Is There an Increased Risk for Atherosclerosis in Children with Asthma?

Astımlı Çocuklarda Ateroskleroz için Artan Bir Risk Var mıdır?

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ABSTRACT Objective: Several chronic inflammatory diseases including asthma have been linked to enhanced risk for atherosclerosis. Carotid intima media thickness which can be assessed by ultrasonography is an established measure for the risk of atherosclerosis. There are some studies showing increased carotid atherosclerosis only in asthmatic adults. We aimed to examine the relationship between asthma and carotid intima media thickness in children. **Material and Methods:** Fifty six asthmatic and 24 healthy children aged 8 to 18 years without increased risk of atherosclerosis were enrolled. Carotid intima media thickness was measured by ultrasonography from the left common carotid arteries. **Results:** There was no significant difference between asthma and control groups in terms of sex, weight, height and weight for height (W/H). Mean carotid intima media thickness of asthmatics was significantly higher than the mean carotid intima media thickness of controls ($p< 0.001$). Carotid intima media thickness was not correlated with age, weight, height and W/H neither in asthmatics nor in controls. Mean carotid intima media thickness didn't differ in the asthmatics according to the severity, skin test positivity and immunotherapy application. **Conclusion:** In our study it was seen that mean carotid intima media thickness of asthmatics was significantly higher than the mean carotid intima media thickness of controls. It is not possible to claim that children with asthma have an increased risk for atherosclerosis only with the results of the current study. Larger studies are needed to evaluate the risk of atherosclerosis in asthmatic children.

Key Words: Asthma; child; ultrasonography; carotid arteries; atherosclerosis

ÖZET Amaç: Astım dahil çok sayıda kronik inflamatuvar hastalık ateroskleroz için artmış risk ile ilişkilendirilmiştir. Ultrasonografi ile değerlendirilebilen karotid intima media kalınlığı ateroskleroz riski için kanıtlanmış bir ölçümdür. Artmış karotid aterosklerozunu gösteren çalışmalar sadece astımlı erişkinlerde mevcuttur. Biz çocuklarda astım ve karotid intima media kalınlığı arasındaki ilişkiyi araştırmayı amaçladık. **Gereç ve Yöntemler:** Ateroskleroz için artmış riski olmayan 8-18 yaşları arasındaki 56 astımlı, 24 sağlıklı çocuk çalışmaya alındı. Karotid intima media kalınlığı sol ana karotid arterlerden ultrasonografi ile ölçüldü. **Bulgular:** Astım ve kontrol gruplarında cinsiyet, vücut ağırlığı, boy ve boya göre ağırlık (W/H) açısından anlamlı farklılık yoktu. Astımlıların ortalama karotid intima media kalınlığı, kontrollerin ortalama karotid intima media kalınlığından anlamlı olarak daha fazla idi ($p< 0.001$). Karotid intima media kalınlığı; ne astımlılarda ne de kontrollerde yaş, vücut ağırlığı, boy ve boya göre ağırlık ile korele değildi. Ortalama karotid intima media kalınlığı astımlılarda hastalığın ağırlığı, deri testi pozitifliği ve immünoterapi uygulamasına göre farklılık göstermiyordu. **Sonuç:** Bizim çalışmamızda astımlı çocukların ortalama karotid intima media kalınlığının sağlıklı çocuklara göre anlamlı şekilde yüksek olduğu görüldü. Sadece bu çalışmanın sonuçları ile astımlı çocukların ateroskleroz için artmış bir riske sahip olduğunu iddia etmek mümkün değildir. Astımlı çocuklarda ateroskleroz riskini değerlendirmek için daha büyük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Astım; çocuk; ultrasonografi; karotis arterler; aterosklerozis

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Atherosclerosis is known to be the leading reason associated with premature death.[1] Presence of minimal vascular pathologic changes was found in children who have a high risk of atherosclerosis.[2,3] Early detection of the lesions and elimination of risk factors slow down the progression of the lesions and can even provide regression.[4,5] Therefore studies concerning early detection of atherosclerotic lesions in the asymptomatic period are significant.[6,7]

Several diseases characterized by chronic inflammation have been linked to enhanced risk for atherosclerosis.[8] A possible association between asthma and cardiovascular disease has been described in several studies.[8-10] High immunoglobuline E levels, eosinophilia, positive skin prick test results and decreased measurements of lung function are associated with increased risk for cardiovascular diseases.[11-13] Leukotrienes may contribute to arterial injury and atherosclerosis by promoting nonspecific leukocyte chemotaxis and by increasing vascular permeability.[14] The mast cell is an active contributor to atherogenesis.[15] Also two proinflammatory cytokines found to be elevated in asthma, interleukine (IL) 6 and tumor necrosis factor a, play key roles in the pathogenesis of atherosclerosis.[16]

