hasta popülasyonu ile daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ortalama trombosit hacmi;
karotis intima-media kalınlığı;
juvenil idiyopatik artrit; ateroskleroz

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Peer review under responsibility of Turkiye Klinikleri Journal of Pediatrics.

Received: 21 May 2022 ***Received in revised form:*** 28 Oct 2022 ***Accepted:*** 02 Dec 2022 ***Available online:*** 08 Dec 2022

Cardiovascular diseases (CVDs) are a primary cause of mortality. Atherosclerosis, as a primary mechanism in the etiopathogenesis of CVDs, is a chronic inflammatory disease that starts with endothelial dysfunction of the arteries. Even though the clinical results of the atherosclerotic process appear during adulthood, this process starts during childhood.[1] Classical risk factors include obesity, dyslipidemia, diabetes, hypertension, age, gender, lifestyle, and family history.[2,3] Chronic inflammatory diseases also have an important role among CVD risk factors. It has been shown that mortality secondary to CVDs is 50% more frequent in patients with adult rheumatoid arthritis (RA).[4]

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory arthritis in childhood.[5] A previous study showed that similar inflammatory cytokines and molecular factors were present in atherosclerosis and in JIA pathogenesis.[6] There are no available data about morbidity and mortality secondary to atherosclerosis in patients with JIA. However, in an autopsy study, atherosclerotic changes were shown at 30% of patients with JIA.[7]

In adults, non-invasive techniques evaluating endothelial functions have been used to predict possible CVD which may develop in the future. Urbina et al. demonstrated that atherosclerosis may also be detected in children by using these techniques.[8] Non-invasive techniques include pulse wave velocity (PWV), augmentation index (AIx), flow mediated dilation, and measurements of intima-media wall thickness of the carotid artery and aorta.[9] Arterial intima-media wall thickness provides information regarding the structure of arterial walls. It is a simple, feasible, and safe method for detecting preclinical atherosclerosis by using B-mode ultrasonography (US).[10]

The aim of our study was to detect preclinical atherosclerosis with carotid intima-media thickness (CIMT) by US and determine the relationship between the disease and the clinical and inflammatory processes in patients with JIA.

MATERIAL AND METHODS

Overall, 112 (62 female, 50 male) patients with a diagnosis of JIA according to International League of Associations of Rheumatology criteria who had been followed for at least 6 months in the Erciyes University Department of Pediatric Rheumatology were included in our study. Exclusion criteria included active and chronic infection, obesity, malignancy, allergy, and concomitant chronic and rheumatologic diseases. We included non-obese JIA patients with normal ranges of blood pressure, lipid, and blood glucose. Fifty-four healthy (32 female, 22 male) children with similar ages and genders, and without any chronic disease, obesity or medication, were selected as the control group.

Data on JIA subtype, age at diagnosis, total disease duration (TDD), active disease duration (ADD), current remission and active disease status, medications [steroid, disease-modifying anti-rheumatic drugs (DMARDs), and biologics], period of medication use and cumulative dosage, and positive results of antinuclear antibody (ANA), human leukocyte antigen (HLA)B-27, and rheumatoid factor were obtained from the patient files and documented. Patients were investigated for second-hand smoking. Disease activity was evaluated according to the activity criteria of Wallace et al.[11] Patients who did not meet the criteria for remission were considered active disease.

Age, gender, weight, height, and body mass index (BMI) of all the children were documented. Following 15 minutes of rest, systolic and diastolic blood pressures were measured with a sphygmomanometer using a suitable size cuff in seated and supine positions. Mean arterial pressure (MAP) was measured. The patients' age, body sizes, blood pressure levels and CIMT values were evaluated Spearman's correlation test. Variables of the patients with statistically significant results in correlation analyses were evaluated by multiple linear regression analysis.

Haemogram, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, blood glucose, triglyceride (TG), total cholesterol, high-density lipoprotein (HDL), and low density lipoprotein (LDL) cholesterol levels of the patient group were measured following 8 to 12 hours of fasting.

