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Assessment of Carotid Artery Distensibility and Elasticity in Patients with Asthma

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ABSTRACT

As asthma and atherosclerosis have similar pathophysiological mechanisms and risk factors, asthmatic patients may have an increased risk of atherosclerosis. This study aimed to determine the possibility of a higher risk of atherosclerosis in asthma patients compared with healthy controls by measuring carotid elasticity and distensibility.

This was a cross-sectional study on 326 participants including 221 patients (129 [58.37%] females) with persistent asthma, aged 46.47±11.58 years, body mass index (BMI) of 29.74±3.99, and 105 healthy control subjects (60 [57.14%] females) aged 46.08±11.35 years, and BMI of 29.42±3.76. Of the 221 patients with asthma, 75 (33.93%) had mild, 74 (33.48%) had moderate and 72 (32.57%) had severe asthma. The carotid distensibility and elasticity were recorded and compared in both patients and control groups.

There was no statistically significant difference between the patients and healthy control groups in terms of age, BMI and gender (p=0.775, p=0.482, and p=0.834, respectively). A statistically significant difference was determined between the patient and control groups in respect of both distensibility and elasticity (10.93±1.64 vs. 11.5±1.31, p=0.002 and 0.21±0.03 vs. 0.22±0.04, p=0.001, respectively). Statistically significant differences were determined between the control group and the asthma subgroups in respect of distensibility and elasticity (p<0.001, for both comparisons). The results showed that the difference was mainly due to the patients with severe asthma.

Carotid distensibility and elasticity were decreased in asthmatic patients, and the main reason for this decrease was the patients in the severe asthma group. These results may suggest that the risk of subclinical carotid atherosclerosis is increased in patients with asthma, especially those with severe asthma

Keywords: Asthma; Atherosclerosis; Carotid artery; Duplex doppler ultrasonography

INTRODUCTION

Asthma, which is commonly seen throughout the world is considered a public health problem with a prevalence of up to 18% in some countries.[1] The pathophysiological process of asthma is quite complex

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but is known to involve the major mechanisms of chronic inflammation, an allergic response caused by mast cells, and oxidative stress.[2-3]

Cardiovascular diseases resulting from atherosclerosis are the most common cause of morbidity and mortality globally. Hypertension, diabetes mellitus, dyslipidemia, smoking, male gender, and family history are known to be major risk factors for atherosclerosis. Many arteries, especially coronary arteries, carotid arteries, and limb arteries may be affected by atherosclerosis.[4-5] Asthma-like processes such as chronic inflammation, oxidative stress, and mast cells also have a role in the pathophysiology of atherosclerosis. Previous studies have shown that there may be an association between asthma and subclinical atherosclerosis.[6-7]

Although many imaging methods can evaluate subclinical atherosclerosis in the carotid arteries, ultrasonography is one of the most preferred methods because it is fast, inexpensive, non-invasive, and reproducible. Ultrasonography can easily evaluate carotid distensibility and elasticity, which are two important parameters showing subclinical atherosclerosis.[8-9]

Since asthma and atherosclerosis have similar pathophysiological mechanisms, patients with asthma may have an increased risk of atherosclerosis. This study aimed to determine whether there is an increased risk, through the measurements of carotid elasticity and distensibility, which are markers of subclinical atherosclerosis, and comparisons of these values between asthmatic patients and a healthy control group.

MATERIALS AND METHODS

The study was cross-sectional in design and included 221 patients who were followed up with the diagnosis of asthma in Baskent University, Faculty of Medicine, Adana Hospital Pulmonary Disease, Outpatients Clinic between January 1, 2017, and December 31, 2018. A control group was formed of 105 healthy volunteers with similar demographic characteristics. The diagnosis of asthma was made by the pulmonologist according to the results of the history, physical examination, and pulmonary function test as per the guidelines.[1] The pulmonary function test was applied to all individuals by the same operator. Blood pressure values of all participants were measured with a sphygmomanometer after sitting for at least 15 minutes. Systolic blood pressure (SBP)>140 mm Hg or diastolic blood pressure (DBP)>90 mm Hg or the use of antihypertensive drugs were defined as hypertension.[10] The height and weight of the participants were measured by the same operator using the same device, and these values were used to calculate the body mass index (BMI). Three subgroups of asthma patients were formed based on asthma severity of mild, moderate, or severe, according to the guidelines.[1] The asthma control questionnaire (ACQ) scores of the individuals in the patient group were calculated and recorded. Carotid elasticity and distensibility were measured and recorded in both groups. Differences in distensibility and elasticity were evaluated between the asthma patients and the control group and then between the asthma subgroups (mild, moderate, severe) and the control group. Any statistically significant correlations between the distensibility and elasticity values and the ACQ score and forced expiratory volume in the first second (FEV_1%) predicted values were also investigated.

