ORIGINAL PAPERS

Evaluation of epicardial adipose tissue and carotid intima-media thickness as a marker of atherosclerosis in patients with inflammatory bowel disease

Nergiz Ekmen[1], Güray Can[2], Ahmet Yozgat[3], Hatice Can[4], Muhammed Fatih Bayraktar[5], Muhammet Emin Demirkol[6], Meral Akdoğan Kayhan[7] and Hadi Sasani[8]

[1]Department of Gastroenterology. Faculty of Medicine. Gazi University. Ankara, Turkey. Departments of [2]Gastroenterology, [5]Cardiology and [6]Internal Medicine. Faculty of Medicine. Abant Izzet Baysal University. Bolu, Turkey. [3]Department of Gastroenterology. Faculty of Medicine. Ufuk University. Ankara, Turkey. [4]Department of Nephrology. Faculty of Medicine. Inönü University. Malatya, Turkey. [7]Department of Gastroenterology. Department of Gastroenterology. Ankara Bilkent City Hospital. University of Health Sciences. Ankara, Turkey. [8]Department of Radiology. Faculty of Medicine. Tekirdağ Namik Kemal University. Tekirdağ, Turkey

Received: 09/07/2020 · **Accepted:** 21/11/2020

Correspondence: Nergiz Ekmen. Department of Gastroenterology. Faculty of Medicine. Gazi University. 60150 Yenimahalle, Ankara. Turkey. **e-mail:** dr_nergisekmen@hotmail.com

ABSTRACT

Background and aim: this study aimed to compare carotid intima media (CIMT) and epicardial adipose tissue (EAT) measurements, which are considered as markers for the detection of early atherosclerosis in healthy controls and inflammatory bowel disease (IBD) cases.

Methods: a total of 60 IBD patients (25 Crohn's disease and 35 ulcerative colitis) and 60 healthy patients (as a control group) were included in the study. The measurements of CIMT and EAT were performed using echocardiography and ultrasonography, respectively. Statistical analysis was used to determine the relationship between the parameters.

Results: the thickness of bilateral (right and left) CIMT and EAT were significantly higher in IBD than in the control group ($p < 0.05$). There was a positive correlation between EAT and bilateral (right and left) CIMT in IBD patients ($p < 0.05$).

Conclusion: IBD is associated with an increased thickness of EAT and CIMT. Chronic inflammation in IBD may increase the risk of atherosclerotic heart disease. Thus, only measuring the thickness of EAT and CIMT can be used as an objective, easy, simple, affordable, non-invasive and accessible assessment method in order to screen for this risk.

Keywords: Carotid intima-media thickness. Echocardiography. Atherosclerosis. Pericardium. Adipose tissue. Inflammatory bowel disease.

INTRODUCTION

Coronary artery disease and myocardial infarction are the major causes of morbidity and mortality worldwide (1). Factors such as smoking, cholesterol levels, body mass index (BMI), frequency of exercising and blood pressure have been shown to play a role in cardiovascular diseases. Furthermore, chronic inflammation has also been shown to contribute to the development of atherosclerosis (2).

Carotid intima media thickness (CIMT) has been proven to be associated with major cardiovascular risk factors and is a precise guide to atherosclerotic events (3). Epicardial adipose tissue (EAT), a visceral adipose tissue compart-

Conflict of interest: the authors declare no conflict of interest.

Funding: the authors declare that this study has not received any financial support.

Availability of data and materials: patient's data was obtained from the hospital data system.

Informed consent and human rights: written informed consent was obtained from the patients who participated in this study.

Ethical approval: no. 116, decision number: 2019/51, dated: 07.03.2019.

Authors contributions: all authors were involved in the study concept and design, analysis and interpretation of the data, and drafting and critical revision of the manuscript for important intellectual content. Nergiz Ekmen edited and reviewed the manuscript, and is the article guarantor. All authors read and approved the final manuscript.

