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Title: Investigation of the Relationship between Asthma and Visceral Obesity by Epicardial Fat Thickness Measurement

Short title: Asthma and Visceral Obesity

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Abstract

OBJECTIVES: Obesity is a risk factor defined in recent years for asthma. It is associated not only with asthma but also with many cardiovascular diseases. Visceral obesity is a more significant risk factor than general obesity in cardiovascular diseases. Although the association of visceral obesity with cardiovascular diseases is well known, the relationship in patients with asthma is not fully understood. The aim of the present study was to investigate whether there is a relationship between asthma and visceral fat by using epicardial fat thickness (EFT) measurement.

MATERIALS AND METHODS: A total of 401 subjects (229 patients with persistent asthma and 172 controls) were enrolled in the study. In our study, EFT was measured, recorded by echocardiography, and was evaluated whether there was a statistical significant difference between the two groups.

RESULTS: The mean EFT was 5.84±0.79 mm in the patient group and 5.71±0.93 mm in the control group. There was no statistically significant difference between the groups (p=0.145). Similarly, when we compared control and asthma severity subgroups, we did not find statistically significant differences (control group mean 5.71±0.93 mm, mild group mean 5.86±0.81 mm, moderate group mean 5.8±0.84 mm, and severe group mean 5.83±0.67 mm,}

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CONCLUSION: In the present study, we observed that the EFT did not increase in patients with asthma compared with the normal population. Based on our results, we suggest that visceral obesity may not be a significant risk factor for asthma.

INTRODUCTION

Asthma is a chronic inflammatory, heterogeneous disease that is considered as a public health problem [1]. Almost 300 million people worldwide were affected by asthma in 2005 according to the World Health Organization. Asthma causes approximately 255,000 deaths worldwide annually [2]. Two types of risk factors have been identified for asthma: genetic and environmental [1]. Obesity is a risk factor defined in recent years for asthma. As the severity of obesity increases, the risk of developing asthma increases as well [3]. It was shown in the National Health and Nutrition Examination Survey that nearly one in three patients with asthma is obese, and the prevalence of obesity in patients with asthma ranges from 21% to 32.8% [4]. Obesity, which has been increasing in prevalence, is a health problem worldwide and is associated not only with asthma but also with many atherosclerotic cardiovascular diseases (ASCVDs) [5]. A number of recent studies have shown that visceral obesity is a more significant risk factor than general obesity in cardiovascular diseases [6-7]. Although the association of visceral obesity with cardiovascular diseases is well known, the relationship in patients with asthma is not fully

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understood. Epicardial fat thickness (EFT) is defined as the fat tissue located between the visceral layer of the pericardium and the myocardium and is the visceral fat tissue of the heart [6]. EFT reflects visceral fat rather than general fat and has been shown to be a significant risk factor for cardiovascular disease in many studies [8,9].

In a previous study, it was shown that pre-atherosclerosis might be higher in patients with asthma. Moreover, EFT measurements were similar between patients with asthma and controls. Visceral adiposity by itself in patients with asthma may not be responsible for the elevated risk of pre-atherosclerosis [10], but we are not sure whether the study population is sufficient. For this reason, we planned the present study. The aim of our study was to investigate whether there is a relationship between asthma and visceral fat by using EFT measurement. We also examined the relationship between EFT and the severity of asthma.

MATERIALS AND METHODS

The study was performed as a cross-sectional study. We included 401 subjects (229 patients with asthma and 172 healthy controls) who had been admitted to Başkent University Adana Hospital outpatient clinic between January 1, 2015 and April 30, 2017 into the study. The diagnosis of persistent asthma was described according to clinical findings (history and physical examination), pulmonary function tests, and the criteria in the Global Initiative for Asthma (GINA) guidelines [1].

