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: Epicardialadipose 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 atrioventricular 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

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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 over126 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 Immage 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.[7] 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.[14,15] 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 15was 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-Smirnovtest. The chi-squareor 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 Spearmen'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±0.08mg/L, p=0.002). In the univariate correlation analysis, age and BMI significantly correlated with EAT

Table-1: Baseline characteristics, echocardiographic and laboratory findings.

Variable	Study group (n=44)	Control group (n=31)	P value
Mean age (years)	45.0 ±14.0	44.1±14.9	0.799
Gender, male/female, numbers (%)	28/16 (63.6/36.4)	14/17 (45.2/54.8)	0.112
Smoke, numbers (%)	6 (13.6)	8 (25.8)	0.238
Hypertension, numbers (%)	4 (9.1)	4 (12.9)	0.711
Diabetesmellitus, numbers (%)	1 (2.3)	1 (3.2)	1
Body massindex, kg/m^2	27.4 (22.0/29.2)	25.6 (23.8/27.3)	0.422
Fasting plasma glucose, mg/dL	97.6 ± 10.9	97.2 ± 14.3	0.909
ALT, U/L	16.3 ± 7.8	13.8 ± 5.8	0.250
AST, U/L	16 (14/19.8)	16(12.8/18.3)	0.564
Plasma creatinine, mg/dL	0.85(0.7/1.0)	0.7(0.6/1.0)	0.141
Leukocytes, 10^3/uL	7.2 ± 2.1	7.2 ± 1.6	0.949
Haemoglobin, g/dL	13.6 ± 1.8	13.1 ± 1.5	0.234
Haematocrit, %	40.8 ± 4.7	38.2 ± 3.3	0.021
Platelet, 10^3/uL	252.9 ± 77.4	267.2 ± 91.6	0.505
ESR, mm/hr	12(8/17)	13(10.5/18)	0.484
Plasma CRP level, mg/L	0.43(0.2/0.61)	0.23(0.2/0.31)	0.074
Mean EAT thickness, mm	4.41 ± 1.54	2.85 ± 1.12	<0.001

ALT = alanine transaminase, AST = aspartate transaminase, CRP = C-reactive protein, EAT = epicardialadiposetissue, ESR = erythrocyte sedimentation rate.

Table-2: Determinants of irritable bowel syndrome.

N=75 Variables	Irritable bowel syndrome (Dependent variable)	
	OR (95%CI)	P value*
Haematocrit, %	1.280 (1.049-1.563)	0.015
Epicardial adipose tissue thickness, mm	1.755 (2.384-14.027)	<0.001
Constant	0.000	0.002
Nagelkerke R Square	0.591	

OR: Odds ration
CI: Confidence Interval.

thickness (p<0.05).

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.[12,16] 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.[17-19] 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.[20] In addition, IBS patients produce higher amounts of pro-inflammatory cytokines compared to healthy controls.[21] Disruption of mucosal barrier function, and a consequent increase in intestinal permeability forms the basis for the increased inflammation in IBS.[22-26] Therefore increased intestinal permeability, low levels of inflammation and hypersensitivity due to prominent mast cell activity might be the key in pathophysiology of IBS.[21,25,27,28]

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.[29,30]

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

echocardiographical epicardial fat thickness, abdominal fat and epicardial fat measurements by MRI.[14] 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.[31]

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. MRIis 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.