Ekmen N, Can G, Yozgat A, Can H, Bayraktar MF, Dermirkol ME, Akdoğan Kayhan M, Sasani H. Evaluation of epicardial adipose tissue and carotid intima-media thickness as a marker of atherosclerosis in patients with inflammatory bowel disease. Rev Esp Enferm Dig 2021;113(9):643-648

DOI: 10.17235/reed.2020.7394/2020

1130-0108/2021/113/9/643-648 • REVISTA ESPAÑOLA DE ENFERMEDADES DIGESTIVAS

ment, is located between the pericardium and myocardial layers and is in direct contact with the coronary vessels and myocardium without any tissue and fascia (4). Like other white adipose tissues, EAT has an endocrine function and secretes hormones and inflammatory cytokines (4,5). The secretion and expression of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) are higher at EAT than subcutaneous adipose tissue in the patients with coronary artery disease. Furthermore, pathologically enlarged EAT is significantly correlated with increased cardiovascular disease risk (6). Thanks to the widespread availability of non-invasive imaging methods such as echocardiography, computed tomography and magnetic resonance imaging, EAT measurement, which is a reliable cardiovascular risk predictor, is applied more frequently (7). Echocardiography is a simple, inexpensive and easily available measurement tool in healthcare facilities.

Inflammatory bowel disease (IBD), including two systemic diseases such as ulcerative colitis (UC) and Crohn's disease (CD), results in inflammation in the intestine (8). In addition to the bowel, one-third of IBD patients experience extra-intestinal symptoms in the eyes, skin, musculoskeletal system and cardiovascular system (9). Systemic or local inflammatory burden differs depending on factors such as the disease duration, the prevalence of bowel involvement and disease activity. Interesting data has been put forward in recent years, suggesting that systemic inflammation plays a role in the development of atherosclerosis in IBD patients (10). This data brings to mind the thought of investigating the development of atherosclerosis among patients with systemic inflammatory disease. However, there is a limited number of studies performed in IBD, which progresses with inflammation for many years. Furthermore, there is no consensus on the results of these studies (11-15).

This study aimed to determine the relationship between CIMT and EAT thickness using sonographic methods (echocardiography, carotid Doppler ultrasonography), echocardiography and the significance of both for the diagnosis of early atherosclerosis in IBD patients.

MATERIAL AND METHODS

Ethical issue

The study was a cross-sectional single center study, approved by the Clinical Research Ethics Committee of the institution (no. 116, decision number: 2019/51, dated: 07.03.2019). Informed consent was obtained from all patients.

Patient selection

Patients admitted to the Gastroenterology outpatient clinic during a four-month period between April and July 2019 were evaluated for the inclusion and exclusion criteria. Inclusion criteria: patients over age 18 years and in remission were included in the study. Exclusion criteria: patients with diabetes mellitus, hypertension, hyperlipidemia, acute and chronic kidney disease, thromboembolic disease, chronic lung disease, malignancy, autoimmune vasculitis and other autoimmune diseases, cardiac disease; patients taking drugs (anti-TNF, active steroids) and those with active disease in terms of IBD were excluded from the study. The control group was specified by matching the age and gender from volunteers with no known chronic or cardiac disease and not taking heart-acting drugs.

The diagnosis of IBD was made clinically, endoscopically, radiologically and histologically according to ECCO consensus criteria. Partial Mayo score was used for ulcerative colitis patients and Harvey-Bradshaw index was used for Crohn's patients to assess disease activation. Personal and clinical information, medical history and IBD-related clinical data of the patients were obtained from the hospital data system.

Laboratory parameters

Pre-prandial blood glucose, C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured by standard procedures from blood samples taken after fasting overnight. Patients with no disease related to lipid profiles in their previous examinations were included in the study and no additional blood tests were performed to obtain a new lipid profile at the time of study.

In both groups, systolic (SBP) and diastolic (DBP) blood pressure were measured three times on the right arm in a seated position after ten-minutes of resting and the mean value was calculated. BMI was calculated by dividing the square of the height by weight.