ULTRASONOGRAPHIC MEASUREMENTS

US examination of the patients and control group was performed in the paediatric radiology department by a single paediatric radiologist blinded to clinical and laboratory findings of the subjects (G.K. 5 years post residency experience). Prior to US examination, patients were allowed to rest in a dark, heat-controlled room for at least 10-15 min. All intima-media thickness (IMT) measurements were performed with a GE LogicS7 Expert US scanner (GE Healthcare, WI, USA). Images were obtained with a 5-15 MHz linear matrix array transducer. All examinations were performed according to a standardised scanning protocol for both common carotid arteries, as described previously.[12] The measurements were performed with mild extension and rotation of the head in the opposite direction of the carotid artery being evaluated while the patient was lying in the supine position. Bilateral common carotid arteries 1-2 cm proximal to the carotid bulb and internal carotid arteries were scanned. IMT measurements were performed manually by using a calliper on the remote wall of the bilateral common carotid arteries.[13] For each side, at least 3 measurements were taken and the mean IMT was reported in millimetres (mm). All images were recorded digitally.

The study protocol was approved by the Local Ethical Committee of School of Medicine of Erciyes University with protocol number of 2015/93 and date February 20, 2015. Children and their parents were informed about the study and included afterwards. The "volunteer and patient information form", which was in accordance with the standards of the faculty ethics committee, was signed and consent was acquired. The study was conducted in accordance with the principles of the Declaration of Helsinki.

STATISTICAL ANALYSIS

Data were evaluated by using IBM SPSS Statistics 22.0 (IBM Corp. Armonk, New York, USA). Shapiro-Wilk normality test and Q-Q graphics were used to evaluate whether the data were distributed normally. Normally distributed variables were expressed as mean±standard deviation and, non-normally distributed variables were expressed as median (minimum-maximum) values. For normally distributed variables, the Mann-Whitney U test was used for comparing two groups, and the Kruskal-Wallis test was used for comparing 3 or more groups. When a difference between groups was found using the Kruskal-Wallis test, the Dunn test was used for multiple comparisons. Categorical variables were compared with the chi-square test, and non-categorical variables were compared with Pearson correlation analysis for normally distributed variables and Spearman correlation analysis for non-normally distributed variables. Retrospectively eliminated multiple regression analysis was used to determine factors influencing the thickness of the carotid intima-media wall. Solely for regression analysis, a statistical significance level of $p<0.10$ was used; for all other statistical analyses, the $p<0.05$ threshold was used to denote statistical significance.

RESULTS

Sixty-two girls (55.4%) and 50 boys (44.6%) were included in the patient group. The median age of the patients was 11 (3-18). Thirty-two girls (59.3%) and 22 boys (40.7%) were included as a control group. The median age of the control group was 11 (3-18). There was no significant difference between groups regarding age, gender, weight, height, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP (Table 1). Glucose, BUN, creatinine, AST, ALT, albumin, total cholesterol, TG, HDL, and LDL cholesterol levels of patients were within the normal ranges. Other clinical and inflammatory features of the patient group are listed in Table 2.

EVALUATION OF CIMT IN THE PATIENT GROUP

The right and left CIMT of the patient and control groups were compared, the measurements of the patient group were higher than those of the control group (p=0.001) (Table 3). There was no significant difference between right and left CIMT values in oligoarticular JIA, polyarticular JIA, enthesitis-related arthritis, and systemic JIA subgroups of the patient group (p=0.441). While the right and left CIMT levels of the 31 patients in the active period were significantly higher than the control group (p=0.001) There was no significant difference of right and left CIMT in comparison with 81 patients in remission

TABLE 1: Demographic and anthropometric data of patients and controls.

Variables	Patients group (n=112)	Control group (n=54)	p value
Gender (F/M)	62/50	32/22	0.738
Age (years) Median (minimum-maximum)	11 (3-18)	11 (3-18)	0.955
Weight (kg) Median (minimum-maximum)	41.5 (10-76)	40.5 (16-68)	0.681
Height (m) Median (minimum-maximum)	1.42 (0.80-1.75)	1.43 (0.95-1.76)	0.639
BMI (kg/m^2) Median (minimum-maximum)	19 (12-27)	20 (15-27)	0.116
SBP (mmHg) Median (minimum-maximum)	100 (80-130)	95 (80-120)	0.120
DBP (mmHg) Median (minimum-maximum)	60 (50-90)	60 (50-90)	0.117
MAP (mmHg) Median (minimum-maximum)	73.3 (60-106.7)	68.7 (57-103.2)	0.115

F/M: Female/male; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure.

TABLE 2: Clinical and laboratory findings of patients.

