The effect of epicardial adipose tissue thickness with irritable bowel syndrome
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Abstract
Objective: To investigate the association of epicardial adipose tissue thickness with irritable bowel syndrome.
Methods: This case-control and observational study was conducted in Recep Tayyip Erdogan University between January and December 2014, and comprised patients of irritable bowel syndrome and healthy controls who underwent a complete transthoracic echocardiographic examination as well as measurements of epicardial adipose tissue. They were screened for psychiatric or organic bowel diseases for the sake of precise diagnosis. Epicardial fat thickness was measured perpendicularly in front of the right ventricular free wall at end-diastole. SPSS 15 was used to analyse the data.
Results: Of the 75 subjects, 44 (59%) were patients and 31 (41%) were controls. There was no statistically significant difference between the groups except epicardial adipose tissue thickness, which was significantly elevated in patients (p<0.001). C-reactive protein was significantly higher in patients (p=0.002). Epicardial adipose tissue (p<0.001) and haematocrit (p<0.05) were independent predictors of irritable bowel syndrome.
Conclusion: Increased epicardial adipose tissue thickness, and accompanying low-grade inflammation appeared to be involved in irritable bowel syndrome pathogenesis.
Keywords: Epicardial adipose tissue, Irritable bowel syndrome, Inflammation, CRP. (JPMA 68: 1456; 2018)

Introduction
Epicardial adipose tissue (EAT), avisceral adipose tissue surrounding the heart and the coronary arteries, has endocrine and paracrine activity. EAT has been implied to influence coronary atherosclerosis development by secreting several pro-inflammatory and anti-inflammatory cytokines and chemokines.1-5

The physiological, biochemical and bio-molecular properties of EAT and the possible paracrine interactions within the heart have been described in previous studies.6 EAT exists mainly in the atroventricular and interventricular groove along the major coronary arteries and branches, to a lesser extent in the atrium, right ventricle and the left ventricular free wall that shows extension to the apex.7 The embryological origin of EAT is similar to intra-abdominal visceral adipose tissue.8

Irritable bowel syndrome (IBS) is a functional disorder characterised with recurrent abdominal pain or discomfort which is associated with alterations in frequency or form of stool and improvement after defecation.9 IBS is highly prevalent, affecting nearly 20% of general population. Although the pathophysiology of this syndrome has not been clarified, impaired autonomic regulation, altered intestinal motility, increased visceral sensitivity, and intestinal low-grade inflammation have been proposed as factors contributing to the development of IBS.10 Histopathological examinations of patients with mostly diarrhoea-predominant symptoms (IBS-D) and even patients with constipation-predominant symptoms (IBS-C), revealed mucosal infiltration of mast cells and lymphocytes in bowel mucosal biopsy specimens.11,12

Since cardiac adipose tissue has profound role in inflammation, EAT may also be involved in IBS due to systemic effects. Therefore the current study was planned to investigate whether EAT and serum C-reactive protein (CRP) levels are independently related to IBS.

Patients and Methods
This case-control and observational study was conducted in Recep Tayyip Erdogan University between January and December 2014 and comprised IBS patients and healthy controls who underwent a complete transthoracic echocardiographic examination as well as measurements of EAT.

Patients were diagnosed with IBS according to Rome III criteria.13 They were all screened for psychiatric or organic bowel diseases for the sake of precise diagnosis. Control group consisted of healthy subjects who had been
evaluated in an outpatient clinic for a routine check-up, and agreed to participate. The study was approved by the institutional review board. Those with presence of concomitant coronary artery disease (CAD), connective tissue disorders, infectious and inflammatory conditions, chronic autoimmune, haemolytic, hepatic, renal diseases, and inadequate transthoracic echocardiographic images were excluded.

Baseline characteristics of the patients were recorded. Hypertension (HT) was defined as the active use of antihypertensive drugs or documentation of blood pressure more than 140/90 mmHg. Diabetes mellitus was defined as fasting plasma glucose levels over 126 mg/dL or glucose level over 200 mg/dL at any measurement or active use of anti-diabetic treatment. Patients who were using tobacco products on admission and those who quitted smoking within the last year were considered smokers.

Blood samples were drawn by venepuncture to measure routine blood chemistry parameters after fasting for at least 8 hours. Fasting blood glucose, serum creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, haemogram and erythrocyte sedimentation rate (ESR) were recorded. Glucose, creatinine, AST, ALT, and ESR were determined by standard methods. Serum CRP was analysed using anephelometric technique (Beckman Coulter Image 800; Fullerton, CA, USA; normal range 0-0.8 mg/dL). Body mass index (BMI) was determined by the following formula: BMI = weight (kg)/height2 (m).