CIMT and EAT measurement methods

EAT thickness was measured by echocardiography with the 4 MHz probe (Vivid 9 Pro, GE Vingmed, Milwaukee, Wisconsin, USA) in the left lateral decubitus position, from the right ventricular free wall on the parasternal long axis images. CIMT were determined by carotid Doppler ultrasonography using a 12 MHz superficial probe of the same device, which provides an image from a linear angle (Fig. 1). All echocardiographic measurements were made in the IBD and control group according to the standards recommended by the American Echocardiography Association (16).

Statistical analysis

The conformity of continuous variables to a normal distribution was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The independent sample t test was used for the comparative analysis between the two groups for the data with a normal distribution and the Mann-Whitney U test was used for non-normally distributed data. The Chi-squared (χ^2) test was used for the comparison analysis of categorical variables between the independent groups and the Spearman correlation analysis was used for the correlation analysis between two factors. p values (two-sided) below 0.05 were considered as statistically significant. All analyses were performed using SPSS version 22. Comparative data are shown as the mean ± standard error.

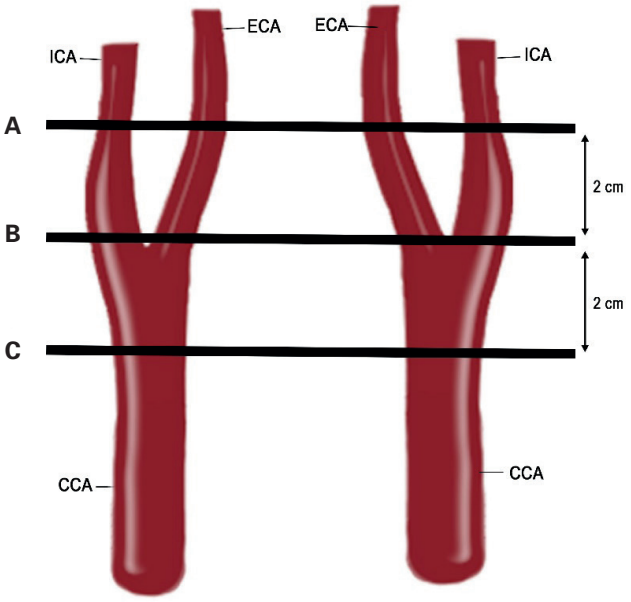

Fig. 1. *The illustration shows CIMT measurements. While lying in a supine position, the patient was moved manually by moving the neck to an angle of approximately 20 degrees towards the opposite side of the neck, with the probe positioned parallel to the common carotid artery (CCA). Measurements were taken from three points: A) the first 2 cm proximal part of the internal carotid arteries; B) bilateral CCA; and C) 2 cm proximal to carotid bifurcation. CIMT measurements were performed with a longitudinal examination using B-mode imaging across the distance defined as the clearance of the vascular lumen echogenicity and media/adventitia echogenicity.*

RESULTS

Of 95 IBD patients who attended the Gastroenterology outpatient clinic within a four-month period, 35 patients (with one or more exclusion criteria) were excluded from the study. Thus, a total of 60 IBD patients (25 CD and 35 UC) were enrolled in the study. The average age and gender distribution of UC (35 patients), CD (25 patients) and the healthy control group (60 volunteers) were similar ($p = 0.387$; $p = 0.070$, respectively). Among the patients included in the study, all patients with UC were receiving 5-aminosalicylates and all patients with CD were receiving azathioprine treatment. Twenty patients (57.1 %) with ulcerative colitis and ten patients (40 %) with Crohn's disease had one or more previous steroid usage history.

There was no difference between the IBD and control group in terms of smoking and BMI ($p > 0.05$). There was no significant difference between the IBD and control group in terms of other cardiovascular parameters (Table 1). The median duration of disease in IBD was four years (1-20). ESR, CRP, DBP, R-CIMT, L-CMIT and EAT (Fig. 2A-C) measurements were significantly higher in IBD patients compared to the control group ($p < 0.05$). Comparisons between clinical and laboratory parameters between groups are summarized in table 1.