The study was conducted following the principles of the Helsinki Declaration and with the approval of the Local Ethics Committee (KA16/335). Informed consent was obtained from all the study subjects.

Evaluation of Carotid Distensibility and Elasticity

Carotid artery imaging was performed according to guidelines.[8,9,11] With the patient positioned supine, the head was moved to the left at an angle of 45° to fully expose the right side of the neck. The carotid artery both above and below the carotid bifurcation was visualized by rotating the probe to obtain a longitudinal view of the common carotid artery and proximal sections of the carotid bulb. The intima-intima distance between the walls was measured on this image to provide the lumen diameter (LD). The maximum LD (LD_{max}) during systole and minimum LD (LD_{min}) during diastole were measured and recorded for 3 consecutive heartbeats. The media-media distance at the end of diastole was measured in 3 consecutive heartbeats to calculate the minimum vessel diameter (VD_{min}), then the same measurements were taken in systole to calculate the maximum vessel diameter (VD_{max}). The average of the 3 measurements was recorded for inclusion in the analysis. Throughout the ultrasonography evaluation, the subjects were monitored with an electrocardiogram (ECG), thereby providing systole and diastole differentiation according

to ECG.

Carotid artery distensibility (%) was calculated using the formula [(VD_{max} –VD_{min})/VD_{min}] x100, and carotid artery elasticity (%/mm Hg) using the formula ([(LD_{max} –LD_{min})/LD_{min}]/ΔP) x100%. The ΔP value was calculated as the difference between SBP and DBP. These formulae are valid and reliable in previous studies.[12-15] All the measurements of distensibility and elasticity were taken automatically using the software.

Exclusion Criteria

Atherosclerotic heart disease, cerebrovascular disease, peripheral artery disease, heart failure, advanced heart valve disease, antihypertensive drug use, familial hypercholesterolemia, collagen tissue disease, chronic kidney failure, pregnancy, chronic liver failure, active infection, anticoagulant drug use, atrial fibrillation, malignancy, untreated major depression, food disorders, untreated psychosis, drug or alcohol addiction, autoimmune diseases, use of systemic steroids, pregnancy, chronic lung disease other than asthma, non-persistent asthma, age>18 or>65 years, poor image quality, or if they were unwilling to participate in the study.

Statistical Analyses

Data obtained in the study were analyzed statistically using SPSS for Windows 26.0 software (IBM Corporation, Armonk, NY, USA). Continuous data were reported as mean± standard deviation (SD) or median (range, interquartile range [IQR]) values and categorical data as number (n) and percentage (%). The Chi-square test was applied to categorical parameters. Conformity to the normal distribution of continuous data was assessed with the Kolmogorov-Smirnov test. Continuous variables showing normal distribution were analyzed with One-way ANOVA or the unpaired t-test as appropriate (if there was a significant difference, post hoc test results were also shown). The Kruskal Wallis test was applied to continuous variables not conforming to normal distribution. Correlations between continuous variables were evaluated with Pearson or Spearman tests as appropriate. A two-sided *p* value of less than 0.05 was considered statistically significant.

RESULTS

The study included a total of 326 subjects, comprising 221 patients with persistent asthma and a control group of 105 healthy individuals. Of the 221 asthma patients, 75 (33.94%) were in the mild, 74 (33.48%) in the moderate, and 72 (32.58%) in the severe asthma group. No statistically significant difference was determined between the control group and the asthma subgroups in respect of age, gender, BMI, blood pressure, and basal laboratory values (p>0.05).

The baseline demographic data, and clinical and laboratory values of both groups are shown in Table 1. A statistically significant difference was observed between the patient and control groups in respect of both distensibility and elasticity (p=0.002, p=0.001, respectively). The distensibility and elasticity values of the patients in both groups and the comparisons are summarized in Table 2. A statistically significant difference was observed between the control group and the asthma subgroups (mild, moderate, severe) in respect of both distensibility and elasticity values (p<0.001, for both comparisons). No significant difference was seen between the mild and moderate groups and the control group in terms of both distensibility and elasticity (p>0.05, for all). A statistically significant difference was determined between the severe group and the control group in respect of both distensibility and elasticity (p<0.001, for both). The distensibility and elasticity values of the control group and asthma subgroups and the comparisons are summarized in Table 2. There was determined to be a statistically significant positive correlation between carotid artery distensibility and FEV_1% of predicted value, and a negative correlation between carotid artery distensibility and the ACQ score (r=0.307, p<0.001 and r=-0.496, p<0.001, respectively). A statistically significant positive correlation was determined between carotid artery elasticity and predicted value of FEV_1% and a negative correlation between carotid artery elasticity and the ACQ score (r=0.389, p<0.001 and r=- 0.54, p<0.001, respectively). The correlations between the distensibility and elasticity and predicted FEV1% and the ACQ score are shown in Figure 1.

