Progress in Nutrition 2019; Vol.21, N. 4: 836-842 DOI: 10.23751/pn.v21i4.8013

An imaging method for the evaluation of early atherosclerosis in inflammatory bowel disease: epicardial adipose tissue

Nevzat Gozel[1], Abdullah Eyvaz[2], Banu Demet Ozel[2], Yasemin Dogan[3], Bahadir Sarli[3], Agah Bahadir Ozturk[4], Omer Bilgehan Poyrazoglu[5], Orhan Kursat Poyrazoglu[6]

[1]Firat University School of Medicine, Department of Internal Medicine - E-mail: drngozel@hotmail.com; [2]Kayseri Education and Research Hospital, Department of Gastroenterology; [3]Kayseri Education and Research Hospital, Department of Cardiology; [4]Adiyaman University School of Medicine, Depertment of Family Medicine; [5]Erciyes University School of Medicine, Department of General Surgery; [6]Firat University School of Medicine, Department of Gastroenterology

Summary. The aim of this study was to detect early atherosclerosis in patients with inflammatory bowel disease (IBD) that were strictly selected according to traditional cardiovascular risk factors, and to demonstrate whether evaluating epicardial adipose tissue can serve as an imaging modality through which to detect early atherosclerosis. Forty-three patients with IBD and 29 controls were enrolled in the study. Participants with well-known cardiovascular risk factors were excluded. Carotid intima media thickness (CIMT) and epicardial adipose tissue (EAT) were evaluated by the same physician blinded to the study groups. CIMT and EAT values were significantly higher in the IBD group when compared to the control group ($p<0.01$ and $p<0.001$, respectively). EAT was correlated with CIMT in the IBD group ($r=0.574$, $p=0.001$). CIMT and EAT are functional imaging methods that are used to detect early atherosclerosis in IBD patients without classic cardiovascular risk factors. EAT may be used as an additional diagnostic tool through which to detect early atherosclerosis in clinical practice in IBD patients.

Keywords: Inflammatory Bowel Disease, Atherosclerosis, Imaging Techniques, Chronic Diseases

Introduction

Inflammatory bowel disease (IBD) is characterized by chronic inflammation and a relapsing clinical course. In addition, it is also associated with increasing cardiovascular risk. Although the exact mechanism underlying this relationship is not clearly understood, substantial studies on chronic inflammatory disorders (including rheumatoid arthritis and systemic lupus erythematosus) have suggested that chronic inflammation plays a crucial role in the development of cardiovascular disease induced by atherosclerosis (1,2).

Therefore, non-invasive imaging methods such as carotid intima media thickness (CIMT), flow-mediated dilatation, and carotid femoral pulse wave velocity have been utilized to assess the subclinical atherosclerosis in IBD patients (3-6). In addition, epicardial adipose tissue (EAT), which is correlated with atherosclerotic coronary artery disease (CAD), can be easily evaluated by a basic imaging method called transthoracic echocardiography (7). On the other hand, the lack of a strict similarity between patients and controls according to their cardiovascular disease risk factors revealed conflicting results in patients with IBD when compared with healthy controls who were evaluated by CIMT (5,8-10).

The aim of this study was to evaluate CIMT and EAT in highly selected group of patients with IBD

and healthy controls with respect to cardiovascular risk factors, and also to assess whether measuring EAT can be used as a diagnostic tool through which to gain knowledge of early atherosclerosis in IBD patients.

Material and Methods

Forty-three patients with IBD (10 with Crohn's disease [CD] and 33 with ulcerative colitis [UC]) and 29 healthy age- and gender-matched volunteers were enrolled in the study; the patients' ages ranged from 18–50 years old. Diagnosis was established according to clinical, endoscopic, and histopathological criteria. Disease activity was assessed according to the Crohn's Disease Activity Index (CDAI) for CD and the Disease Activity Index (DAI) for UC (11,12). All patients were under treatment for their respective conditions. The exclusion criteria for both groups included a history of coronary, peripheral artery, or cerebrovascular diseases; inflammatory disorders other than IBD; chronic renal failure; total colectomy for IBD; and cardiovascular risk factors including diabetes mellitus, hypertension, hyperlipidemia, and smoking. Participants using anti-hypertensive drugs and vitamin supplements (including B_{12} and folic acid) were also excluded. The study was conducted in accordance with the tenets of the Declaration of Helsinki. In addition, the study protocol was also approved by the local ethics committee. Written informed consent was obtained from all participants.