Measurements by B-mode ultrasonography (USG) of intima-media wall thickness in the extracranial carotid arteries are generally considered as early markers of systemic atherosclerosis.[17] Adult-onset asthma is associated with increased carotid atherosclerosis among women.[10] Bronchial hyperresponsiveness is associated with common carotid artery intima media thickness (cIMT) in men.[17] To our knowledge, there is no study in the literature that evaluated the association between asthma and cIMT in children. We aimed to examine the relationship between asthma and cIMT in children for the first time in the literature.

MATERIAL AND METHODS

This is a case-control study conducted in patients diagnosed as bronchial asthma in Pediatric Allergy and Pulmonology Department of Dokuz Eylül University Hospital during June 1st and July 1st 2008. Fifty six children with asthma and 24 healthy controls between 8 and 18 years of age were enrolled into the study.

The study was started after the approval of clinical and laboratory studies ethics committee of Dokuz Eylül University Faculty of Medicine. Informed consent was taken from the families and children.

Demographical data of the asthmatic patients and the control group including age, sex, body weight, height and weight for height (W/H) measurements were recorded. Physical examinations and anthropometric measurements of all patients were performed. Body weight was measured to the nearest 0.1 kg and height to the nearest 0.5 cm using a stadiometer. W/H index of all children were calculated as [observed weight/median weight (same height and sex)] x 100. Children whose W/H index was above 120% were evaluated as obese.[18]

Systolic and diastolic blood pressure (SBP and DBP) were measured by a mercurial sphygmomanometer with proper-sized cuff (9 to 12.5 cm according to the body size) using right arms at sitting position in all of the children. Korotkoff sounds 1 and 5 were used to determine SBP and DBP, respectively. Measurements were performed after a resting period of 30 minutes. A blood pressure higher than the 95th percentiles of blood pressure to age, gender, and height-specific norms was accepted as hypertension.[19]

Smoking, alcohol consumption, hypertension, obesity, chronic liver disease, premature atherosclerosis, familial hypercholesterolemia, and diabetes mellitus detected by history and physical examination were the exclusion criteria. Also the children with a family history of coronary artery disease were excluded from the study. The patients' asthma severity was classified according to the Global Initiative For Asthma (GINA).

The control group consisted of 24 children who admitted to the hospital for medical control.

All children included in the control group were received no chronic medications and smoking. None had a history of familial hypercholesterolemia and chronic disease. Anthropometric and BP measurements of the control patients were in normal range.

ULTRASONOGRAPHY MEASUREMENTS

Before USG measurements, subjects were rested quietly in a temperature controlled dark room for 10 to 15 minutes. All the carotid artery USG studies were performed by the same experienced radiologist who was blinded to the clinical and laboratory data of the patients. USG examinations (ATL 5000-Philips, Bothell, WA) were performed with linear wide band 5-12 mHz transducer. Patients were in supine position, the head slightly extended and rotated to the other side during the examination. Left carotid arteries were scanned according to a predetermined standard scanning protocol. Common carotid artery (CCA) (1-2 cm proximal segment of carotid bulb) was scanned and the far wall was measured. Each imaging was recorded on digital system and was analyzed manually by the other radiologist blinded to the clinical data. Due to poor imaging quality of proximal, distal wall measurements were performed. cIMT was defined as the mean of three distinct measurements from the left CCA.[10,20]

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 11.0 (SPSS, Chicago, IL). Data were expressed as mean ± standard deviation. Student t test and Mann-Whitney U test were used for comparing group averages. $p< 0.05$ was considered statistically significant. Pearson correlation coefficients were used to evaluate correlations between patients' characteristics and intima-media thicknesses.

RESULTS

Fifty six patients with asthma and 24 healthy children between 8 and 18 years of age were enrolled into the study. The mean age of the children was 12.8 ± 2.5 (8-17.5) years. The sex distribution was equal in the study population.

There were 30 boys (53.6%) and 26 girls (46.4%) in the asthma group whereas there were 10 boys (41.7%) and 14 girls (58.3%) in the control group. The mean age of the asthmatic children was 12.4 ± 2.5 (8-17) years and controls were 14 ± 2.4 (8.5-17.5) years. The mean weight and height in the asthmatic group was 46.8 ± 12.5 kg (24-78) and 155.4 ± 14.4 cm (131-181), while the mean weight and height in the control group was 47.2 ± 12 kg (24.1-69.6) and 158.3 ± 13.8 cm (131-182). The mean W/H index in children with asthma was 96.7 ± 11 (77-119) whereas it was 92.4 ± 8.4 (81-116) in the control group. There was no significant difference between asthma and control groups in terms of sex, weight, height and W/H measurements (respectively $p= 0.332$, $p= 0.9$, $p= 0.468$, $p= 0.1$). Mean age of the children in the control group was found significantly higher than the mean age of the participants in the asthma group ($p= 0.01$).