Oligo JIA (%)	48 (42.8)
Poly (%)	28 (25)
ERA (%)	20 (17.8)
Systemic JIA (%)	16 (14.2)
Active/inactive patients (%)	31/81 (27.6/72.3)
ANA positivity (%)	38/85 (44.7)
HLA-B27 positivity (%)	21/56 (37.5)
Second handsmoking (%)	54/112 (48.2)
Patients on steroid treatment (%): 48 (42.8)	
Duration of prednisolone (m) [median (minimum-maximum)]: 3 (1-24)	
Cumulative dose of prednisolone (g) [median (minimum-maximum)]: 2.04 (0.07-21)	
Patients on MTX treatment (%): 93(83)	
Duration of MTX (m) [median (minimum-maximum)]: 22 (1-144)	
Cumulative dose of MTX (mg) [median (minimum-maximum)]: 860 (60-3920)	
Patients on biologic treatments (%): 35 (31.2)	
Hb (mg/dL) (X±SD): 13.04±1.25	
WBC (103/µL) [median (minimum-maximum)]: 7080 (4200-13930)	
PLT (103/µL) (X±SD): 344.56±95.13	
MPV (fL) [median (minimum-maximum)]: 7.10 (5.50-10.20)	
ESR (mm/h) [median (minimum-maximum)]: 10 (2-80)	
CRP (mg/L) [median (minimum-maximum)]: 3.36 (3.00-89.30)	

JIA: Juvenile idiopathic arthritis; Oligo: Oligoarticular; Poly: Polyarticular; ERA: Enthesitis related arthritis; ANA: Antinuclear antibody; HLA: Human leukocyte antigen; MTX: Methotrexate; SD: Standard deviation; Hb: Haemogram; WBC: White blood cell; PLT: Platelets; MPV: Mean platelet volume; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

and 31 active period patients (p=0.992/0.772). There was no statistically significant difference of right and left CIMT detected compared patients with ANA (p=0.016/0.410) and HLA-B27 positive or negative (p=0.206/0.031), and presence of cigarette exposure or not (p=0.594/0.983). There was no significant difference in right and left CIMT values in those patients receiving steroid, methotrexate (MTX) and biologic treatments compared to those who did not receive (Table 3).

The positive correlation between CIMT and age, height, weight, and BMI was detected (r=0.458, 0.409, 0.382, 0.334 respectively, p=0.001). There was no correlation between CIMT and SBP, DBP, and MAP (r=0.128, 0.131, 0.136 respectively, p>0.05).

Relationship of the Biochemical Atherosclerotic Risk Factors, Inflammatory Markers, Disease Durations, and Medications with CIMT

Since CIMT is a variable depending on age, weight, height, and BMI, partial correlation and regression analyses were used to remove the effect of dependent variables on CIMT values.

In the patient group, no relation was detected between the right and left CIMT values and glucose, total cholesterol, TG, HDL cholesterol, and LDL cholesterol values, which are the routine tests performed to exclude conventional atherosclerotic risk factors.

When partial correlation analysis between CIMT and inflammatory markers was performed, no statistically significant relation was found between CIMT and white blood cell (WBC), ESR, and CRP levels (r=0.032, p=0.746, r=0.027, p=0.781, r=0.041, p=0.670). However, a negative correlation was detected between the right CIMT and mean platelet volume (MPV) was detected (r=-0.230, p=0.017). Such a relation could not be detected between the left CIMT and MPV (r=-0.108, p=0.266) (Table 4).

TABLE 3: Evaluation of CIMT in the patient group.

