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Arterial Stiffness, Distensibility, and Strain in Asthmatic Children

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Background: We hypothesized that since asthma is a chronic inflammatory disease, it could lead to the early development of atherosclerosis in childhood-onset asthma. The aim of this study was to investigate arterial stiffness, distensibility, and strain of different peripheral arteries, the parameters of which can be used to detect atherosclerosis in asthmatic children.

Material/Methods: We studied 22 pediatric patients with asthma and 18 healthy children. Fasting blood glucose and cholesterol levels were evaluated to exclude children with diabetes and hyperlipidemia, which are risk factors for atherosclerosis. Renal, carotid, and brachial arteries diameters were measured. Using the measured data, stiffness, distensibility, and strain of the arteries of all children were calculated.

Results: Pulse pressure, systolic and diastolic blood pressure, heart rate, cholesterols, and glucose levels of the obese individuals were similar to the controls. In carotid arteries there were no statistical differences regarding stiffness, distensibility, and strain. According to multiple ANCOVA analysis, distensibility and strain of right and left brachial arteries and right renal artery were higher, whereas right renal artery stiffness was lower in asthmatic children than in controls. Approximately one-fifth of the change in the left and right brachial arteries and right renal artery distensibility and strain and a small portion of the change in the right renal artery stiffness were associated with asthma. In contrast, left renal artery distensibility, strain, and stiffness were not associated with asthma.

Conclusions: Peripheral arteries had higher distensibility and strain, and lower stiffness in asthmatic children than in controls.

MeSH Keywords: Arteries • Asthma • Child • Vascular Stiffness

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Background

Asthma is a chronic inflammatory disorder of the airways, associated with airway obstruction and hyper-responsiveness. It is characterized by recurrent episodes of wheezing, breathlessness, and coughing [1]. Asthma is a multifactorial disease and interactions between genetic and environmental factors play roles in its pathogenesis. A meta-analysis suggested that IL13–1112C/T and +2044A/G polymorphisms were associated with increased pediatric asthma risk [2]. Some studies revealed that the genetic pathogenic variants may be responsible for the reduced immunity, reporting low cellular eosinophilic response and relatively low expression of IL-12, IFN-γ, and TNF-α in children in remission. It has also been suggested that the consequent prolonged psychological stress can disturb recovery from asthma and may contribute to the development of chronic asthma in children [3]. Atherosclerosis and asthma are both chronic inflammatory disorders. Asthma is not only associated with multiple markers of chronic systemic inflammation, but also with increased risk of atherogenesis [4]. Chronic inflammation via common inflammatory pathways [5,6] is associated with atherosclerosis [7], endothelial dysfunction [8], arterial stiffness [9], and subsequent adverse cardiovascular events [10]. Some studies reported that peripheral arterial stiffness is related to atherosclerosis and adverse cardiovascular outcomes [11,12]. Inflammation causes impairment of endothelial cell function, and accelerates atherosclerosis [8].

Elevated arterial stiffness is associated with myocardial infarction, heart failure, renal disease, stroke, and increased total mortality rates in adults. Thus, elevated arterial stiffness is considered as a marker of subclinical atherosclerosis [13]. Arterial stiffness is a mechanical property related to vascular impedance and the afterload presented to the left ventricle. Reduction in arterial distensibility leads to increased pulse pressure, and impedance of arterial flow and pulsatile cardiac workload [14].

The present case-control study was designed to measure arterial stiffness, distensibility, and strain from different peripheral arteries in asthmatic children and to compare these to healthy control subjects to determine the impact of asthma on cardiovascular outcome.

Material and Methods

We studied 22 pediatric patients (14 male and 8 female) selected randomly from those with bronchial asthma, and 18 healthy subjects. The individuals who met the criteria for bronchial asthma (1) diagnosis were included in the study. Exclusion criteria were: comorbid diseases, such as upper or lower respiratory infection, allergic rhinitis, gastroesophageal reflux, or obesity; chronic cardiovascular or pulmonary diseases; acute asthma attack during the last 4 weeks; a history of chronic inflammation/rheumatological disorders, diabetes, hypertension, or hypercholesterolemia; and with autoimmune diseases and smoking exposure. The control group consisted of 18 healthy children chosen from the population referred to the pediatric cardiology out-patient clinics. After approval of the Ethics Committee of the institution, informed consents signed by the parents were obtained.

Present and past history, symptoms, and signs of all patients were recorded by the same physician. Heart rate (HR) and blood pressure (BP) of all children were recorded. After 12-hour fasting, the blood samples of the patients were measured for glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

All asthmatic patients involved in this study were receiving inhaled corticosteroids treatment for various periods of time and in various doses

BP measurements were performed after 15 minutes of rest; the right brachial artery pressure was measured by sphygmomanometer with an appropriate cuff. Both systolic (Ps) and diastolic blood pressure (Pd) were measured, and after 3 measurements, the mean value was recorded. Pulse pressure (PP) was calculated as PP = Ps – Pd.