On the day of the assessment, the patients' detailed medical histories were obtained, and physical examinations were performed. In addition, current medications, disease duration, involvement of disease, history of surgical intervention, and smoking status were also evaluated. Body weight (kg) and height (m) were measured, and body mass index (BMI) was calculated according to the formula (kg/m^2) for all participants. In addition, blood samples for laboratory evaluation were also obtained after a 12-hour fasting period. Hemoglobin, hematocrit, platelet, white blood cell, and glucose levels, as well as lipid parameters, electrolytes, liver, and renal functions were determined using autoanalyzers. C-reactive protein (CRP) was measured using the nephelometric method.

Measurement of Carotid Intima Media Thickness

Carotid artery intima-media thickness (IMT) measurements were ascertained with a high-frequency (3.0–12.0 MHz) ultrasound scanning probe (Philips L12-3 broadband linear array, Best, Netherlands) while the patients were in the supine position, with their necks extended and chins turned away from the side being examined. The right and left common carotid arteries were imaged proximal to the bulb in multiple longitudinal planes for the clearest resolution of the IMT of the far wall. The mean IMT was obtained by manually tracing the intima-media in the far wall of the artery. Measurements were performed on three end diastolic images and they were subsequently averaged.

Evaluation of Epicardial Adipose Tissue

The EAT of the participants was evaluated by two-dimensional transthoracic echocardiography with a 4 MHz, sector-type transducer probe (Philips HD11 XE Ultrasound System, Best, Netherlands). Images were digitally stored with standard parasternal long- and short-axis views, and they were reviewed by one echocardiologist. The maximum EAT was measured at a point on the free wall of the right ventricle at end-systole, perpendicular to the aortic annulus for the parasternal long-axis view, and perpendicular to both the interventricular septum at the mid-chordal view and the tip of the papillary muscle level for the parasternal short-axis view. Epicardial fat was defined as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. EAT was defined as the average of three cardiac cycles from each echocardiographic view. CIMT and EAT were evaluated by the same physician, who was blinded to the study groups.

Statistical Analysis

Data were evaluated by IBM SPSS version 21 (SPSS inc., Chicago, IL, USA). The normal distribution of the variables was evaluated with the Kolmogorov–Smirnov test, and logarithmic transformations were performed to normalize data with skewed distributions. Student's t-test and the χ^2 test were performed for continuous variables and categorical variables, respectively. The Mann–Whitney U test was also performed for

non-parametric data. Pearson's correlation analysis of the variables was performed. Categorical variables are expressed as numbers and percentages. All continuous variables are expressed as the mean ± standard deviation. Finally, p<0.05 was considered significant.

Results

Baseline Features of the Study Population

Among the patients in the IBD group, 33 with UC and 10 with CD participated in the study. In addition, the control group included 29 participants. The patients' mean age was 31.3±7.3 years in the IBD group, while it was 31.3±6.9 years in the control group. There were 26 (60.5%) men and 17 (39.5%) women in the IBD group, and 12 (41.4%) men and 17 (58.6%) women in the control group. The mean BMI of the study groups (IBD versus control) was 23.7±3.9 kg/m^2 and 24.3±3.3 kg/m^2, respectively. Furthermore, the patients in the IBD and control groups did not exhibit signs of cardiovascular diseases, including hyperlipidemia, hypertension, diabetes mellitus, smoking, or a family history of cardiovascular disease, according to the exclusion criteria. No significant differences were observed between the IBD group and the control group with respect to age, gender, and BMI (Table 1).

Clinical Characteristics and Biochemical Evaluation of IBD Patients

The clinical characteristics of the IBD patients are shown in Table 2. In the IBD patients, the disease duration was 16.8±9.7 months. Among patients with UC, 7 had proctitis, 21 had left-sided colitis, and 5 had extensive colitis, whereas among patients with CD, 8 cases had ileocolonic involvement and 2 cases had colonic involvement. The inflammatory type was predominant in CD patients (8 of 10, 80%), and a previous enterocutanous fistula was determined in one patient with CD. The CD patients' mean CDAI score and the mean DAI score among UC patients was 90±51 and 3.9±2.2, respectively. The erythrocyte sedimentation rate (ESR) and CRP values were significantly higher in IBD patients than in the control group (Table 1). At the time of the study, there were 18 (41.9%) patients in remission and no patients with