	Right CIMT	p value	Left CIMT	p value
Patient (n=112)/control (n=54)	0.55 (0.45-0.75)/ 0.50 (0.35-0.60)	0.001	0.55 (0.45-0.75)/ 0.50 (0.35-0.60)	0.001
Oligo/poly/systemic JIA/ERA (n=48/28/16/20)	0.55 (0.45-0.75)/ 0.57 (0.45-0.70)/ 0.60 (0.50-0.65/ 0.57 (0.50-0.75	0.441	0.55 (0.50-0.70)/ 0.55 (0.45-0.70)/ 0.55 (0.50/0.65)/ 0.60 (0.50-0.75)	0.122
Active/remission period (31/81)	0.60 (0.50-0.70)/ 0.55 (0.45-0.75)	0.992	0.55 (0.45-0.75)/ 0.50 (0.35-0.60)	0.772
ANA (+/-) (38/47)	0.55 (0.45-0.70)/ 0.55 (0.50-0.70)	0.016	0.66 (0.50-0.70)/ 0.55 (0.50-0.75)	0.410
HLA-B27 (+/-) (21/35)	0.60 (0.50-0.75)/ 0.55 (0.50-0.70)	0.206	0.60 (0.50-0.75)/ 0.55 (0.50-0.70)	0.031
Cigarette exposure (+/-)	0.55 (0.45-0.75)/ 0.55 (0.45-0.75)	0.594	0.55 (0.45-0.75)/ 0.55 (0.45-0.75)	0.983
DMARDs (+/-) (93/19)	0.55 (0.45-0.75)/ 0.55 (0.50-0.75)	0.700	0.55 (0.50-0.75)/ 0.55 (0.50-0.75)	9.927
Steroid (+/-) (48/64)	0.60 (0.50-0.75)/ 0.55 (0.45-0.75)	0.157	0.60 (0.50-0.75)/ 0.55 (0.45-0.75)	0.423
Biologic (+/-) (35/77)	0.60 (0.45-0.65)/ 0.55 (0.45-0.75)	0.127	0.60 (0.50-0.75)/ 0.55 (0.45-0.75)	0.281

CIMT: Carotid intima-media thickness; Oligo: Oligoarticular; Poly: Polyarticular; JIA: Juvenile idiopathic arthritis; ERA: Enthesitis related arthritis; ANA: Antinuclear antibody; HLA: Human leukocyte antigen; DMARDs: Disease-modifying anti-rheumatic drugs.

No statistically significant correlations were detected between CIMT values and doses and durations of steroids and MTX (Table 4).

A statistically significant positive correlation was detected between the right CIMT and TDD (r=0.221, p=0.022), and ADD (r=0.248, p=0.010; Table 4).

With the performed modelling, it was statistically shown that MPV, TDD and ADD were independent variables for right CIMT when the effects of age, weight, height, and BMI on CIMT were excluded (p<0.01) (Table 5).

Since CIMT is a variable depending on age, weight, height, and BMI, partial correlation and re-

TABLE 4: Relations of CIMT with inflammatory markers, disaese durations, and medications.

	Right CIMT		Left CIMT	
	r value	p value	r value	p value
WBC	0.032	**0.746**	-0.016	0.872
MPV	-0.230	0.017	-0.108	0.266
ESR	0.027	0.781	0.059	0.543
CRP	0.041	0.670	-0.028	0.774
TDD	0.221	**0.022**	0.121	0.212
ADD	0.248	**0.010**	0.171	0.077
Steroid dose	0.166	0.326	0.073	0.667
Duration of steroid usage	0.135	0.426	0.125	0.459
Dose of MTX	0.286	0.086	0.175	0.300
Duration of MTX	0.230	0.170	0.162	0.339

CIMT: Carotid intima-media thickness; WBC: White blood cell; MPV: Mean platelet volume; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; TDD: Total disease duration; ADD: Active disease duration; MTX: Methotrexate.

TABLE 5: Multiple regression analysis of variables related with right CIMT.

Dependent variable		Model 1			Model 2			Model 3	
Right CIMT	Independent variable	β	p value	Independent variable	β	p value	Independent variable	β	p value
	Age	0.018	<0.001*	Age	0.021	<0.001*	Age	0.020	<0.001*
	Weight	0.001	0.794	Weight	0.002	0.404	Weight	0.002	0.392
	Height	-0.192	0.199	Height	-0.296	0.044*	Height	-0.303	0.040*
	BMI	-0.005	0.338	BMI	-0.009	0.095*	BMI	-0.009	0.106
				MPV	-0.016	0.037*	MPV	-0.018	0.015*
				ADD	0.001	0.021*	TDD	0.001	0.019*
		R2=0.224 p<0.001			R2=0.301 p<0.001			R2=0.302 p<0.001	

*p<0.10; CIMT: Carotid intima-media thickness; BMI: Body mass index; MPV: Mean platelet volume; ADD: Active disease duration; TDD: Total disease duration.

gression analyses were used to remove the effect of dependent variables on CIMT values (Table 5).