Distensibility, strain, and stiffness were calculated as follows:
Distensibility (cm^2. dyn-1) = 2 × (arterial diameter systolic – arterial diameter diastolic) / (arterial diameter diastolic × pulse pressure [14].
Strain = (systolic diameter-diastolic diameter)/diastolic diameter) [14].
Stiffness (mm Hg) = Logarithm (systolic BP/diastolic BP)/ strain [15].

Carotid arteries were measured from 1 cm proximal to the bifurcation level, brachial arteries were measured in the middle of the plane arm, and renal arteries were measured 1 cm from the origin of the abdominal aorta. Every measurement was performed at the widest systolic and diastolic arterial diameter. All measurements were performed by the same radiologist. Arterial measurements were made by use of a GE Logic 7S Duplex ultrasonography device with probe at a frequency of 3.1–10 MHz for B scan.

Statistical analyses

The statistical analyses were performed using SPSS. Independent *t* test and ANCOVA test were used to analyze the data. The arithmetic average of radiological measurements of asthmatic and healthy children was compared with the independent *t*

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Table 1. Characteristics of the asthmatic children and control group.

	Asthma patients 22 (M/F=14/8)	Control group 18 (M/F=10/8)	*p* value
Age (year)	9.09±3.19	12.15±3.71	**0.009***
Systolic BP (mmHg)	106.742±6.450	100.796±7.666	0.115
Diastolic BP (mmHg)	65.136±6.636	60.481±5.061	0.157
Pulse pressure	41.606±5.831	38.315±6.908	0.110
Heart rate (bpm)	84.68±14.93	86.42±10.87	0.537
Glucose (mg/dL)	89.19±7.19	88.45±9.13	0.650
Total cholesterol (mg/dl)	152.5±32.6	147.5±24.6	0.125
LDL cholesterol (mg/dl)	82.16±11.8	75.1±15.1	0.135
HDL cholesterol (mg/dl)	53.6±12.3	50.5±12	0.128
Triglyceride (mg/dL)	84.88±32	80±25	0.145

* Statistically significant ($p<0.05$); BP – blood pressure; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

Table 2. Radiological measurements of carotid arteries in children with asthma compared to the control group.

Radiological measurements	Groups	n	Mean	S.D.	t	Sig.
Arterial CCA R-distensibilty	Asthma	22	17.426	7.685	–.413	.682
	Control	18	18.508	8.884		
Arterial CCA R-strain	Asthma	22	.207	.082	–1.017	.316
	Control	18	.234	.085		
Arterial CCA R-stiffness	Asthma	22	2.775	1.206	1.788	.082
	Control	18	2.190	.755		
Arterial CCA L-distensibility	Asthma	22	15.666	6.502	1.638	.110
	Control	18	12.685	4.594		
Arterial CCA L-stiffness	Asthma	22	3.004	1.234	–.453	.653
	Control	18	3.218	1.749		
Arterial CCA L-strain	Asthma	22	.185	.061	.854	.398
	Control	18	.169	.058		

CCA – common carotid artery; R – right; L – left; SD – standard deviation.

test. The important parameters according to the independent *t* test were evaluated by using multiple ANCOVA analysis. The mean age of controls (mean age, 9.09 years) was higher than asthmatic children (mean age, 12.15 years). Therefore, age variability was taken as covariate variable in multiple ANCOVA analysis. ANCOVA analysis was performed in asthma and control groups as fixed factors and age variables as covariate variable. Statistical significance was defined as $p<0.05$.

Results

The study group consisted of 22 children with asthma. There was no difference between the groups in terms of Ps, Pd, pulse pressure, (HR), fasting glucose, or cholesterols. The mean age was higher in the control group than in asthmatic patients (Table 1).

We evaluated stiffness, distensibility, and strain from carotid, renal, and brachial arteries. Carotid arteries measurements showed statistically significant differences regarding stiffness, distensibility and strain (Table 2).

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Table 3. Radiological measurements of brachial arteries in children with asthma compared to the control group.