The following patients were excluded from the study: ASCVD (coronary, cerebral, or peripheral artery disease), heart failure, high degree heart valve disease, asset of active infection, pregnancy, malignancy, end-stage kidney disease, diabetes mellitus, advanced...
liver disease, autoimmune diseases, use of systemic steroids, chronic lung disease other than asthma, age >65 years or <18 years, and patients with asthma other than persistent. We categorized patients into three groups based on asthma severity in accordance with the GINA 2016 guidelines as mild, moderate, and severe [1]. The baseline clinical characteristics of the subjects were recorded. Pulmonary function tests were performed according to the American Thoracic Society guidelines [11] by a single physician using a spirometer (SensorMedics Vmax spectra 229; Bilthoven, The Netherlands) to determine forced expiratory volume in 1 second (FEV₁) % of predicted, forced vital capacity (FVC) % of predicted, and FEV₁/FVC ratio. The same operator made height and weight measurements, and the same weighing and measuring instruments were used for each individual. The date of onset of symptoms and the date of first diagnosis of the disease were recorded for each patient. EFT was measured and recorded during echocardiographic evaluation in both groups. The statistical difference between the two groups was examined.

We used a Philips EPIQ 7 (Philips, Seattle, USA) ultrasound system and a Philips X5-1 (Philips, Seattle, USA) probe (broadband transducer) for echocardiographic assessment. All subjects were evaluated by standard two-dimensional and Doppler evaluation according to the recommendations of the American Society of Echocardiography [12] and the European Association of Cardiovascular Imaging. The modified Simpson method was used to calculate ejection fraction.

EFT is described as the echo-free distance between the outer surface of the myocardium and the visceral stratum of the pericardium [6]. We measured EFT from the parasternal...
long-axis imaging at the end of the diastole and at three cardiac cycles, vertical to the right ventricular free wall (Figure 1). Two different operators who were blinded to subjects performed echocardiographic evaluations twice at different times, and the average of the measurements of both operators was obtained.

The study was performed in accordance with the criteria of the Declaration of Helsinki. The study was approved by Başkent University Research Ethics Committee and supported by Başkent University Research Fund (project no.: KA16/335). All participants signed a written consent form.

**Statistical Analysis**

A statistician performed a power analysis before starting the study. According to the power analysis result, we had to have at least a total of 90 patients (power analysis of two-sample T-test for testing equivalence using differences, numeric results for testing equivalence using a parallel-group design, reference group sample size n1=45, treatment group sample size n2=45, alpha=0.0500, beta=0.1948). Continuous variables are expressed as mean±standard deviation or median (range, interquartile range). Categorical data are presented as proportion. Chi-square test was used to analyze categorical parameters. One-way analyses of variance (ANOVA) or unpaired t-test was used to analyze continuous variables with normal distribution. Mann–Whitney U test was used to analyze continuous variables with non-normal distribution. Continuous variables were checked by Kolmogorov–Smirnov test to assess whether they were normally distributed. A p value of <0.05 was considered as
statistically significant. The SPSS statistical software was used for statistical analysis Statistical Package for the Social Sciences (SPSS version 21.0 for Windows; SPSS Inc.; Chicago, IL, USA).

RESULTS

A total of 401 patients were enrolled in the study, including 229 patients with a diagnosis of asthma and 172 healthy volunteers. There was no significant difference between the groups in terms of baseline clinical characteristics (p>0.05). Table 1 shows the baseline clinical characteristics of the groups. Table 2 shows the asthma control grade, grade of severity, and duration of asthma of the study subjects. Baseline echocardiographic measurements and cardiac void measurements were similar in both groups. Table 3 shows the echocardiographic measurements.

The mean EFT was 5.84±0.93 mm in the patient group and 5.71±0.93 mm in the control group. There was no statistically significant difference between these two groups (p=0.145).

Similarly, when we compared control and asthma severe subgroups (mild, moderate, and severe asthma groups), there were no statistically significant differences in the control and asthma subgroups (control group 5.71±0.93 mm, mild group 5.86±0.81 mm, moderate group 5.8±0.84 mm, and severe group 5.83±0.67 mm, p=0.505).