A moderate negative correlation between EAT thickness and R-CIMT was found in the control group ($r = -0.308$, $p = 0.017$), whereas in IBD patients there was a moderate positive correlation between EAT and R-CIMT ($r = 0.474$, $p < 0.001$) and a weak positive correlation with L-CIMT ($r = 0.275$, $r = 0.035$) (Fig. 3A and B). No correlation was found between age and EAT, R-CIMT, L-CIMT in the control group (Table 2). In IBD patients, R-CIMT, L-CIMT and EAT measurements showed a moderately positive correlation with age ($r = 0.566$, $p < 0.001$; $r = 0.472$, $p < 0.001$; $r = 0.553$, $p < 0.001$, respectively).

No correlation was found between the disease duration and EAT, R-CIMT, L-CIMT in IBD (Table 2). No statistically significant association was found between glucose, gender and smoking with CIMT and EPA in the healthy control and IBD group ($p > 0.05$).

DISCUSSION

IBD is thought to play a role in the development of atherosclerosis due to its chronic inflammatory nature (15,17). Although traditional cardiovascular risk factors are not present at higher levels in IBD patients compared to the general population, there are higher rates of cardiovascular mortality and morbidity and cardiovascular events in IBD patients (18-20). This high risk may be associated with inflammation-mediated atherosclerosis (18). It is known that inflammation may have an independent role in the pathogenesis of atherosclerosis or act synergistically with traditional risk factors (21) CIMT is a widely accepted inflammatory marker in clinical practice to predict early atherosclerosis (22).

EAT and CIMT thickness are valuable predictors of atherosclerotic vascular disease and are considered as an independent risk factor for coronary artery disease (23,24). CIMT and EAT have been studied together in some chronic inflammatory diseases in recent years and have been shown to be a new parameter to predict atherosclerosis (25,26). To the best of our knowledge, there is a limited number of studies evaluating the thickness of EAT and CIMT together to predict early atherosclerosis in IBD patients. In our study, CIMT thickness was found to be significantly higher in IBD patients compared to the control group, suggesting that they have an increased risk of early atherosclerosis. The results in the current study were similar to the several previous studies that investigated CIMT and early atherosclerosis in IBD (15,27-29). There was no difference in CIMT thickness between IBD patients and the control group in a study involving only CD patients (12) and in three different studies including CD and UC patients (11,13,14). Furthermore, the risk of ischemic heart disease decreased in IBD patients using anti-inflammatory 5-ASA treatment compared to the control group. Immunomodulatory therapy (such as azathioprine) reduces arterial stiffness (20) and it is also noteworthy that CIMT thickness is greater in the IBD group compared to healthy controls.

In the current study, while EAT showed a positive correlation with CIMT and age in the IBD group, there was a moderate negative correlation between EAT and CIMT in the healthy control group. There was no correlation with age. EAT was significantly higher in IBD patients than in the control group. The negative correlation between EAT and CIMT in the healthy control group can be explained by the

Table 1. *Comparison of the clinical and laboratory characteristics of study participants*

