# Vascular involvement in pediatric inflammatory bowel disease

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#### ABSTRACT

**Objective:** Patients with inflammatory bowel disease (IBD) have a higher incidence of cardiovascular disease (CVD). Early diagnosis of arterial damage is essential to prevent future vascular risk. We aimed to assess the vascular involvement IBD by monitoring inflammation parameters, echocardiography, augmentation index (Alx); carotid pulse wave velocity (PWV), carotid intima-media thickness (cIMT), and blood pressure.

**Method:** The patient population included 25 subjects with a previously biopsy-proven diagnosis of IBD who had been on treatment for at least one year. Carotid PWV, AIx, and cIMT of the patients were measured.

**Results:** Twenty-five patients (15 female and 10 male) with IBD and 25 healthy controls were included in this present study. There was a significant difference between the carotid PWV values (mean 4.84 $\pm$ 0.39, 4.49 $\pm$ 0.17, respectively, p <0.001), but no differences were observed in the cIMT and Alx values.

**Conclusion:** The carotid PWV values assessing arterial stiffness may be effective, safe, and easy to detect subclinical atherosclerosis in children with IBD. Larger studies should be carried out to evaluate other indicators of early atherosclerosis and arterial stiffness such as cIMT and AIx.

Keywords: Alx, cIMT, children, inflammatory bowel disease, PWV

# **INTRODUCTION**

Inflammatory bowel disease (IBD) is a chronic inflammatory, dysfunctional immune-mediated disorder of the gastrointestinal tract in genetically predisposed children.<sup>1-3</sup> It is classified as Ulcerative Colitis (UC) and Crohn's Disease (CD).<sup>1,3</sup> Approximately, 20-30% of patients are diagnosed in childhood and adolescence.<sup>4</sup> In children with IBD, host factors, and genetic, environmental, and microbial effects result in a dysregulated mucosal immune response against the intestinal microbiota.<sup>5</sup> Consequently, IBD develops due to abnormal recognition of microbiota antigens by innate immune cells, resulting in

inflammation in the bowel.<sup>3</sup> Inflammation plays a critical role in the pathophysiology of IBD.<sup>6,7</sup> Chronic inflammation causes an increase in reactive oxygen species (ROS). The production of free radicals leads to tissue remodeling and the intensification of the process of atherosclerosis.<sup>8</sup> Recently, a relationship between atherosclerosis and chronic inflammation has been identified, and early endothelial dysfunction has been observed in chronic inflammatory disorders such as IBD.<sup>3</sup> Patients with IBD have a higher incidence of cardiovascular disease (CVD).<sup>9-11</sup> The vascular disease risk in IBD is estimated to be three to four-fold higher than that in the general population.<sup>2,4,7,8</sup>



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Early diagnosis of arterial damage is essential to prevent future vascular risk considering that subclinical atherosclerosis can be reversed with early diagnosis and intervention. Measurement of increased carotid intima-media thickness (cIMT), carotid pulse wave velocity (PWV), and augmentation index (AIx) are early diagnostic tools. Carotid intima-media thickness, which is assessed using B-mode ultrasonography, is a valid surrogate marker of atherosclerotic disease.<sup>12</sup> Arterial stiffness due to reduced arterial compliance is one of the major signs of vascular aging. Arterial stiffness, the main index for estimating arterial elasticity, is assessed by carotid PWV and AIx measurement.<sup>13</sup> These methods are repeatable, reliable, easy, and noninvasive for early detection of increased arterial stiffness at an early stage.<sup>14</sup>

Several studies have investigated the relationship between cardiovascular and inflammatory bowel diseases so far. The present study aimed to assess the vascular involvement in pediatric inflammatory bowel disease by monitoring inflammation parameters, echocardiography, Alx; carotid PWV, cIMT, and blood pressure.