Radiological measurements	Groups	n	Mean	S.D.	t	Sig.
Brachial artery R-distensibilty	Asthma	22	9.522	4.030	4.209	**.000**
	Control	18	5.370	2.055		
Brachial artery R-strain	Asthma	22	.116	.051	4.012	**.000**
	Control	18	.068	.020		
Brachial artery R-stiffness	Asthma	22	5.128	2.395	–2.841	**.007**
	Control	18	7.428	2.723		
Brachial artery L-distensibilty	Asthma	22	9.556	3.275	4.046	**.000**
	Control	18	5.845	2.318		
Brachial artery L-strain	Asthma	22	.115	.039	3.664	**.001**
	Control	18	.076	.027		
Brachial artery L-stiffness	Asthma	22	4.758	1.656	–3.093	**.004**
	Control	18	6.785	2.474		

R – right; L – left; SD – standard deviation.

Table 4. Radiological measurements of renal arteries in children with asthma compared to the control group.

Radiological measurements	Groups	n	Mean	S.D.	t	Sig.
Renal artery R-distensibilty	Asthma	22	7.470	1.953	3.397	**.002**
	Control	18	4.979	2.681		
Renal artery R-strain	Asthma	22	.092	.030	3.087	**.004**
	Control	18	.063	.028		
Renal artery R-stiffness	Asthma	22	6.231	3.284	–2.158	**.037**
	Control	18	8.358	2.860		
Renal artery L-distensibilty	Asthma	22	7.366	2.083	3.062	**.004**
	Control	18	5.200	2.388		
Renal artery L-strain	Asthma	22	.088	.019	2.875	**.007**
	Control	18	.067	.027		
Renal artery L-stiffness	Asthma	22	5.859	1.457	–2.489	**.020**
	Control	18	7.769	2.977		

R – right; L – left; SD – standard deviation.

The mean values of distensibility and strain of right and left brachial arteries were higher, whereas stiffness was lower in asthmatic children than in controls (Table 3).

In comparison with the healthy individuals, the right and left renal arteries means had higher distensibility and strain and lower stiffness in the asthmatic group (Table 4).

When the age factor was considered as covariates in ANCOVA analysis (Table 5), the right and left brachial artery distensibility and strain were approximately 2 times higher in the asthmatic group than in controls. Approximately one-quarter of the difference (22.2–28.5%) was due to asthma for both left and right arteries. The distensibility and strain of the right renal artery were higher, whereas right renal artery stiffness was lower in asthmatic children; 19.2% the differences in right renal artery distensibility and 15.7% of the differences in the right artery strain were due to asthma. A very small portion of the change in the right renal artery stiffness (7.9%) was associated with asthma; 26.4% of the differences in left renal artery distensibility and 23.4% of the differences in strain in the same artery were due to age, not associated with asthma. The results of the analyses that were not statistically significant are not included in the Table 5.

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Table 5. The radiological values derived by ANCOVA analyses based on age *vs.* groups.

Radiological measurements	Variables	F	Sig.	Partial eta squared	R^2	Adj. R^2
Brachial artery R-distensibility	Age	1.61	.212	.042		
	Groups	6.67	**.014**	.153	.322	.285
Brachial artery R-strain	Age	.87	.358	.023		
	Groups	6.47	**.015**	.149	. 284	.245
Brachial artery L-distensibility	Age	.34	.565	.009		
	Groups	8.90	**.005**	.194	.307	.270
Brachial artery L-strain	Age	.06	.803	.002		
	Groups	8.10	**.007**	.180	.267	.222
Renal artery R-distensibility	Age	.01	.944	.000		
	Groups	7.45	**.010**	.168	.233	.192
Renal artery R-strain	Age	.00	.948	.000		
	Groups	6.15	**.018**	.142	.201	.157
Renal artery R-stiffness	Age	.71	.405	.019		
	Groups	5.06	**.030**	.120	.126	.079
Renal artery L-distensibility	Age	5.524	**.024**	.130		
	Groups	1.821	.185	.047	.302	.264
Renal artery L-strain	Age	4.827	**.034**	.115		
	Groups	1.566	.219	.041	.273	.234

Groups: Children with Asthma and normal children. R – right; L – left. No statistically significant variables were excluded from the table.

The multiple ANCOVA analysis revealed that approximately one-fifth of the change in left and right brachial arteries distensibility, strain and right renal artery distensibility, strain, and stiffness were associated with asthma. In contrast, left renal artery distensibility, strain, and stiffness were not associated with asthma.

Discussion

This study aimed to assess the elasticity properties of various arteries in children with asthma. On the basis of the association between chronic inflammation and atherosclerosis, we hypothesized that the impaired elasticity in children with asthma could increase the risk of atherosclerotic disease. For this purpose, left and right brachial arteries, left and right renal arteries, and left and right carotid arteries were assessed as markers of atherosclerosis. During the atherosclerotic process, increased arterial stiffness and decreased arterial distensibility and strain have been reported among adults [16]. Our results showed increased distensibility and strain in renal and brachial arterial structures, while stiffness was reduced. Carotid arteries measurements did not change. We believe that these results probably are due to the use of inhaled corticosteroids in these children with asthma. Therefore, it appears that inhaled corticosteroids may have a protective effect against atherosclerosis. In this study the results of multiple ANCOVA analysis showed that almost one-fifth of the changes in both left and right brachial arteries distensibility and strain and right renal artery distensibility, strain, and stiffness were associated with asthma.