DISCUSSION

In this study, the CIMT values of the patient group were higher than the healthy control group (p=0.001) (Table 3). Similar to the literature, this situation showed that children with JIA have a higher risk of atherosclerosis compared to the healthy population.[3,4] Considering the relationship between CIMT and inflammation markers, no relationship was found between CIMT and WBC, ESR and CRP, although there are different results in the literature. However, an important finding of this study is the negative correlation between CIMT and MPV. The determination of TDD and ADD as independent variables for CIMT, similar to adult RA studies, emphasized the importance of early and aggressive treatment in the prevention of CVD.

Atherosclerosis, the main cause of CVDs, is a chronic inflammatory process. The first step in this process is endothelial dysfunction.[14] Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1 play an important role in pathogenesis.[6] It is also known that the same cytokines play an important role in JIA pathogenesis.[6]

Risk factors for CVDs include family history, hypercholesterolemia, dyslipidemia, insulin resistance, obesity, physical inactivity, and smoking.[9] In patients with JIA, classical risk factors also contribute to the endothelial dysfunction caused by chronic inflammation. We included patients with non-obese, normal ranges of blood pressure, lipid, and blood glucose levels to exclude classic risk factors. The right and left CIMT values of the patient group were significantly higher than those of the control group. In the majority of the previous studies in JIA, CIMT levels of the patient groups were higher than those of the controls and correlated with corticosteroid treatment, disease activation, BMI, blood pressure, dyslipidemia, and age.[15-19] Satija et al. studied 31 JIA patients and found that arterial elasticity was decreased, but there was no difference in CIMT levels.[20] Our study is more valuable because the classical risk factors were excluded and a large number of patients were included compared to other studies. We suggested that increased CIMT is important for endothelial dysfunction and may be an early stage of atherosclerosis that can develop in the future.

In this study, there was no correlation between disease subtypes, activation status, ANA, HLA-B27 and CIMT levels. In contrast to our study, The FINNS study suggested that positive ANA results are a risk factor for CVDs, in the young women.[21] In adult studies, no significant relation was detected between CIMT and HLA-B27 in patients with spondyloarthritis.[22] We did not find any study investigating CIMT and relation of ANA, and HLA-B27 positivity in JIA patients. Studies on CIMT level differences in JIA subtypes are controversial. While no significant difference was detected between subgroups in some studies, other studies found that CIMT levels were higher in polyarticular and systemic JIA patients.[15,16,18,19,23] In 2 studies investigating the effect of disease activity on CIMT levels, it was stated that

there was no difference regarding remission.[19,23] Sozeri et al. found that PWV and AIx considered direct and indirect signs of arterial stiffness higher in patients during the active stage of systemic JIA.[24] In our study, we could not detect any difference in the CIMT values of patients during the active disease stage. We believe that this should be further investigated in patient groups during active and remission stages, with more homogeneously disturbed age and disease subgroups.

Relationships between CIMT and body size, BMI, and blood pressure were reported in healthy children.[25] Our results showed that there was a significant positive relation between right and left CIMT and weight, height, and BMI. In our patients with blood pressure within normal ranges according to their age, no correlation was detected between CIMT and blood pressure. Since CIMT levels were dependent on age and body sizes, statistical analyses performed by excluding these factors. Our results showed that CIMT values were related to MPV, TDD, and ADD levels.

In our study, there was no significant correlation between CIMT and some inflammatory markers including WBC, ESR, and CRP. In adult studies, 3 increased parameters were suggested to be independent risk factors for CVDs.[26-28] In our juvenile patient group, no differences in CIMT values in the active and remission stages indicated that CIMT levels were related to duration of disease and inflammation.

MPV is a marker of thrombocyte function and activation. There is an inverse relation between thrombocyte count and MPV. During inflammation, multiple large-sized thrombocytes with increased reactivity migrate to inflamed areas and thus MPV decreases.[29] Multiple adult studies have suggested that MPV can be used as a cardiovascular risk factor and that an increase in MPV indicates an increased risk for CVD.[30] When we investigated the relationship between MPV and inflammatory diseases in the current literature, there was a decrease in MPV recorded during periods of Familial Mediterranean fever attack.[31,32] In studies of patients with RA and ankylosing spondylitis, it was reported that MPV decreases during activation periods, with an increase in thrombocyte count and MPV during inactive periods, along with a decrease in thrombocyte count. It is suggested that a decrease in MPV levels in JIAs caused by the accumulation of thrombocytes in inflamed areas, along with an increase in thrombocyte consumption. It was reported that the opposite change occurred secondary to the suppression of inflammation by anti-inflammatory medications and anti-TNF agents.[33] In our study, we detected a negative correlation between CIMT and MPV. In regression analysis, it was shown that MPV was an independent risk factor. This emphasises the value of low MPV levels in patients with JIA regarding the increased risk of CVD.