Table 1. Characteristics and Values of CIMT and EAT of Study Population

Parameters	IBD (n=43)	Control (n=29)	*p*-value
Age (year)	31.4±7.4	31.3±6.9	*NS*
Gender (M:F)	26:17	12:17	*NS*
BMI (kg/m^2)	23.7±3.9	24.3±3.3	*NS*
EAT (cm)	0.448±0.208	0.238±0.119	<0.001
CIMT (mm)	0.541±0.150	0.413±0.182	<0.01
ESR (mm/h)	22.7±21.3	6.8±5.9	<0.001
CRP (mg/dl)	23.9±45.9	4.6±2.8	<0.001

IBD: Inflammatory bowel disease, BMI: Body mass index, EAT: Epicardial adipose tissue, CIMT: Carotid intima media thickness, ESR: Erythrocyte sedimentation rate, CRP:C-reactive protein, M: Male, F: Female.

Table 2. Clinical Features of IBD Patients

	IBD (n=43)	UC (n=33)	CD (n=10)
Disease duration (months)	16.8±9.7	16.2±8.6	18.8±13.2
Disease Activity n (%)			
Remission	18	10	8
Mild	21	19	2
Moderate	4	4	-
Severe	-	-	-
Extent of UC			
Proctitis		7	-
Left sided colitis		21	-
Extensive colitis		5	-
DAI		3.9±2.2	
Extent of CD			
Ileal			-
Ileocolonic			8
Colonic			2
Behavior of CD			
Non-stricture non-penetrating			8
Stricture			1
Penetrating			1
CDAI			90±51
Current Treatment			
5-ASA	43	33	10
Steroid	3	2	1
Azathiopurine	7	3	4
Anti-TNFα	4	3	1

IBD: Inflammatory bowel disease, UC: Ulcerative colitis, CD: Crohn disease

IBD had previous surgery. IBD patients were taking 5-ASA (100%), steroids (7%), azathioprine (16.3%), and anti-tumor necrosis factor (TNF)-α (9.4%).

Imaging Methods: CIMT and EAT

CIMT and EAT were significantly higher in the IBD group when compared to the control group ($p<0.01$ and $p<0.001$, respectively; Table 1, Figure 1). EAT was correlated with CIMT in the IBD group ($r=0.574$, $p<0.001$, Figure 2). On the other hand, there were no significant correlations between imaging modalities and disease duration, involvement, and activity. In addition, when we organized the IBD group according to remission type, we did not reveal any significant differences with respect to the CIMT and EAT values (CIMT [active versus remission]: 0.544±0.153 mm versus 0.537±0.151 mm; and EAT [active versus remission]: 0.460±0.222 cm versus 0.430±0.191 cm). When we stratified the different groups of patients with IBD, we did not observe any significant difference between UC and CD in terms of CIMT and EAT ($p>0.05$, for both). However, CIMT and EAT were significantly higher in patients with UC and CD when compared to controls (Figure 1). In addition, we allocated participants according to their BMI (≥25 kg/m^2). In all, 23 of 43 cases in the IBD group and 11 of 29 cases in the control group had a BMI ≥25 kg/m^2. We did not find a significant difference in the distribution of obese participants in the study groups. In addition, we did not observe a significant difference between a BMI ≥25 kg/m^2 and a BMI <25 kg/m^2 in terms of the CIMT and EAT values in IBD patients.

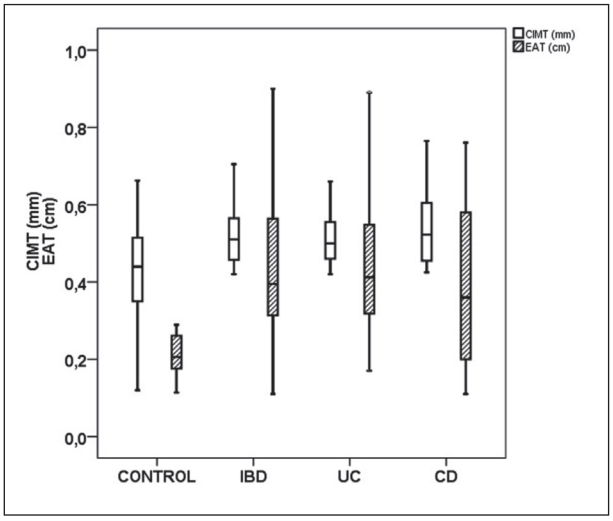

Figure 1. Carotid Intima Media Thickness (CIMT) and Epicardial Adipose Tissue (EAT) values of Study Groups; IBD vs Control (CIMT and EAT $p<0.01$, $p<0.001$ respectively), UC vs Control (CIMT and EAT $p<0.01$, $p<0.001$ respectively), CD vs Control (CIMT and EAT $p<0.05$, $p<0.05$ respectively), IBD: Inflammatory bowel disease, UC: Ulcerative colitis, CD: Crohn disease 220x185mm (300 x 300 DPI)