Variables	IBD (n = 60)	Control (n = 60)	p
Age (years)	36.90 ± 11.53	36.90 ± 11.53	0.877*
Gender		36.61 ± 8.09	
Male	35 (58.3)	34 (56.7)	0.853†
Female	25 (41.7)	26 (46.3)	
Smoker, n (%)	19 (31.7)	21 (35)	0.699†
BMI, kg/m^2	24.35 ± 4.84	25.97 ± 4.30	0.059*
Disease duration (years)	4 (1-20)		
ESR, mm/h	11.50 (1.00-32.00)	5.50 (1.00-15.00)	*< 0.001‡*
CRP, mg/l	1.00 (0.10-16.00)	0.58 (0.06-8.00)	*0.046‡*
FPG, mg/dl	93.09 ± 9.73	89.93 ± 8.92	0.073*
SBP, mmHg	128.53 ± 9.43	127.61 ± 10.74	0.623*
DBP, mmHg	79.03 ± 7.84	74.80 ± 4.91	*0.001**
EF, %	60 (55-66)	62 (55-69)	0.258‡
LV-ESD, cm	2.8 (2.4-3.2)	2.8 (2.1-3.4)	0.398‡
LV-EDD, cm	4.6 (4.1-5.2)	4.7 (3.4-5.3)	0.300‡
AAR, cm	3.2 (2.8-3.9)	3.2 (2.9-3.7)	0.383‡
AR, cm	3.2 (0.8-4.2)	3.2 (2.8-3.7)	0.858‡
PW, cm	0.9 (0.7-2.9)	0.8 (0.7-1)	0.085‡
IVS, cm	0.9 (0.7-4.5)	0.9 (0.7-1)	0.098‡
LA, cm	3.4 (2.8-4)	3.2 (2.8-4)	*0.006‡*
RCIMT, mm	0.50 (0.40-0.70)	0.40 (0.40-0.50)	*< 0.001‡*
LCIMT, mm	0.50 (0.35-0.70)	0.40 (0.40-0.60)	*0.001‡*
EAT, mm	0.70 (0.50-0.90)	0.50 (0.40-0.70)	*< 0.001‡*

BMI: body mass index; IBD: inflammatory bowel disease; RCIMT and LCIMT: right and left carotid intima-media thickness; EAT: epicardial adipose tissue thickness; FPG: fasting plasma glucose; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SBP: systolic blood pressure; DBP: diastolic blood pressure. EF: ejection fraction, LV-ESD: left ventricular end-systolic diameter; LV-EDD: left ventricular end-diastolic diameter; AAR: ascending aortic root diameter; AR: aortic root diameter; PW: posterior wall thickness; IVS: interventricular septum thickness; LA: left atrium diameter. *Student t test. †Chi-squared analysis. ‡Mann-Whitney U test.

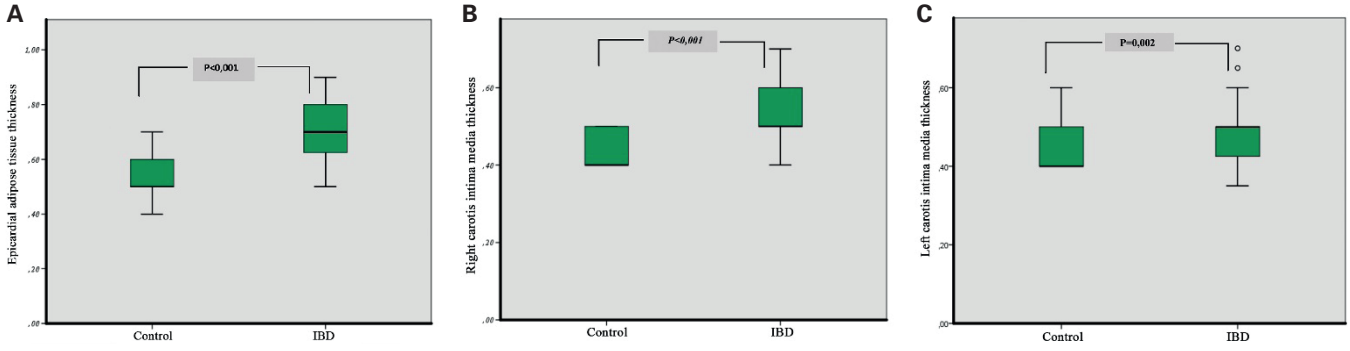

Fig. 2. *A. Comparison of epicardial adipose tissue thickness in control and IBD patients. B. Comparison of right carotid intima media thickness in control and IBD patients. C. Comparison of left carotid intima media thickness in control and IBD patients.*

absence of chronic inflammatory processes in this group. With regard to the increase in CIMT and EAT with age in the IBD group, this could be due to the inflammatory load created by IBD with advancing age and may have accelerated the atherosclerotic process.