The treatment of JIA has evolved in the last 30 years. With the increasing use of DMARDs in adjunct with NSAID and steroids and the use of biological agents after 2000, early and aggressive multidisciplinary treatment strategies have been developed. It is known that corticosteroids cause obesity, dyslipidemia, hypertension, and insulin resistance, thereby increasing the risk of CVDs. It was shown that prednisolone treatment increased CVD risk depending on dosage in adult RA patients. In contrast, the APPLE study on children with systemic lupus erythematosus showed that low dose glucocorticoid use was negatively correlated with CIMT.[34] Many adult studies suggested that anti-TNF treatment is related to a decrease in both CIMT and CVD. Similarly, it was shown that MTX treatment reduced CVD in RA patients. Breda et al. investigated the potential cardiovascular effect of anti-TNF treatment on JIA in the prospective study.[17] Decreased CIMT measurement was detected following 12 months of treatment in both subgroups, regardless of whether patients received biologic agents or not.[17] The study of Berezhny et al., investigating the relationship between CIMT and the duration and dose of MTX and prednisolone, there was a correlation between CIMT and the duration of disease and MTX treatment in patients with the articular form of JIA.[35] However, there was no correlation between CIMT and the duration of disease, glucocorticoid and MTX treatment, and cumulative dose of glucocorticoid in patients with the systemic form of JIA. In our study, we did not detect any significant difference among CIMT values in patients regardless of whether they

were receiving steroids, DMARDs, and biological agents. Cumulative steroid and MTX doses and periods did not correlate with CIMT. These findings suggest that, since patients treated more aggressively during the active period and reduced dose of treatment during remission, the atherogenic effect of disease was balanced by the anti-atherogenic effect of medications and thus not causing differences regarding CIMT levels.

In the literature, especially in studies on adults with RA, it was stated that there is a positive correlation between disease duration and CIMT levels.[22] In the study by Guidice et al. published in 2018, CIMT and aortic IMT measurements of the 39 children with rheumatologic disease (23 JIA, 9 juvenile spondyloarthropathy, and 7 connective tissue disease) were higher than the control group.[36] This thickness was also correlated with age of diagnosis. Our study also indicated that TDD and ADD were correlated with CIMT and independent risk factors.

The reason for the higher thickness of right CIMT in our study may be secondary to the atherosclerotic alterations started in the right carotid artery. Several autopsy studies have suggested that the distal aorta is affected first, followed by the carotid arteries.[3] We could not claim anything about this alignment.

There were some limitations to our study. We did not consider the lifestyle or daily physical activities (or inactivities) of the patients. In order to analyse the real influence of treatment on CIMT, the patients need follow up. We believe that it would be better to investigate the relationship between biological agents with CIMT in another study.

CONCLUSION

In conclusion, our study indicated that children with JIA have an increased risk of atherosclerosis compared to healthy children, regardless of subtype of the disease. Decreases in MPV, and increases in TDD, and ADD were detected as independent risk factors for an increase of CIMT. Our results suggest that the adequate and timely treatment of patients will decrease CVD risk.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mustafa Armut;* ***Design:*** *Mustafa Armut, Ayşenur Paç Kısaarslan;* ***Control/Supervision:*** *Ruhan Düşünsel, Betül Sözeri;* ***Data Collection and/or Processing:*** *Mustafa Armut, Gonca Koç;* ***Analysis and/or Interpretation:*** *Mustafa Armut, Ruhan Düşünsel, Ferhan Elmalı;* ***Literature Review:*** *Mustafa Armut, Betül Sözeri;* ***Writing the Article:*** *Mustafa Armut;* ***Critical Review:*** *Ruhan Düşünsel, Betül Sözeri, Ayşenur Paç Kısaarslan;* ***Other:*** *Gonca Koç, Ferhan Elmalı, Mustafa Armut.*

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