There is little published data on the association between childhood-onset asthma and atherosclerosis and few studies have evaluated elasticity in asthmatic children. Using carotid-femoral pulse wave velocity measurements, Steinman et al. showed increased arterial stiffness in children with asthma [17]. Weiler et al. examined the arterial stiffness in peripheral large arteries and small arteries and found no difference between asthmatic adults and control subjects. These authors also reported a positive correlation between the small arterial elasticity index and forced expiratory volume at 1 second (FEV1) [18]. Brachial-ankle pulse wave velocity measurements were performed to assess the arterial stiffness in a study by Sun et al., where an increased arterial stiffness was found among adult asthmatic patients with stable disease as compared to the healthy controls. In that study, a negative correlation between brachial-ankle pulse wave velocity and FEV1 was found [19]. In a recent

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study by Ulger et al., a difference between asthmatic children and control subjects was found in terms of aortic stiffness parameters, and inhaled steroids were reported as a possible reason for decreasing aortic stiffness [16]. Ayer et al. suggested that the reduction in lung volume during the early childhood could be associated with increased arterial stiffness [20]. On the other hand, Bhatt et al. reported no significant difference between the markers of systemic inflammation and arterial stiffness in patients with chronic obstructive pulmonary disease [21].

In the current study we found that using inhaled corticosteroids may have protective effects against atherosclerosis. Many previous studies have also found a tendency toward decreased arterial stiffness with the use of inhaled corticosteroids/long-acting beta agonists, and there was a more marked decrease in stiffness in adult patients with higher arterial stiffness [21–23]. A proposed mechanism that may explain the decrease in arterial stiffness involves nitric oxide synthesis and vasodilation [24]. Otsuki et al. compared healthy controls with adult asthmatic patients receiving inhaled corticosteroids. They found decreased carotid atherosclerosis and concluded that the inhaled corticosteroids may provide protection against atherosclerosis [25]. Since inhaled corticosteroids exert a strong anti-inflammatory effect on airways, they are the most effective agents for long-term disease control [26]. On the other hand, corticosteroids also have some potential pro-atherogenic and metabolic effects, such as the induction or worsening of hypertension, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia [27]. Clinicians must also be careful in prescribing steroids to patients who live in endemic areas. For instance, Alsharif et al. diagnosed a woman, who lived Mexico, with hyperinfection syndrome due to *Strongyloides stercoralis*, most probably exacerbated by prednisone given for asthma. Steroid was discontinued and she improved with treatment [28]. Due to such effects, it has been proposed that the use of corticosteroids may be associated with the development of atherosclerosis, although until now this connection has not been clearly established [29]. Also, since there is an increased risk of atherosclerosis in inflammatory conditions [30], it can be suggested that corticosteroids may somehow alleviate the atherosclerotic vascular diseases through their anti-inflammatory properties. A cohort study from the UK indicated that treatment with oral corticosteroids was associated with risk of myocardial infarction, whereas inhaled corticosteroids were not associated with increased risk of myocardial infarction in the general population [31]. On the other hand, another study showed inhaled corticosteroids were associated with decreased the risk of acute myocardial infarction in asthmatic patients [32]. These findings indicate that inhaled corticosteroids might have properties that protect against atherosclerosis, whereas oral corticosteroids might increase risk of atherosclerosis.

Several studies suggest the utility of aortic distensibility as a non-invasive method in the detection early atherosclerosis among adults. Mikola et al. studied the aorta and carotid arteries in children and found that aortic and carotid distensibility decreased with age and this decrease was more pronounced in boys than in girls [33]. Increased stiffness leads to decreased diastolic blood pressure and increased pulse pressure, causing increased left ventricular afterload and a wear-and-tear effect on the arterial wall tissue.

We failed to find any study evaluating renal, brachial, and carotid arteries distensibility, strain, and stiffness together in childhood-onset asthma patients; therefore, we were unable to compare our results with other studies in children.

Conclusions

We found decreased stiffness and increased distensibility and strain in some peripheral arteries in asthmatic children. The use of inhaled corticosteroids in this group of asthmatic children could have provided certain protective effects. We believe that inhaled corticosteroids may protect against atherosclerosis. Further studies with larger sample sizes are warranted to better elucidate the association of stiffness, distensibility, and strain in childhood asthma.

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