TABLE 1: Clinical, demographic and cIMT findings of the asthma and control groups

	Asthmatic group (n= 56)	Control group (n= 24)	p
Age (year) (mean ± SD) (min-max)	12.4 ± 2.5 (8-17)	14 ± 2.4 (8.5-17.5)	0.01
Sex, Boys/Girls	30/26	10/14	0.332
Weight (kg) (mean ± SD) (min-max)	46.8 ± 12.5 (24-78)	47.2 ± 12 (24.1-69.6)	0.9
Height (cm) (mean ± SD) (min-max)	155.4 ± 14.4 (131-181)	158.3 ± 13.8 (131-182)	0.468
W/H index (mean ± SD) (min-max)	96.7 ± 11 (77-119)	92.4 ± 8.4 (81-116)	0.1
cIMT (mm) (mean ± SD) (min-max)	0.45 ± 0.05 (0.28-0.63)	0.35 ± 0.05 (0.26-0.44)	<0.001

Data were presented as mean ± SD (min-max)

The data about clinical, demographic, and cIMT characteristics of children were presented in Table 1.

cIMT measurements of asthma and control group were 0.45 ± 0.05 mm (0.28-0.63) and 0.35 ± 0.05 mm (0.26-0.44) respectively. Mean cIMT measurement of asthma group was statistically and significantly higher than the mean cIMT measurement of control group (p< 0.001). Mean cIMT measurement did not differ according to the sex in the whole study group (p= 0.172). cIMT was not correlated with age, weight, height and W/H values in asthma or control groups (respectively p= 0.172, p= 0.639, p= 0.754, p= 0.118).

When the patients with asthma were grouped according to the severity of asthma according to GINA criteria, 53.5% (n= 30) of them were considered as mild, 46.5% (n= 26) of them as moderate asthma. No patients in our study groups were evaluated as severe asthma. In the mild asthma group, 53.3% (n= 16) of the patients were boys, 46.7% (n= 14) were girls, while in the moderate asthma group, 53.8% (n= 14) of them were boys and 46.2% (n= 12) were girls. Skin test positivity was found in 73.3% (n= 22) and 61.5% (n= 16) of the patients with mild and moderate asthma respectively. Immunotherapy was performed to 12 (40%) of the mild asthmatics while to 8 (30.8%) of the moderate asthmatics. cIMT was found 0.45 ± 0.04 mm (0.37-0.56) in the mild asthma and 0.44 ± 0.06 mm (0.28-0.63) in the moderate asthma group. Mean cIMT measurement did not differ in the asthma group according to the severity of asthma, skin test positivity and immunotherapy application (respectively p= 0.888, p= 0.518, p= 0.904).

There was no significant difference between mild and moderate asthma groups in terms of age, sex, weight, height and W/H measurements (respectively p= 0.655, p= 0.970, p= 0.505, p= 0.379, p= 0.934).

Clinical and laboratory findings of the children with mild and moderate asthma were given as mean ± SD (min-max) in Table 2.

TABLE 2: Clinical, demographic and cIMT findings of the of the mild and moderate asthma groups

	Mild asthmatic group (n= 30)	Moderate asthmatic group (n= 26)	p
Age (year) (mean ± SD) (min-max)	12.5 ± 2.6 (8-17)	12.2 ± 2.4 (9-17)	0.655
Sex, Boys/Girls	16/14	14/12	0.97
Weight (kg) (mean ± SD) (min-max)	48.1 ± 13.7 (28-78)	45.3 ± 11.1 (24-64)	0.505
Height (cm) (mean ± SD) (min-max)	157 ± 14.6 (131-181)	153.5 ± 14.2 (133-175)	0.379
W/H index (mean ± SD) (min-max)	96.8 ± 10.9 (77-119)	96.7 ± 11.3 (78-118)	0.934
cIMT (mm) (mean ± SD) (min-max)	0.45 ± 0.04 (0.37-0.56)	0.44 ± 0.06 (0.28-0.63)	0.888

Data were presented as mean ± SD (min-max)