# **MATERIAL AND METHODS**

This case-controlled study was performed at a single center between January 2018 and January 2019. The patient population included 25 patients with a previous biopsy-proven diagnosis of IBD who had been on treatment for at least one year and had come for follow-up visits between 2018-2019. There were no known co-morbidities such as hypothyroid, hypertension, dyslipidemia; systemic autoimmune disease, active infection, diabetes mellitus; and Mediterranean fever syndrome. The control group was selected from healthy pediatric nephrology outpatients of similar age and sex to the patient group (n=25) and without any chronic disease. The study was approved by the Ethical Committee of the Ege University Hospital, Medical School. Written informed consent was signed by parents or caregivers. The study was conducted in accordance with the Declaration of Helsinki guidelines.

Inflammatory bowel disease is diagnosed with a detailed clinical story, physical examination, laboratory tests, and gastrointestinal endoscopy/colonoscopy. Age at the time of IBD diagnosis, complaints, gender, and family history were recorded. The patients' weight, height, body mass index (BMI), and standard deviation scores (SD) at the initial and last visits were also recorded. All patients underwent a physical examination, including measurement of weight using a digital scale and height using a stadiometer. Their body mass index was calculated as weight in kilograms divided by height in meters squared. We used the standard deviation scores that were calculated

according to the Turkish growth charts to evaluate the weight, height, and BMI values across different age and gender groups.<sup>15</sup>

Blood samples were drawn by venipuncture to assess routine blood parameters. Complete blood count, biochemical parameters, and acute phase reactant levels (sedimentation, C-reactive protein) were evaluated after overnight fasting for at least eight hours at the time of the last visit. The samples were analyzed in a local laboratory.

Blood pressure was measured in the rested sitting position using the Omron automatic blood pressure device and a suitable sized cuff. The average systolic and diastolic blood pressure values over %95 according to age, sex, and height were considered as hypertension after at least three measurements.<sup>16</sup>

Carotid pulse wave velocity (PWV), AIx, and cIMT of the patients were measured. Carotid-femoral peripheral wave velocity and AIx were calculated using Vicorder three times (Skidmore Medical Limited, Bristol, UK). AIx was calculated as the difference between the first and second systolic peaks of the central aortic waveforms and defined as the percentage of the wavelength. Siemens Acuson Antares instrument and VFX-7-13 MhZ linear probe were used for the measurements of cIMT.

### Statistical analysis

Statistical analysis was performed using basic statistical methods. The distribution of the data was calculated using the Kolmogorov-Smirnov normality test. Independent sample t-test was used to compare numerical data between groups. Pearson test was used to calculate the correlation between cIMT, carotid PWV, and Alx with laboratory parameters. The significance level was accepted as p<0.05. Data were analyzed using IBM SPSS 22.0 software package (IBM Corp., Armonk, NY).

# **RESULTS**

Twenty-five patients (15 female and 10 male) with IBD, mean age 14.12±4.04 years, were included in this present study. The mean duration of follow-up was 3.33±3.00 years. Twenty-five age-matched (mean 13.20±4.03 years) subjects were selected as healthy control. Of the healthy controls, 11 were female and 14 were male. The anthropometric measurements of IBD patients and the control group were presented in Table 1.

Eight (32.0%) patients had diarrhea, five (20.0%) abdominal pain, three (12.0%) weight loss; three (12.0%) diarrhea and abdominal pain, one patient (4.0%) fatigue, and five had (20.0%) all of the symptoms.

Table 1. Anthropometric measurements of IBD patients at the time of diagnosis					
Patient group	Minimum	Maximum	mean±SD		
Height SD	-2.95	0.76	-0.94±1.20		
Weight SD	-5.52	1.29	-1.26±1.69		
BMI SD	-6.34	2.51	-0.89±1.97		
Healthy controls					
Height SD	0.53	1.34	0.99±0.22		
Weight SD	0.22	1.27	0.76±0.43		
BMI SD	0.77	1.37	0.87±0.57		
SD: standard deviation score, BMI: body mass index, cm: centimeter; kg: kilogram, IBD: inflammatory bowel disease					

Based on the complaints, acute phase reactant, symptoms, and values stool examination at the last visit; 15 (60%) IBD patients were considered to be in remission. The remaining 40% of the patients

The mean value of three blood pressure measurements was normal in all of the IBD patients. Echocardiographic evaluation was normal in all IBD patients.

had active disease.