Table 1. Baseline clinical and demographic data, laboratory values, and pulmonary function test characteristics of the study population

	Control (n=105)	Mild (n=75)	Moderate (n=74)	Severe (n=72)	*p*
Age, years, (mean±S.D.)	46.08±11.35	45.31±11.19	47.53±11.57	46.58±10.98	0.688
Female gender n (%)	60 (57.1)	48 (64)	39 (52.7)	42 (58.3)	0.573
BMI (kg/m^2), (mean±S.D.)	29.42±3.76	29.48±3.86	29.55±3.84	30.21±4.28	0.566
Creatinine (mg/dL), (mean±S.D.)	0.77±0.1	0.78±0.14	0.77±0.14	0.8±0.14	0.467
Hemoglobin (gr/dL), (mean±S.D.)	13.69±1.38	13.6±1.48	13.98±1.37	13.67±1.34	0.352
WBC ($/mm^3$), (mean±S.D.)	8047±1407	8056±1703	8263±1761	8459±1756	0.338
Platelets ($100/mm^3$), (mean±S.D.)	279±69	280±72	258±65	282±68	0.116
EF (%), (mean±S.D.)	58.83±3.06	59.32±3.11	59.01±3.13	58.88±2.68	0.741
SBP (mm Hg), (mean±S.D.)	115.54±12.07	116.24±7.82	114.64±9.64	118.18±8.88	0.8
DBP (mm Hg), (mean±S.D.)	67.89±6.53	68.93±4.97	68.82±4.18	67.31±3.67	0.167
TC (mg/dL), (mean±S.D.)	194.06±35.36	197.3±32.92	201.22±29.78	193.18±38.04	0.452
LDL (mg/dL), (mean±S.D.)	118.58±29.16	124.02±29.89	127.22±27.24	120.84±31.56	0.245
HDL (mg/dL), (mean±S.D.)	46.71±9.45	46.57±7.68	46.63±8.69	47.5±7.93	0.904
Triglyceride (mg/dL), (mean±S.D.)	137.49±53.06	140.69±46.08	141.54±43.8	144.18±49.81	0.84
Inhaled corticosteroids n (%)	NA	75 (100)	74 (100)	72 (100)	NA
β2-Mimetics n (%)	NA	28 (37.33)	45 (60.81)	72 (100)	**0<0.001**
Theophylline n (%)	NA	0 (0)	23 (31.08)	55 (76.38)	**0<0.001**
Antihistaminic n (%)	NA	21 (28)	27 (36.48)	19 (26.38)	0.359
$LTRA_4$ n (%)	NA	36 (48)	30 (40.54)	33 (45.83)	0.643
FEV_1, % of predicted	NA	86.8±7.56	76.53±10.53	63.82±13.11	**0<0.001**
ACQ Score	NA	0.5 (0.18)	1.08 (0.46)	1.71 (0.67)	**0<0.001**

ACQ: Asthma control questionnaire, BMI: Body mass index, DBP: Diastolic blood pressure, EF: Ejection fraction, FEV_1: Forced expiratory volume in 1 second, HDL: High-density lipoprotein, LDL: Light density lipoprotein, $LTRA_4$: leukotriene receptor antagonist, NA: Non-available, SBP: Systolic blood pressure, SD: Standard deviation, TC: Total cholesterol, WBC: White blood cell

Table 2. Comparison of carotid artery distensibility and elasticity between the groups

	Control (n=105)	Asthma (n=221)	*p*1	Mild (n=75)	Moderate (n=74)	Severe (n=72)	*p*2
Distensibility (%), (mean±S.D.)	11.5±1.31	10.93±1.64	**0.002**	11.65±1.31*	11.55±1.72*	9.55±0.8**	**0<0.001**
Elasticity (% / mm Hg), (mean±S.D.)	0.22±0.04	0.21±0.03	**0.001**	0.22±0.03*	0.21±0.02*	0.18±0.03**	**0<0.001**

*p*1: comparison of carotid artery distensibility and elasticity between patient and control groups, *p*2: comparison of carotid artery distensibility and elasticity between the control group and asthma subgroups,
According to the post-hoc analyses * the *p* is non-significant when compared to the control group ($p>0.05$). ** The p is significant when compared to the control group ($p<0.001$). S.D: Standard deviation