DISCUSSION

Asthma is the most common chronic childhood disease which has significant public health impacts.[21] It has recently been linked to increased risk of atherosclerosis as inflammation underling the pathogenesis of both diseases.[22] However, the importance of asthma as a risk factor for atherosclerosis is not well established. There are only a few studies evaluating the relationship between asthma and atherosclerosis in adulthood. A study of individuals with severe asthma indicated an overall standardized coronary heart disease mortality ratio of 1.9 compared with the general population.[23] In an Australian study of people with asthma, men were 33% and women 28% more likely to have died from coronary heart disease than people from the general population.[24] Schanen et al suggested that asthma may be an independent risk factor for incident stroke in the middle aged adults.[9] Subjects with allergic disorders were at a significantly increased

risk for high IMT in the "Atherosclerosis Risk Factors in Male Youngsters" study which was a cross-sectional evaluation of 141 young men.[8] To the best of our knowledge, there is no report in the medical literature evaluating the cIMT in children with bronchial asthma.

Mean cIMT measurement of asthmatic children in our study was significantly higher than the mean cIMT measurement of healthy controls. But cIMT measurements did not differ in this study according to the severity of asthma. Onufrak et al found that decreasing lung function was significantly associated with greater cIMT in both men and women with asthma.[10] Although the children with moderate asthma were expected to have higher cIMT than the children with mild asthma, the low number of children included and having no children with severe asthma in our study may contribute to this result.

Increased cIMT was quantitatively related to age, male sex, smoking, elevated SBP, serum cholesterol, homocysteine, fibrinogen, and C-reactive protein (CRP) levels.[25] In Jourdanet et al's study, cIMT was positively correlated with age, height, body mass index and SBP.[26] In adults, age is one of the most important determinants of cIMT.[27] However, age associated changes of IMT in children have not yet been fully explored.[28] Jourdanet et al showed that IMT increases in the second decade of life at a very low rate.[26] Between 10 and 20 years of age, median cIMT values increased almost linearly from 0.38 to 0.40 mm in their study. In a recent Japanese study conducted in 5–14-year-olds, cIMT increased by 9 mm/year.[28] In our study, although healthy children were older than the asthmatics, cIMT measurements of asthmatics were found higher than the cIMT measurements of the healthy controls. But in both groups, cIMT was not correlated with age, weight, height and W/H values. Also, cIMT measurement did not differ according to the sex in our study.

The physiopathological mechanism underlying the associations between asthma and atherosclerosis is still unknown.[17] Inflammation mediates a key role in the pathogenesis of atherosclerosis.[29] Localized allergic diseases elicit a systemic inflammatory response mediated by the release of vasoactive peptides and cytokines into the circulation. Endothelial cells were found to enhance adhesion molecule expression, thus facilitating leukocyte trafficking into the vessel wall and potentially promoting atherosclerosis.[8] Mast cells, cells involved in the pathogenesis of asthma, are key players in the regulation of inflammation and fibrosis in the heart and vasculature. Mast cells can also act as antigen-presenting cells increasing inflammation in the heart through Toll-like receptor-4 signaling and increased proinflammatory cytokine production.[22] Leukotrienes may be also involved in the association between arterial wall thickening and asthma.[14] Polymorphisms in the 5 lipoxygenase and 5-lipoxygenase activating protein genes predict a high risk for atherosclerosis. It has been shown that variant 5-lipoxygenase genotypes were associated with common cIMT in 470 healthy middle-aged women and men.[30] Vascular and airway remodeling, which are characterized by airway smooth muscle and arterial vascular smooth muscle proliferation, contribute to the pathology of asthma and atherosclerosis.[31]

Wu et al measured multiple risk markers for atherogenesis in 55 patients with asthma.[32] CRP, serum amyloid A, adhesion molecules, urinary microalbumin and IL-6 levels were found useful for predicting risk of cardiovascular disease. Yang et al found higher serum total cholesterol and low density lipoprotein (LDL) levels in the cIMT thickened children than in those with normal cIMT.[1] Cohort studies reported that obesity and serum LDL cholesterol levels at childhood were the most important factors effecting adulthood cIMT.[33,34] In our study, we could not evaluate the serum cholesterol and the triglyceride levels of the children. But it is known that cIMT is closely related to obesity, dyslipidemia, hypertension, and even with a positive family history of the mentioned diseases.[1] In order to exclude these factors, we did not include children with increased risk of atherosclerosis into the study.

CONCLUSION

Our results suggest that early findings of atherosclerosis can be detected more commonly in children with asthma than in healthy children. But it is not possible to claim that children with asthma have an increased risk for atherosclerosis based only on the results of the current study. Further studies are needed to evaluate the increased risk of atherosclerosis in children with asthma.

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