There was no significant difference in cIMT, Aix, and carotid PWV values between the two groups, and their weight SD and height SD were significantly lower, while the CRP and sedimentation

values were significantly higher in patients with active disease compared to patients in remission (Table 2).

When the patient and healthy control groups were compared, there was a significant difference in carotid PWV values (mean  $4.84\pm0.39$ ,  $4.49\pm0.17$ , p<0.001, respectively), while no difference was observed in cIMT and Alx values (Table 3).

There was no significant relationship between the CRP and sedimentation values and the carotid PWV, cIMT, and AIx levels in patients with inflammatory bowel disease.

disease activity					
	Patients with an active disease mean±SD	Patients with remission mean±SD	p value		
Age (year)	14.85±3.89	13.63±4.20	0.09		
Weight SD	-2.26±1.02	-0.9±1.49	0.019		
Height SD	-1.81±1.15	-0.47±1.23	0.039		
BMI SD	-1.62±-0.31	1.39±1.47	0.085		
CRP (mg/dL)	2.34±2.65	0.13 ±0.17	0.004		
Sedimentation (mm/h)	35.00±16.79	10.23±3.70	<0.001		
25 OH vitamin D (ng/mL)	19.50±12.79	22.62±9.03	0.631		
Hemoglobin g/L	11.37±1.67	11.62±2.21	0.731		
White blood cell 10*3/uL	11.605±6.421	10.188±4.971	0.540		
Absolute neutrophils count 10*3/uL	7.705±3.930	6.469±5.147	0.527		
cIMT (mm)	0.47±0.03	0.47±0.02	0.663		
Alx	31.60±7.98	23.33±10.95	0.052		
Carotid PWV (m/s)	4.85±0.17	4.81±0.48	0.652		

Table 2. Comparative analysis of the demographic, anthropometric and biochemical data of the IBD patients according to disease activity

SD: standard deviation score, BMI: body mass index, cm: centimeter; kg: kilogram, IBD: inflammatory bowel disease, CRP: C reactive protein, PWV: pulse wave velocity, cIMT: carotid intima-media thickness, AIx: augmentation index

Table 3. Comparative analysis of the cIMT, AIx, and carotid PWV values between the IBD patients and healthy control group					
	IBD patients mean±SD	Healthy controls mean±SD	p value		
cIMT (mm)	0.47±0.07	0.47±0.02	0.819		
Carotid PWV (m/s)	4.84±0.39	4.49±0.17	<0.001		
Alx	26.80±10.10	23.24±8.37	0.181		
SD: standard deviation score, IBD: inflammatory bowel disease, PWV: pulse wave velocity, cIMT: carotid intima-media thickness, AIx: augmentation index					

# DISCUSSION

There are limited published data on vascular involvement in pediatric patients with IBD. The present study was the first to report the evaluation of preclinical atherosclerosis using carotid PWV, Alx, cIMT measurements; ECG and blood pressure values altogether in pediatric IBD patients.