All subjects underwent complete transthoracic examination, including two-dimensional, colour flow and pulsed Doppler, tissue Doppler imaging as well as epicardial fat thickness measurement with a GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5-3.5 MHz transducer. An experienced cardiologist, unaware of patient's clinical information, performed all examinations. The intra-observer correlation coefficient was 0.96. Epicardial fat thickness was evaluated on the free wall of right ventricle from the parasternal long axis view, using aortic annulus as an anatomic reference. We preferred the area above the right ventricle to measure EAT thickness, because this area is known to have the thickest EAT layer. Epicardial fat thickness, identified as an echo-free space between the pericardial layers on 2-dimensional echocardiography, was measured perpendicularly in front of the right ventricular free wall at end-diastole. We magnified each still image for better visualisation and accurate measurement of EAT thickness and measured the thickest point of EAT in each cycle. To standardise the measuring axis, we used the aortic annulus as the anatomical reference. The measurement was performed at a point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus. The average value comprising three cardiac cycles was used for the statistical analysis.

SPSS 15 was used for all statistical calculations. Nominal variables were presented as number of cases with percentages and continuous variables as mean±standard deviation or median (25/75 interquartile ranges [IQR]), where applicable. Data were tested for normal distribution using the Kolmogorov-Smirnov test. The chi-square or Fisher's exact tests were used for comparison of categorical variables between 2 groups. Continuous variables were compared using the Student's t-test and the Mann-Whitney U-test where appropriate. Univariate correlation analysis was performed by Pearson's or Spearman's tests to identify variables that potentially effect EAT thickness. Variables with p <0.05 in the univariate correlation analysis were included in a multivariate stepwise linear regression analysis model to assess the independent determinants of EAT thickness. Logistic regression analysis was performed in order to demonstrate predictors of irritable bowel syndrome. All tests of significance were two-tailed. Statistical significance was defined as p <0.05.

Results

Of the 75 patients, 44(58.67%) were patients and 31(41.33%) were controls. Among the patients, 28(63.64%) were men and 16(36.36%) were women, having overall mean age of 45.0± 14.0 years. Among the controls, 14(45.16%) were men and 17(54.84%) were women, having overall mean age of 44.1±14.9 years. Clinical characteristics of the study population were noted (Table-1). There was no statistically significant difference between the two groups with respect to age, gender, presence of hypertension or diabetes mellitus, and smoking habit (p>0.05).

EAT thickness was significantly elevated in the patients compared to the control subjects (4.41±1.54 mm vs. 2.85±1.12 mm, p<<0.001). Although ESR was similar between groups, CRP was significantly higher in patients with IBS compared to the control group (0.54±0.45 vs. 0.23±0.08 mg/L, p=0.002). In the univariate correlation analysis, age and BMI significantly correlated with EAT.
The only independent determinant of EAT thickness was age in multivariate stepwise linear regression analysis (p= 0.017). Logistic regression analyses revealed EAT and haematocrit as independent predictors of IBS (Table-2).

Discussion
In the present study, we revealed significantly higher EAT thickness in patients with IBS compared to control group. To the best of our knowledge, this is the first report demonstrating the relationship of IBS with increased EAT thickness.

The exact pathophysiological mechanism of IBS has not been unequivocally determined; several mechanisms have been suggested as being involved in the pathogenesis of IBS. Increased numbers of lymphocytes have been reported in the colon and small intestine in a subset of patients with IBS. These cells release mediators like nitric oxide, histamine and proteases which lead to stimulation of the enteric nervous system, causing inflammation leading to abnormal motor and visceral reactions within the intestine. There has been a report demonstrating a correlation between the severity and frequency of abdominal pain and the presence of activated mast cells only in proximity to colonic nerves in patients with IBS. In addition, IBS patients produce higher amounts of pro-inflammatory cytokines compared to healthy controls. Disruption of mucosal barrier function, and a consequent increase in intestinal permeability forms the basis for the increased inflammation in IBS. Therefore increased intestinal permeability, low levels of inflammation and hypersensitivity due to prominent mast cell activity might be the key in pathophysiology of IBS.

Epicardial fat is an endocrine and paracrine source of cytokines. The thickness of EAT is correlated with several circulatory pro-atherogenic and pro-inflammatory adipokines such as visfatin, plasminogen activator inhibitor-I, monocyte chemoattractant protein-I, and CRP.