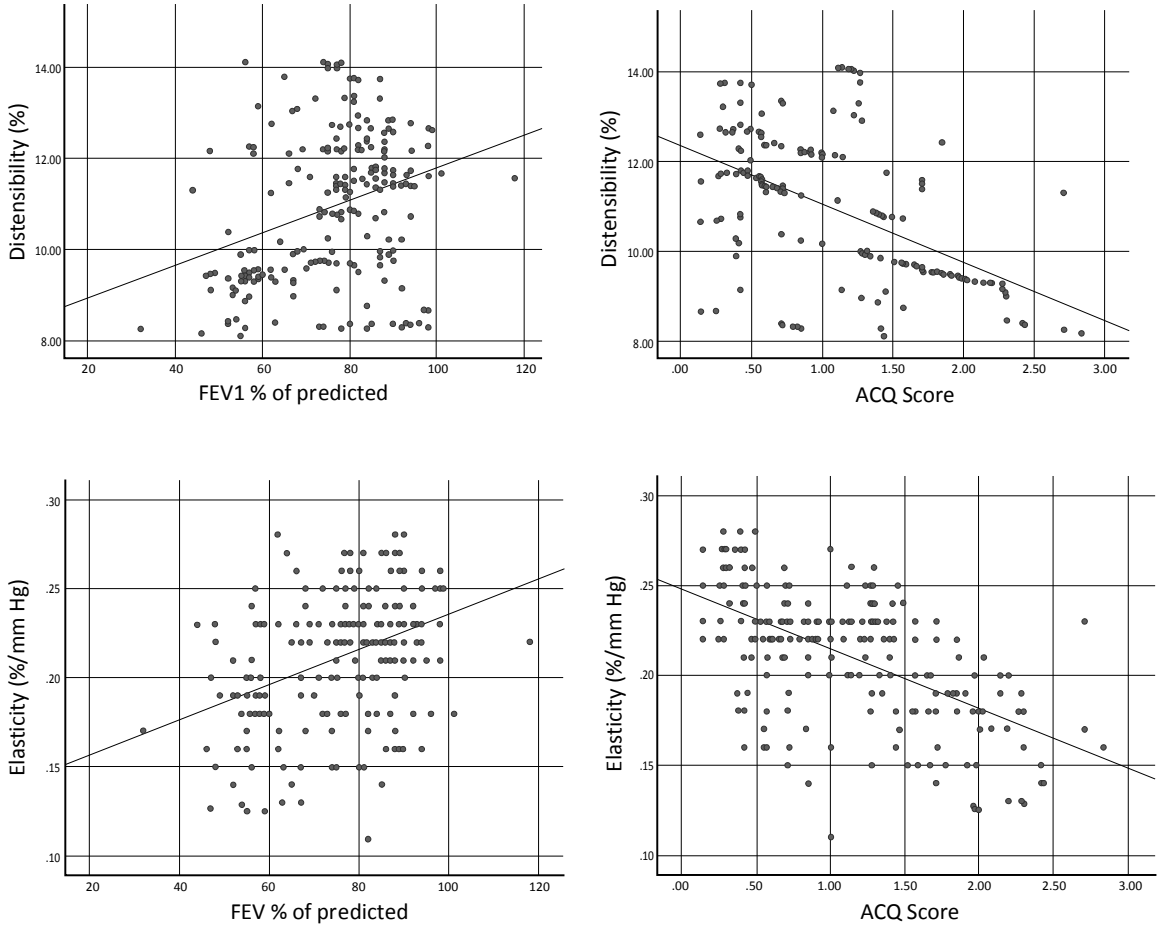

Figure 1. Correlation analysis between carotid distensibility/elasticity and forced expiratory volume in the first second (FEV_1), % of predicted and asthma control questionnaire (ACQ) score.

DISCUSSION

This study evaluated carotid artery distensibility and elasticity in asthmatic patients, and according to the study results, carotid distensibility and elasticity were decreased in patients with asthma, mainly due to the patients in the severe asthma group. These results suggest that the risk of atherosclerosis may be indirectly increased in patients with asthma.