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References

1. Wang TD, Lee WJ, Shih FY, Huang CH, Chen WJ, Lee YT, et al. Association of epicardial adipose tissue with coronary atherosclerosis is region-specific and independent of conventional risk factors and intra-abdominal adiposity. Atherosclerosis 2010;213:279-87.
2. Bettencourt N, Toschke AM, Leite D, Rocha J, Carvalho M, Sampaio F, et al. Epicardial adipose tissue is an independent predictor of coronary atherosclerotic burden. Int J Cardiol 2012;158:26-32.
3. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. Atherosclerosis 2010;210:150-4.
4. Oka T, Yamamoto H, Ohashi N, Kitagawa T, Kunita E, Utsunomiya H, et al. Association between epicardial adipose tissue volume and characteristics of non-calcified plaques assessed by coronary computed tomographic angiography. Int J Cardiol 2012;161:45-9.
5. Eroglu S, Sade LE, Yildirir A, Bal U, Ozbicer S, Ozgul AS, et al. Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease. Nutr Metabol Cardiovasc Dis 2009;19:211-7.
6. Taguchi R, Takasu J, Itani Y, Yamamoto R, Yokoyama K, Watanabe S, et al. Pericardial fat accumulation in men as a risk factor for coronary artery disease. Atherosclerosis 2001;157:203-9.
7. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J 2007;153:907-17.
8. Marchington JM, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. Comp Biochem Physiol B 1989;94:225-32.
9. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006;130:1480-91.
10. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology 2002;123:2108-31.
11. Weston AP, Biddle WL, Bhatia PS, Miner PB Jr. Terminal ileal mucosal mast cells in irritable bowel syndrome. Dig Dis Sci 1993;38:1590-5.
12. Tornblom H, Lindberg G, Nyberg B, Veress B. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology 2002;123:1972-9.
13. Rome F. Guidelines--Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders. J Gastrointestin Liver Dis 2006;15:307-12.
14. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-10.
15. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003;88:5163-8.
16. O'Sullivan M, Clayton N, Breslin NP, Harman I, Bountra C, McLaren A, et al. Increased mast cells in the irritable bowel syndrome. Neurogastroenterol Motil 2000;12:449-57.
17. Bueno L. Protease activated receptor 2: a new target for IBS treatment. Eur Rev Med Pharmacol Sci 2008;12 Suppl 1:95-102.
18. Gecse K, Roka R, Ferrier L, Leveque M, Eutamene H, Cartier C, et al. Increased faecal serine protease activity in diarrhoeic IBS patients: a colonic lumenal factor impairing colonic permeability and sensitivity. Gut 2008;57:591-9.
19. Guilarte M, Santos J, de Torres I, Alonso C, Vicario M, Ramos L, et al. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. Gut 2007;56:203-9.
20. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004;126:693-702.
21. Dinan TG, Quigley EM, Ahmed SM, Scully P, O'Brien S, O'Mahony L, et al. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker?

Gastroenterology 2006;130:304-11.

22. Chadwick VS, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, et al. Activation of the mucosal immune system in irritable bowel syndrome. Gastroenterology 2002;122:1778-83.

23. Cremon C, Gargano L, Morselli-Labate AM, Santini D, Cogliandro RF, De Giorgio R, et al. Mucosal immune activation in irritable bowel syndrome: gender-dependence and association with digestive symptoms. Am J Gastroenterol 2009;104:392-400.

24. Barbara G. Mucosal barrier defects in irritable bowel syndrome. Who left the door open? Am J Gastroenterol 2006; 101: 1295-8.

25. Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 2012;303:G775-85.

26. Barbara G, Zecchi L, Barbaro R, Cremon C, Bellacosa L, Marcellini M, et al. Mucosal permeability and immune activation as potential therapeutic targets of probiotics in irritable bowel syndrome. J Clin Gastroenterol 2012;46 Suppl: S52-5.

27. Barreau F, Salvador-Cartier C, Houdeau E, Bueno L, Fioramonti J. Long-term alterations of colonic nerve-mast cell interactions induced by neonatal maternal deprivation in rats. Gut 2008;57:582-90.

28. Morris-Yates A, Talley NJ, Boyce PM, Nandurkar S, Andrews G. Evidence of a genetic contribution to functional bowel disorder. Am J Gastroenterol 1998;93:1311-7.

29. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr 2009;22:1311-9.

30. Malavazos AE, Ermetici F, Cereda E, Coman C, Locati M, Morricone L, et al. Epicardial fat thickness: relationship with plasma visfatin and plasminogen activator inhibitor-1 levels in visceral obesity. Nutr Metabol Cardiovasc Dis 2008;18:523-30.

31. Tamakoshi K, Yatsuya H, Kondo T, Hori Y, Ishikawa M, Zhang H, et al. The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. Int J Obes Relat Metab Disord 2003;27:443-9.