In a study performed by Uysal et al. in IBD patients, CIMT thickness was similar to the controls, while EAT thickness was greater in IBD patients compared to controls. Furthermore, the same study found that CIMT and EAT thickness correlated only in CD patients (15).

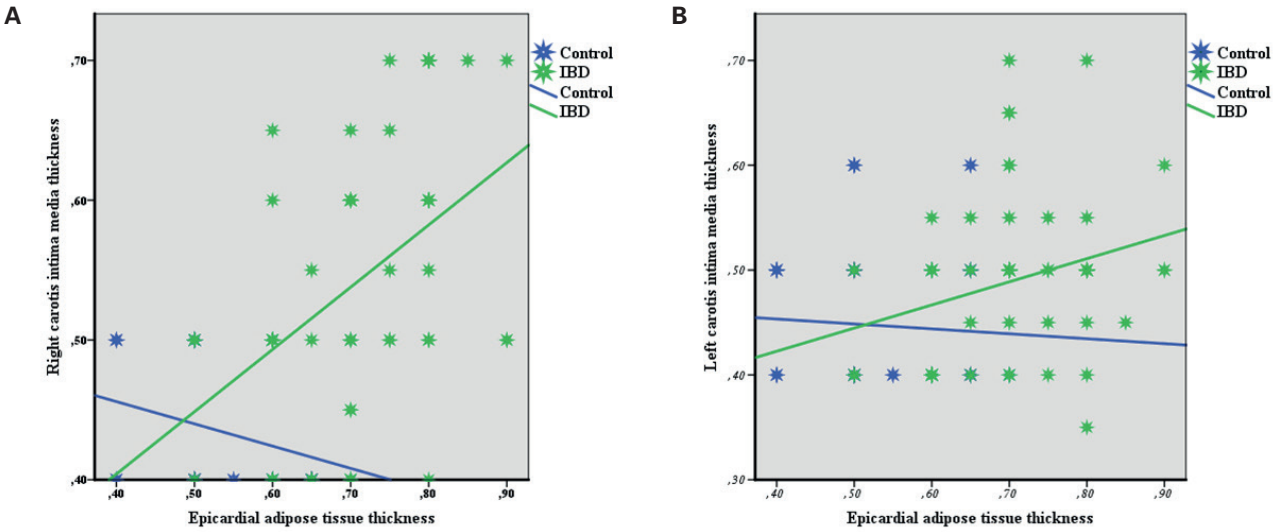

Fig. 3. *A. Correlation between epicardial adipose tissue and right carotid intima-media thickness. B. Correlation between epicardial adipose tissue and left carotid intima-media thickness.*

Table 2. *Correlation of study parameters with EAT thickness, CIMT and age*

Variables	Control		IBD	
EAT	**r**	**p**	**r**	**p**
RCIMT	-0.308	*0.017*	*0.474*	*< 0.001*
LCIMT	-0.087	0.507	*0.275*	*0.035*
Age (years)				
EAT	-0.163	0.213	*0.553*	*< 0.001*
RCIMT	0.071	0.592	*0.566*	*< 0.001*
LCIMT	-0.152	0.245	*0.472*	*< 0.001*
Disease duration (years)				
EAT			0.179	0.171
RCIMT			0.206	0.114
LCIMT			0.202	0.126

EAT: epicardial adipose tissue thickness; RCIMT and LCIMT: right and left carotid intima-media thickness; IBD: inflammatory bowel disease.

In a study of ankylosing spondylitis patients, a correlation was found between the disease duration and EAT and CMT (25), whereas there was no correlation between the disease duration and EAT in another study with patients with psoriasis (26). The reason may be due to the nature of the disease, which has activation and remission periods. As the frequency and length of activation are different in each patient, the effect of inflammation in the body differs from person to person in the same group of patients. In our study, there was no correlation between disease duration and EAT and CIMT.