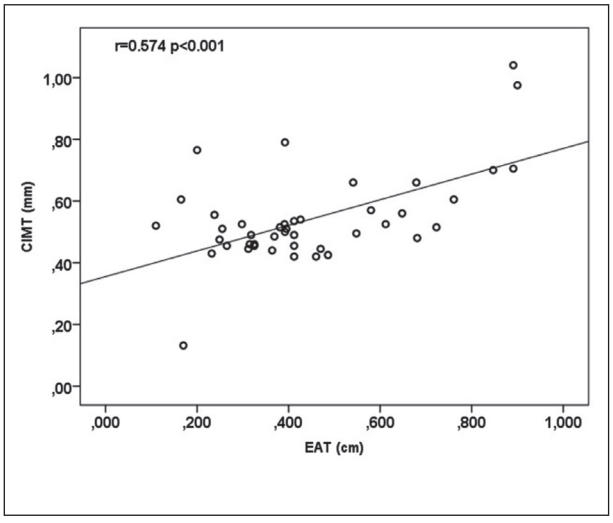

Figure 2. Correlation between carotid intima media thickness and epicardial adipose tissue thickness in IBD patients (n=43), CIMT: Carotid Intima Media Thickness, EAT: Epicardial Adipose Tissue 220x166mm (300 x 300 DPI)

Discussion

In this study, we demonstrated that IBD patients without well-known cardiovascular risk factors had significantly higher CIMT and EAT values when compared to the control group. Furthermore, EAT was positively correlated with CIMT in the IBD group. To the best of our knowledge, this study is the first to suggest that the EAT measurement could be used to evaluate early atherosclerosis in IBD.

Growing evidence has indicated that several chronic inflammatory and immunological disorders are associated with increased cardiovascular morbidity and mortality due to atherosclerosis (13). Furthermore, substantial increasing consequences suggested that chronic inflammatory disorders such as rheumatoid arthritis, Hashimoto's thyroiditis, psoriasis, and systemic vasculitis have some capacity to cause future

cardiovascular events in an independent manner, even without the presence of traditional cardiovascular risk factors (14-17). Nevertheless, the clinical course of IBD is also based upon chronic and relapsing inflammation. Bernstein et al reported that the risk of ischemic heart diseases increased in all IBD patients, regardless of diagnosis and the sex of the patients (18). However, studies that investigate the relationship between IBD and cardiovascular disease present conflicting results due to the undetermined and strict cardiovascular risk factors observed between the IBD and control groups (8-10). Therefore, the IBD and control groups in our study were selected to compose strictly stated groups without cardiovascular risk factors. Conversely, even though the study groups did not exhibit cardiovascular risk factors, the levels of inflammatory markers (including ESR and CRP) in our IBD patients were significantly higher when compared with the control group. This finding pointed to the idea that chronic inflammation alone may cause inflammatory disorders in our study groups, despite the use of anti-inflammatory medications.

Geroulakos et al suggested that CIMT is a non-invasive marker that reflects early vascular structural changes due to atherosclerosis, and it also predicts the presence of CAD with a specificity of 77%, a sensitivity of 43%, and a positive predictive value of 83% (19,20). Furthermore, the current epidemiological data concluded that the normal range of CIMT could change in accordance with age. When analyzing age, the normal CIMT ranges for those <30 years, 31–40 years, and 41–50 years are 0.44–0.57 mm, 0.42–0.50 mm, and 0.44–0.57 mm, respectively. However, a CIMT ≥1 mm at any age is related to significant cardiovascular risk (21,22). The mean age of our study groups, including the IBD patients and controls, was 31.3±7.4 years and 31.3±6.9 years, respectively. Our patients had higher CIMT values according to their age range. In addition, the CIMT value in our IBD patients was significantly elevated when compared to that of the control group (IBD versus control: 0.541±0.150 versus 0.413±0.182 mm, respectively).