Cardiovascular risk is a well-known complication of chronic inflammatory conditions. Systemic inflammation has been associated with premature endothelial dysfunction and atherosclerosis is considered as a chronic inflammatory process.<sup>17,18</sup> Although relatively rare in the pediatric IBD population, atherosclerosis is a significant comorbidity that requires early diagnosis and management. Early diagnosis of arterial damage is essential to prevent future vascular risk since subclinical atherosclerosis can be reversed with early diagnosis and intervention. In a study with pediatric patients<sup>19</sup>, carotid PWV values were significantly higher in patients with IBD. In the present study, we similarly found that carotid PWV values were significantly higher than the control group (mean 4.84±0.39, and 4.49±0.17, respectively, p <0.001). We could speculate that the patients' high PWV values due to the changes in the vascular wall could be related to the inflammation underlying IBD, considering that many of our IBD patients are in the active phase (40%), unlike the healthy controls. Lurz et al. found that PWV was normal in children with IBD in remission or with mild disease activity.<sup>20</sup> Nonetheless, in our study, we found that our patients in remission had higher PWV values than control patients. We may have achieved such different results (60% vs. 68%, respectively) as the remission rate of our patients was lower than the rate in the study conducted by Lurz et al.<sup>20</sup> Another important finding in our study was the insignificant increase in Alx and cIMT in IBD patients compared to healthy controls. Similar to our study, Yildirim et al. found PWV to be more useful than the cIMT in detecting vascular damage in Behcet Disease.<sup>21</sup> Multicenter studies with a larger sample size may be needed to obtain a significant difference for these two parameters. We speculate that this insignificant result might be related to the overall high rate of clinical remission (60%).

When we compared the IBD patients in the active phase and those in remission, the latter group had higher Alx and carotid PWV values than the former. However, this difference was not significant. Chronic low-grade inflammation might be the cause of increased atherosclerotic burden and vascular aging in IBD patients despite remission. Chronic exposure to even moderate levels of inflammatory factors appears to promote atherosclerosis.<sup>22,23</sup>

When the IBD patients were compared according to disease activity, the SD of weight and height were significantly lower, and CRP and sedimentation values were significantly higher in the patients with active disease. We may have observed low weight SD values due to sudden weight loss as a result of increased catabolism and gastrointestinal loss during the active disease period. The tissue damage that ensues triggers a host of events including increased energy expenditure, fat mobilization, proteolysis, negative nitrogen balance, gluconeogenesis, and anorexia and weight loss. Increased CRP and sedimentation values due to inflammation may be observed. Cortisol, which is elevated during a chronic inflammatory response, can cause growth stunting by impairing protein synthesis.<sup>24</sup> Corticosteroids are anti-inflammatory agents which are effective and commonly used in the treatment of CD and UC in children.<sup>1,2</sup> The beneficial effects of corticosteroids as immunosuppressive and antiinflammatory agents are accompanied by adverse effects on growth, especially when supra-physiological doses are administered long-term. The fact that our patients who were included in the study received steroid therapy over physiological limits until induction may have caused the height SD rates to be lower than normal for their age. Besides, as a limitation of our study, we did not know whether our patients with short stature suffered from structural short stature as their parent height was not recorded.

Interestingly, in IBD patients, there was no significant relationship between the CRP and sedimentation values and carotid PWV, cIMT and AIx levels. A more significant result could have been obtained if the sample group was larger. Another reason might have been the patients with protein and energy malnutrition, leading to impaired acute phase reactant response in our study. In conclusion, the carotid PWV values assessing arterial stiffness may be effective, safe, and easy to detect subclinical atherosclerosis in children with IBD. Larger studies should be carried out to evaluate other indicators of early atherosclerosis and arterial stiffness such as CIMT and Alx.

#### **Ethical approval**

This study has been approved by the Ege University Medical Research Ethics Committee (approval date 17/12/2020, number 20-12.1T/35). Written informed consent was signed by parents or caregivers.

#### Author contribution

Surgical and Medical Practices: EKT, ST, ED, EL, SA, FÇ; Concept: EKT, MK, EL, FÇ; Design: EKT, ST, ED, MK; Data Collection or Processing: EKT, ST, ED, MK, İKB, EL, SA, FÇ; Analysis or Interpretation: EKT, MK, EL, FÇ; Literature Search: EKT, İKB, FÇ; Writing: EKT, İKB, SA, FÇ. All authors reviewed the results and approved the final version of the article.

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#### **Conflict of interest**

The authors declare that there is no conflict of interest.

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