There were several limitations in our study. The first limiting factor was the fact that all IBD patients were in remission. Therefore, the effect of the active period in IBD could not be evaluated for EAT and CIMT. The second limiting factor was the exclusion of an IBD group receiving anti-TNF therapy. There are recent studies reporting that biologics, such as anti-TNF and immunomodulatory therapy, such as methotrexate, led to cardiovascular improvement in rheumatoid arthritis patients with chronic inflammation. We think that the inclusion of a group receiving anti-TNF therapy would be meaningful in terms of investigating the effects of these drugs on CIMT and EAT in IBD patients. The third limiting factor was the inability to examine the effects of active steroid use in the study population with a history of steroid use, considering the cardio protective effect of corticosteroid treatment used in IBD patients (20). Another limitation was related to the small number of patients in the study cohort.

In conclusion, the usefulness is greater in IBD patients of EAT thickness and CIMT, which can be evaluated as a non-invasive, easily applicable method, being also markers of atherosclerosis and cardiovascular disease. The data obtained from the study showed that both EAT thickness and CIMT are more effective to diagnose early atherosclerosis in patients with IBD. Large-group multicenter prospective studies are needed to evaluate the effect of EAT and CIMT measurement on early atherosclerosis and cardiovascular mortality and morbidity in IBD patients.

REFERENCES

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2197-223. DOI: 10.1016/S0140-6736(12)61689-4

2. Matsuura E, Atzeni F, Sarzi-Puttini P, et al. Is atherosclerosis an autoimmune disease? BMC Med 2014;12:47.

3. Polak JF, Pencina MJ, Pencina KM, et al. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med 2011;365(3):213-21. DOI: 10.1056/NEJMoa1012592 DOI: 10.1056/NEJMoa1012592

4. Nagy E, Jermendy AL, Merkely B, et al. Clinical importance of epicardial adipose tissue. Arch Med Sci 2017;13(4):864-74. DOI: 10.5114/aoms.2016.63259

5. Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 2003;108(20):2460-6. DOI: 10.1161/01.CIR.0000099542.57313.C5

6. Guzzardi MA, Iozzo P. Fatty heart, cardiac damage, and inflammation. Rev Diabet Stud 2011;8(3):403-17. DOI: 10.1900/RDS.2011.8.403

7. Sacks HS, Fain JN. Human epicardial fat: what is new and what is missing? Clin Exp Pharmacol Physiol 2011;38(12):879-87. DOI: 10.1111/j.1440-1681.2011.05601.x

8. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2009;361(21):2066-78. DOI: 10.1056/NEJMra0804647

9. Ardizzone S, Puttini PS, Cassinotti A, et al. Extraintestinal manifestations of inflammatory bowel disease. Dig Liver Dis 2008;40(Suppl 2):S253-9. DOI: 10.1016/S1590-8658(08)60534-4

10. Libby P, Ridker PM, Hansson GK, et al. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol 2009;54(23):2129-38. DOI: 10.1016/j.jacc.2009.09.009

11. Maharshak N, Arbel Y, Bornstein NM, et al. Inflammatory bowel disease is not associated with increased intimal media thickening. Am J Gastroenterol 2007;102(5):1050-5. DOI: 10.1111/j.1572-0241.2007.01086.x

12. Broide E, Schopan A, Zaretsky M, et al. Intima-media thickness of the common carotid artery is not significantly higher in Crohn's disease patients compared to healthy population. Dig Dis Sci 2011;56(1):197-202. DOI: 10.1007/s10620-010-1235-0

13. Kayahan H, Sari I, Cullu N, et al. Evaluation of early atherosclerosis in patients with inflammatory bowel disease. Dig Dis Sci 2012;57(8):2137-43. DOI: 10.1007/s10620-012-2148-x

14. Principi M, Mastrolonardo M, Scicchitano P, et al. Endothelial function and cardiovascular risk in active inflammatory bowel diseases. J Crohns Colitis 2013;7(10):e427-33. DOI: 10.1016/j.crohns.2013.02.001

15. Uysal F, Akbal E, Akbal A, et al. Epicardial adipose tissue is increased in patients with inflammatory bowel disease. J Ultrasound Med 2016;35(9):1859-64. DOI: 10.7863/ultra.14.09040

16. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019;32(1):1-64. DOI: 10.1016/j.echo.2018.06.004

17. Roifman I, Sun YC, Fedwick JP, et al. Evidence of endothelial dysfunction in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2009;7(2):175-82. DOI: 10.1016/j.cgh.2008.10.