Few studies in the literature have examined the risk of atherosclerosis in patients with asthma. Yılmaz et al reported that carotid and femoral intima-media thickness values were higher in asthmatic patients than in the normal population.[6] In a cohort study by Tattersall et al, there was found to be an association between late-onset asthma and increased cardiovascular risk.[16] Yao et al evaluated patients with asthma and reported a higher risk for the development of peripheral artery disease, for which it was emphasized that poorly controlled asthma may be the key factor.[17]

There may be several reasons for an increased risk of atherosclerosis in asthmatic patients. One is that similar mechanisms and processes are involved in the pathophysiology of both diseases. Atherosclerosis is characterized by chronic inflammation in the arterial wall. The intima layer of the atherosclerotic artery is very rich in macrophages, monocytes, lymphocytes, neutrophils, and mast cells.[18] It is known that similar cells are found in large amounts in the bronchoalveolar wall of patients with asthma. In experimental studies, these cells have been shown to have similar effects on both diseases and play a role in similar processes.[7]Mast cells are known to have a key role in the lungs of asthmatic patients. Allergen-induced release of IgE activates mast cells and this process releases histamine and other mediators to create a strong inflammatory response in these activated cells.[7] In addition to the direct demonstration of mast cells in atherosclerotic tissues, the role of mast cells in atherosclerosis has been demonstrated by many in vitro and in vivo studies.[19] Mast cells are primarily responsible for the progression of atherosclerotic lesions. Atherosclerosis begins with the infiltration of low-density lipoprotein particles into the intima layer of the arteries. These particles are modified and ingested by macrophages in the intima layer, which causes the formation of cholesterol-filled foam cells, and mast cells play a key role in this process.[19] In addition to mast cells, many other mediators play a common role in the pathophysiology of both diseases. It is well known that C-reactive protein (CRP), interleukin (IL)-4, IL-5, IL-6, and tumor necrosis factor-alpha (TNF-α) have an important role in both asthma and atherosclerosis.[6]

Apart from inflammation, another mechanism that has a role in the pathophysiology of both diseases is oxidative stress. Oxidative stress is the disruption of the balance between oxidant and antioxidant substances in the body in favor of antioxidants. It has been shown many times that the number of antioxidant substances decreases and the amount of oxidant substance increases in patients with asthma.[20] Similar processes have been seen to develop in atherosclerosis and deteriorating oxidative stress is known to play an important role in both triggering and the progression of atherosclerosis.[21]

Another reason for the increased risk of atherosclerosis in patients with asthma may be that there are common risk factors in both diseases, and both are affected by similar environmental factors. Obesity is known to be a risk factor for both atherosclerosis and asthma, and the prevalence of asthma in obese patients has been reported to be as high as 30%.[22] In addition, changes in the western diet, exercise, and diet habits are considered to be risk factors for the development of both diseases.[23]

Another result of the current study was that both carotid distensibility and elasticity are negatively correlated with FEV% of the predicted value. Some studies in the literature have reported that airway obstruction is associated with an increased risk of atherosclerosis. In a previous study, carotid and femoral intima-media thicknesses were found to be correlated with FEV1% of the predicted value.[6] Chandra et al, reported that low FEV1 was found to be an independent risk factor for increased risk of atherosclerosis, and airflow limitation was shown to be an independent predictor of atherosclerosis.[24] The results of those studies are compatible with the findings of the current study and support the conclusions.

Another interesting topic is that of non-atopic asthma and atherosclerosis interaction. In the current study, patients were not separated as non-atopic and allergic asthmatics. However, common risk factors may be the cause of an increased risk of atherosclerosis in non-atopic asthmatics (such as obesity, smoking). Thomson et al showed that asthma patients who smoke have worse symptoms, increased chronic mucus hypersecretion, and more exacerbations, in addition to

an impaired therapeutic response to corticosteroids.[25] In another study, Çolak et al showed that smokers with asthma have higher rates of cardiovascular comorbidities.[26] It was shown that the endotype of smokers with asthma is more pro-inflammatory than that of non-smokers, which could cause an increased risk of atherosclerosis.[27-28] In addition, some common mediators (IL-4, IL-6, IL-9, IL-17A, IL-33 but also IFN-γ and TNF-α) involved in the pathophysiology of both diseases could be responsible for the increased risk of atherosclerosis in this patient group.[29]

This study was conducted in a single center and with a limited number of patients. There is a need for further multicenter studies involving a large number of patients to confirm these results. Moreover, as the current study was cross-sectional, these results may need to be verified with prospective studies. Both carotid distensibility and elasticity provide indirect information about carotid atherosclerosis, but it is not currently known how carotid atherosclerosis will develop in these patients in the long-term. Due to the lack of data, it was not possible to provide total IgE, FeNO, and eosinophil count.

The results of this study demonstrated that carotid distensibility and elasticity were decreased in patients with asthma, and the main reason for this decrease was the patients in the severe asthma group. These results may indirectly suggest that the risk of subclinical carotid atherosclerosis is increased in patients with asthma, especially in those with severe asthma.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare. The authors have no financial relationships relevant to this article to disclose.

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