DISCUSSION

In the present study, we observed that the EFT did not increase in patients with asthma.
when compared with the normal population. The second finding of the study was that there was no association of asthma severity subgroups with visceral adiposity assessed by EFT. Based on our results, we suggest that visceral obesity may not be a significant risk factor for asthma.

Obesity and asthma are two health problems that are increasing in frequency worldwide. For the first time, Seidel et al. [13] reported a relationship between obesity and asthma, especially in female patients. A lot of study has been performed since the present study, and the relationship between asthma and obesity has been shown clearly in children, adolescents, and adults [3, 14]. Although the relationship between asthma and obesity is well known, it is not fully understood whether general obesity or visceral obesity is the more important risk factor and what the mechanism explains the relationship between obesity and asthma. This point should be discussed and clarified.

Some suggestions for possible mechanisms by which general obesity leads to asthma have been explained in previous studies. One of these potential mechanisms is the mechanical effect of obesity on the lungs. General obesity may cause dyspnea by preventing diaphragm movements. It has also been shown that functional residual capacity (FRC) decreases in obese patients, and there is an inverse relationship between body mass index and FRC [15]. Apart from the mechanical effect of obesity on the diaphragm, immunological and inflammatory effects may cause asthma or its worsening. For example, levels of C-reactive protein, interleukin 6, tumor necrosis factor-α, plasminogen activator inhibitor 1, eotaxin, vascular endothelial growth factor, and monocyte chemotactic protein 1 were found to be
high in obese individuals and obese asthmatics. These markers have been shown to cause chronic systemic inflammation and are one of the causes of low-grade chronic airway inflammation in patients with asthma [16,17].

A number of possible mechanisms discussed above may explain the relationship between asthma and general obesity. The results of our study suggest that visceral obesity may not be an additional risk factor for asthma. There are also other studies that contradict the results of our work. Capelo et al. [18] showed that visceral obesity is negatively correlated with asthma control and lung function in female patients in a study of 83 women with asthma. Reproducibility is very important in operator-dependent techniques. In the present study, a single operator made measurements of visceral fat and subcutaneous fat using an ultrasound device. The intraobserver and interobserver variability are the biggest problems in operator-dependent measurements. Several different measurements with multiple operators followed by calculation of the averages can be a solution in order to obtain more accurate results. Performing the study only in women and the measurements once by a single operator might affect the results. In another study, Brumpton et al. [19] found that general obesity is a risk factor for asthma in men and women; additionally, they reported that waist circumference is high in women with asthma, and abdominal obesity increases the incidence of asthma in addition to general obesity in women. The measurement of the waist circumference is frequently used as a parameter to assess abdominal obesity; however, its predictor value for visceral obesity is weak [20], and its sensitivity, specificity, and reproducibility are low. It gives inaccurate results, especially in the aged and morbidly obese patients [21,22]. Fenger et al. [23] speculated that the effect of adiposity on asthma is
mainly seen in non-atopics and did not seem to be attached on the distribution of adiposity. Increasing adiposity was associated with lower pulmonary function independent of atopic condition. In another study, Song et al. showed that the relationships between obesity and asthma in the elderly population may be mediated by factors including abdominal subcutaneous adiposity [24].

Our study has some limitations. First, the study was not a prospective study. Our study population consists of patients who have been already diagnosed with asthma and have been on appropriate treatment. We do not know whether the EFT has changed with treatment. The number of patients is relatively limited, and the study was not a multicenter study and so may not reflect the general population. EFT in the study was measured by echocardiography from the right ventricular free wall. The site where the measurements were obtained may not reflect the volume of all subepicardial fat tissue; however, it has been shown to be highly correlated in previous studies [6-8]. EFT is not a gold standard method to measure visceral fat, but it is cheap and easy to perform and was found to be reflecting correctly to the visceral obesity measured by magnetic resonance imaging and/or computed tomography.