18. Singh S, Kullo IJ, Pardi DS, et al. Epidemiology, risk factors and management of cardiovascular diseases in IBD. Nat Rev Gastroenterol Hepatol 2015;12(1):26-35. DOI: 10.1038/nrgastro.2014.202

19. Singh S, Singh H, Loftus EV, et al. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014;12(3):382-93e1:quize22. DOI: 10.1016/j.cgh.2013.08.023

20. Rungoe C, Nyboe Andersen N, Jess T. Inflammatory bowel disease and risk of coronary heart disease. Trends Cardiovasc Med 2015;25(8):699-704. DOI: 10.1016/j.tcm.2015.03.010

21. Libby P. Inflammation in atherosclerosis. Nature 2002;420(6917):868-74. DOI: 10.1038/nature01323

22. Han QF, Wu L, Li T, et al. There is a link between carotid intima media thickness and coronary artery disease: it might be inflammation. Int J Cardiol 2016;203:1144-5. DOI: 10.1016/j.ijcard.2015.10.236

23. Colak Y, Karabay CY, Tuncer I, et al. Relation of epicardial adipose tissue and carotid intima-media thickness in patients with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2012;24(6):613-8. DOI: 10.1097/MEG.0b013e3283513f19

24. Kocaman SA, Durakoglugil ME, Cetin M, et al. The independent relationship of epicardial adipose tissue with carotid intima-media thickness and endothelial functions: the association of pulse wave velocity with the active facilitated arterial conduction concept. Blood Press Monit 2013;18(2):85-93. DOI: 10.1097/MBP.0b013e32835ebbb5

25. Resorlu H, Akbal A, Resorlu M, et al. Epicardial adipose tissue thickness in patients with ankylosing spondylitis. Clin Rheumatol 2015;34(2):295-9. DOI: 10.1007/s10067-014-2568-4

26. Akyildiz ZI, Seremet S, Emren V, et al. Epicardial fat thickness is independently associated with psoriasis. Dermatology 2014;228(1):55-9. DOI: 10.1159/000354726

27. Akdogan RA, Durakoglugil ME, Kocaman SA, et al. Increased pulse wave velocity and carotid intima-media thickness in patients with ulcerative colitis. Dig Dis Sci 2013;58(8):2293-300. DOI: 10.1007/s10620-013-2634-9

28. Papa A, Santoliquido A, Danese S, et al. Increased carotid intima-media thickness in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2005;22(9):839-46. DOI: 10.1111/j.1365-2036.2005.02657.x

29. Theocharidou E, Gossios TD, Griva T, et al. Is there an association between inflammatory bowel diseases and carotid intima-media thickness? Preliminary data. Angiology 2014;65(6):543-50. DOI: 10.1177/0003319713489876

30. Karpouzas GA, Ormseth SR, Hernández E, et al. Biologics may prevent cardiovascular events in rheumatoid arthritis by inhibiting coronary plaque formation and stabilizing high-risk lesions. Arthritis Rheumatol 2020;72(9):1467-75. DOI: 10.1002/art.41293

31. Plein S, Erhayiem B, Fent G, et al. Cardiovascular effects of biological versus conventional synthetic disease-modifying antirheumatic drug therapy in treatment-naïve, early rheumatoid arthritis. Ann Rheum Dis 2020;79(11):1414-22. DOI: 10.1136/annrheumdis-2020-217653