EAT is associated with conventional cardiovascular risk factors and cardiovascular events due to subclinical atherosclerosis. Ahn et al reported that EAT is higher in patients with CAD, as compared to patients without CAD. In addition, EAT ≥0.3 cm was an independent factor for CAD on multiple logistic analysis (odds ratio=3.357; 95% CI: 2.177–5.175; p<0.001) (7). On the other hand, EAT may exert detrimental effects by releasing inflammatory mediators (23). Overall, it is suggested that EAT has an effect on coronary vascular abnormalities via atherosclerosis (24-27). Therefore, we thought that EAT could be used as a non-invasive marker to detect early atherosclerosis in IBD patients. Interestingly, we observed that EAT in the IBD group had significantly higher values than in the control group (IBD versus control: 0.448±0.208 versus 0.238±0.119 cm, respectively; p<0.001). Furthermore, EAT was also significantly correlated with CIMT. In fact, Ahn et al also pointed out that EAT was not only thicker in patients with metabolic syndrome, but it also increased linearly with respect to metabolic syndrome components (7). Despite the fact that we did not evaluate insulin resistance, our study groups had homogenous features irrespective of the presence of metabolic syndrome components, including hypertension, hypertriglyceridemia, and diabetes mellitus. On the other hand, we had participants with a BMI ≥25 kg/m^2. Therefore, we evaluated BMI to determine whether a BMI ≥25 kg/m^2 had an effect on CIMT and EAT values; we found out that a BMI ≥25 kg/m^2 had no effect on CIMT or EAT.

We did not observe any relationships between the imaging modalities and disease-related factors including disease duration, activity, and involvement. However, these findings could be a consequence of our highly selected IBD patients, who did not have well-known cardiovascular risk factors. In addition, the presence of inflammatory burden in IBD patients was the most powerful factor observed across a number of imaging modalities, despite the absence of cardiovascular risk factors, as was mentioned previously. Furthermore, CRP – which is a predictor of cardiovascular events (28) – was significantly higher in IBD patients than in the control group. Therefore, CRP may also actively play a crucial role in the development of atherosclerotic cardiovascular diseases via inflammation. Overall, long-term patient follow-up to illuminate the relationship between the aforementioned IBD-related factors, as well as imaging methods to detect early atherosclerosis, might constitute a prudential approach.

In conclusion, this study suggests that patients with IBD without well-known cardiovascular risk factors exhibit an increased risk of early atherosclerosis. In addition, both CIMT and EAT serve as functional imaging methods that can detect atherosclerosis in patients with IBD. EAT may be used as an additional diagnostic tool through which to extrapolate early atherosclerosis in clinical practice.

Authors' contributions

Nevzat Gozel, Orhan Kursat Poyrazoglu and Bahadir Sarli designed the studies and wrote the protocols. Yasemin Dogan, Abdullah Eyvaz and Banu Demet Ozel were followed patients in the study and were collected data. Agah Bahadir Ozturk and Omer Bilgehan Poyrazoglu undertook the literature searches and statistical analyses. Nevzat Gozel wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of interest

The authors report no conflict of interest and have not received any payment for the preparation of this manuscript. The authors alone are responsible for the content and writing of the paper.