CONCLUSION

Although it has been shown in many studies that obesity is a risk factor for asthma, it is not clear whether general obesity or visceral obesity is a more important risk factor. We did not find EFT, a good indicator of visceral obesity, to be high in patients with asthma. We conclude that visceral obesity may not be a risk factor for asthma.

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Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Başkent University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.


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Conflict of Interest: The authors have no conflicts of interest to declare.

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### Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
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<th>Asthma (n=229)</th>
<th>Control (172)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>43.86±13.18</td>
<td>45.11±11.36</td>
<td>0.318</td>
</tr>
<tr>
<td>Sex, female gender, n (%)</td>
<td>135 (59)</td>
<td>100 (58.7)</td>
<td>0.870</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>25 (10.9)</td>
<td>21 (12.2)</td>
<td>0.688</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>65 (28.4)</td>
<td>40 (23.3)</td>
<td>0.248</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>29.72±3.98</td>
<td>29.18±3.62</td>
<td>0.167</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.78±0.14</td>
<td>0.76±0.12</td>
<td>0.096</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.72±1.41</td>
<td>13.8±1.38</td>
<td>0.560</td>
</tr>
<tr>
<td>White blood cell count (/mm^3)</td>
<td>8234±1717</td>
<td>8085±1409</td>
<td>0.353</td>
</tr>
<tr>
<td>Platelets (100/mm^3)*</td>
<td>280 (245–317.5)</td>
<td>280 (246–324)</td>
<td>0.439</td>
</tr>
</tbody>
</table>

*Data are expressed as median with interquartile range

BMI: body mass index
Table 2. Asthma control, severity, and time since onset of asthma

<table>
<thead>
<tr>
<th>Asthma control</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Well controlled, n (%)</td>
<td>93 (40.6)</td>
</tr>
<tr>
<td>Partly controlled, n (%)</td>
<td>85 (37.1)</td>
</tr>
<tr>
<td>Uncontrolled, n (%)</td>
<td>51 (22.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Asthma severity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild, n (%)</td>
<td>117 (51)</td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>73 (31.9)</td>
</tr>
<tr>
<td>Severe, n (%)</td>
<td>39 (17)</td>
</tr>
</tbody>
</table>

| Time since onset of asthma* | 12 (6–24; IQR=18) |

*Data are expressed as median with interquartile range
IQR: interquartile range
Table 3. Measurements of two-dimensional echocardiographic parameters

<table>
<thead>
<tr>
<th></th>
<th>Asthma (n=229)</th>
<th>Control (n=172)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>59.07±2.96</td>
<td>58.77±2.97</td>
<td>0.316</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>43.06±3.28</td>
<td>42.90±3.32</td>
<td>0.644</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>26.59±1.56</td>
<td>26.54±1.57</td>
<td>0.737</td>
</tr>
<tr>
<td>Septum (mm)</td>
<td>0.91±0.15</td>
<td>0.92±0.15</td>
<td>0.868</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>0.91±0.15</td>
<td>0.91±0.15</td>
<td>1</td>
</tr>
<tr>
<td>Left atrium (mm)</td>
<td>37.50±2.52</td>
<td>37.39±2.55</td>
<td>0.664</td>
</tr>
<tr>
<td>Right atrium (mm)</td>
<td>37.41±2.57</td>
<td>37.72±2.58</td>
<td>0.225</td>
</tr>
<tr>
<td>Right ventricle (mm)</td>
<td>28.15±2.06</td>
<td>28.48±2.12</td>
<td>0.117</td>
</tr>
</tbody>
</table>

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Figure-1: Measurements of epicardial fat thickness on the free wall of the right ventricle from the parasternal long-axis views.
Figure 1. Measurements of epicardial fat thickness on the free wall of the right ventricle from the parasternal long-axis views