Until recently, magnetic resonance imaging (MRI) had been accepted as the gold standard for measuring epicardial fat thickness. A study reported the echocardiographical measurement of epicardial fat and revealed an excellent correlation between

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study group (n=44)</th>
<th>Control group (n=31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>45.0 ±14.0</td>
<td>44.1±14.9</td>
<td>0.799</td>
</tr>
<tr>
<td>Gender, male/female, numbers (%)</td>
<td>28/16 (63.6/36.4)</td>
<td>14/17 (45.2/54.8)</td>
<td>0.112</td>
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<td>Smoke, numbers (%)</td>
<td>6 (13.6)</td>
<td>8 (25.8)</td>
<td>0.238</td>
</tr>
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<td>Hypertension, numbers (%)</td>
<td>4 (9.1)</td>
<td>4 (12.9)</td>
<td>0.711</td>
</tr>
<tr>
<td>Diabetes mellitus, numbers (%)</td>
<td>1 (2.3)</td>
<td>1 (3.2)</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4 (22.0/29.2)</td>
<td>25.6 (23.8/27.3)</td>
<td>0.422</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>97.6 ± 10.9</td>
<td>97.2 ± 14.3</td>
<td>0.909</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>16.3 ± 7.8</td>
<td>13.8 ± 5.8</td>
<td>0.250</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>16 (14/19.8)</td>
<td>16(12.8/18.3)</td>
<td>0.564</td>
</tr>
<tr>
<td>Plasma creatinine, mg/dL</td>
<td>0.85(0.7/1.0)</td>
<td>0.7(0.6/1.0)</td>
<td>0.141</td>
</tr>
<tr>
<td>Leukocytes, 10³/uL</td>
<td>7.2 ± 2.1</td>
<td>7.2 ± 1.6</td>
<td>0.949</td>
</tr>
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<td>Haemoglobin, g/dL</td>
<td>13.6 ± 1.8</td>
<td>13.1 ± 1.5</td>
<td>0.234</td>
</tr>
<tr>
<td>Haematocrit, %</td>
<td>40.8 ± 4.7</td>
<td>38.2 ± 3.3</td>
<td>0.021</td>
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<tr>
<td>Platelet, 10³/uL</td>
<td>252.9 ± 77.4</td>
<td>267.2 ± 91.6</td>
<td>0.505</td>
</tr>
<tr>
<td>ESR, mm/hr</td>
<td>12(8/17)</td>
<td>13(10.5/18)</td>
<td>0.484</td>
</tr>
<tr>
<td>Plasma CRP level, mg/L</td>
<td>0.43(0.2/0.61)</td>
<td>0.23(0.2/0.31)</td>
<td>0.074</td>
</tr>
<tr>
<td>Mean EAT thickness, mm</td>
<td>4.41 ± 1.54</td>
<td>2.85 ± 1.12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ALT = alanine transaminase, AST = aspartate transaminase, CRP = C-reactive protein, EAT = epicardial adipose tissue, ESR = erythrocyte sedimentation rate.
echocardiographical epicardial fat thickness, abdominal fat and epicardial fat measurements by MRI. Therefore, echocardiographically measured epicardial fat may provide a highly reliable index of true visceral fat content, avoiding the possible confounding effect of increased subcutaneous abdominal fat.

Elevation of serum high sensitive-CRP (hs-CRP) concentration seven within the upper normal range indicates systemic low-grade inflammation, which is associated with cardiovascular risk factors.

Since inflammation has a role in the pathogenesis of IBS, we may speculate that either increased EAT might reflect the presence of low-grade inflammation, which may play a role in the pathogenesis of IBS, or increased EAT might enhance increased inflammation in the bowel mucosa by several endocrine and paracrine mediators.

Our study has several limitations, the most important being small sample size. Moreover, our study is cross-sectional and does not implicate causality. We did not utilise a proper method for sample size calculation. MRIs is the gold standard diagnostic method for measuring epicardial fat thickness at the moment. Not using MRI in our research is a study limitation. Although epicardial fat is readily visualised with the high-speed computed tomography (CT) and MRI, widespread use of these methods for assessment of EAT is not practical. Echocardiography provides an objective, non-invasive, readily available method and is certainly less expensive than MRI or CT for measuring epicardial fat.

Conclusion
Our study revealed increased echocardiographic EAT and CRP concentrations in patients with IBS. Although a direct causative relationship could not be derived from this study, interaction among low-grade inflammation, IBS, and EAT may be a subject of great interest in future studies.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References