References

1. Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med.* 2003; 349(25):2399-2406.
2. Salmon JE, Roman MJ. Subclinical atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. *Am J Med.* 2008; 121(10 Suppl 1):S3-8.
3. Ozturk K, Guler AK, Cakir M, Ozen A, Demirci H, Turker T, et al. Pulse Wave Velocity, Intima Media Thickness, and Flow-mediated Dilatation in Patients with Normotensive Normoglycemic Inflammatory Bowel Disease. *Inflamm Bowel Dis.* 2015;21(6):1314-1320.
4. Kocaman O, Sahin T, Aygun C, Senturk O, Hulagu S. Endothelial dysfunction in patients with ulcerative colitis. *Inflamm Bowel Dis.* 2006; 12(3):166-171.
5. Papa A, Santoloquido A, Danese S, Covino M, Di Campli C, Urgesi R, et al. Increased carotid intima-media thickness in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2005; 22(9):839-846.
6. Dagli N, Poyrazoglu OK, Dagli AF, Sahbaz F, Karaca I, Kobat MA, et al. Is inflammatory bowel disease a risk factor for early atherosclerosis? *Angiology.* 2010; 61(2):198-204.
7. Ahn SG, Lim HS, Joe DY, Kang SJ, Choi BJ, Choi SY, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. *Heart*. 2008; 94(3):e7.
8. Kayahan H, Sari I, Cullu N, Yuksel F, Demir S, Akarsu M, et al. Evaluation of early atherosclerosis in patients with inflammatory bowel disease. *Dig Dis Sci.* 2012; 57(8):2137-2143.
9. Theocharidou E, Gossios TD, Griva T, Giouleme O, Douma S, Athyros VG, et al. Is There an Association Between Inflammatory Bowel Diseases and Carotid Intima-media Thickness? Preliminary Data. *Angiology.* 2014; 65(6):543-550.
10. Maharshak N, Arbel Y, Bornstein NM, Gal-Oz A, Gur AY, Shapira I, et al. Inflammatory bowel disease is not associated with increased intimal media thickening. *Am J Gastroenterol.* 2007;102(5): 1050-1055.
11. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology.* 1976; 70(3): 439-444.
12. Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology.* 1987; 92:1894–1898.
13. Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868-874. Review.
14. Raza K, Thambyrajah J, Townend JN, A.R. Exley, C. Hortas, A. Filer, et al. Suppression of inflammation in primary systemic vasculitis restores vascular endothelial function: lessons for atherosclerotic disease? *Circulation* 2000; 102(13):1470-1472.
15. Ciccone MM, Balbarini A, Teresa Porcelli, Scicchitano P, Caldarola P, Iacoviello M, et al. Increased carotid IMT in overweight and obese women affected by Hashimoto's thyroiditis: an adiposity and autoimmune linkage? *Eur J Cardiovasc Prev Rehabil.* 2011;18(4):650-655.
16. Balci DD, Balci A, Karazincir S, Ucar E, Iyigun U, Yalcin F, et al. Increased carotid artery intima-media thickness and impaired endothelial function in psoriasis. *J Eur Acad Dermatol Venereol.* 2009; 23(1):1-6.
17. Van Doornum S, McColl G, Jenkins A, Green DJ, Wicks IP. Screening for atherosclerosis in patients with rheumatoid arthritis: comparison of two in vivo tests of vascular function. *Arthritis Rheum.* 2003; 48(1):72-80.
18. Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. *Clin Gastroenterol Hepatol.* 2008; 6(1):41-45.
19. Geroulakos G, O'Gorman DJ, Kalodiki E, Sheridan DJ, Nicolaides AN. The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease *Eur Heart J.* 1994; 15(6):781-785.
20. Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. *J Hypertens.* 2002;20(2):159-169. Review.

21. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. *Stroke.* 1993; 24(9):1297-1304.
22. Gariepy J, Salomon J, Denarié N, Laskri F, Mégnien JL, Levenson J, et al. Sex and topographic differences in associations between large-artery wall thickness and coronary risk profile in a French working cohort: the AXA Study. *Arterioscler Thromb Vasc Biol.* 1998;18(4):584-590.
23. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation.* 2003;108(20):2460-2466.
24. Park JS, Ahn SG, Hwang JW, Lim HS, Choi BJ, Choi SY, et al. Impact of body mass index on the relationship of epicardial adipose tissue to metabolic syndrome and coronary artery disease in an Asian population. *Cardiovasc Diabetol.* 2010;9:29. doi: 10.1186/1475-2840-9-29.
25. Djaberi R, Schuijf JD, van Werkhoven JM, Nucifora G, Jukema JW, Bax JJ. Relation of epicardial adipose tissue to coronary atherosclerosis. *Am J Cardiol.* 2008;102(12):1602-1607.
26. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. *J Am Soc Echocardiogr.* 2009;22(12):1311-1319
27. Aslanabadi N, Salehi R, Javadrashid A, Tarzamni M, Khodadad B, Enamzadeh E, et al. Epicardial and pericardial fat volume correlate with the severity of coronary artery stenosis. *J Cardiovasc Thorac Res*. 2014;6(4):235-239.
28. Scirica BM, Morrow DA. Is C-reactive protein an innocent bystander or proatherogenic culprit? The verdict is still out. *Circulation.* 2006;113(17):2128-2134. Review

Correspondence:
Nevzat Gozel
Firat University, School of Medicine, Department of Internal Medicine, 23119, Elazig/Turkey
Tel: +90 (424) 233 35 55
Fax: +90 (424) 238 80 96
E-mail: drngozel@hotmail.com