Evaluation of Early Atherosclerosis Markers in Patients with Inflammatory Bowel Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABC 1 Yusuf Üstün
E 1 Serta Kilincalp
AB 1 Şahin Çoban
BC 1 Yusuf Coşkun
C 1 İlhami Yüksel
BD 2 Aydan Ongun
DF 3 İrfan Soykan
F 3 Mehmet Bektaş
DE 3 Murat Törüner
AD 3 Hülya Çetinkaya
AE 3 Necati Örmeci

1 Department of Gastroenterology, Dıskapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey
2 Department of Cardiology, Ankara University, School of Medicine, Ankara, Turkey
3 Department of Gastroenterology, Ankara University, School of Medicine, Ankara, Turkey

Corresponding Author: Yusuf Üstün, e-mail: yusufus@hotmail.com
Source of support: Departmental sources

Background: The aim of this study was to investigate relationships between early atherosclerosis and inflammatory bowel disease (IBD) using laboratory, functional, and morphological markers of atherosclerosis.

Material/Methods: In the present prospective single-center study, 96 patients with IBD (58 patients with ulcerative colitis and 36 patients with Crohn's disease) and 65 healthy control subjects were included. The demographic data of each patient and control subject were recorded. The patients with IBD and healthy controls were compared in terms of the carotid intima-media thickness (CIMT), the values of flow-mediated dilatation (FMD) and nitroglycerine-mediated dilatation (NMD), and the levels of von Willebrand factor antigen (VWF-Ag), D-dimer, and lipoprotein (a).

Results: There were no significant differences between the IBD patients and controls in terms of age, sex, BMI, systolic and diastolic BPs, serum levels of total cholesterol, low-density lipoprotein, or triglycerides. IBD patients had significantly higher levels of VWF-Ag (156.6±58.9 *vs.* 104.2±43.3, *P*<0.001) and D-dimer (337.2±710.8 *vs.* 175.9±110.9, *P*<0.001) as compared to the controls. No significant differences were determined between the 2 groups in terms of FMD and NMD values. Although statistically not significant, the CIMT values were higher in the IBD patients than in the controls (0.517±0.141 mm *vs.* 0.467±0.099 mm, *P*=0.073). In the correlation analysis, the CIMT was found to be correlated negatively with FMD and positively with high sensitive C-reactive protein, VWF-Ag, and D-dimer.

Conclusions: These findings suggest that VWF-Ag and D-dimer can be beneficial early atherosclerosis markers in IBD patients.

MeSH Keywords: Atherosclerosis • Carotid Intima-Media Thickness • Inflammatory Bowel Diseases • Lipoprotein(a) • von Willebrand Factor

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/898160

📄 2700 　 🗄 4 　 📊 — 　 📚 55

Background

Inflammatory bowel disease (IBD) is a group of disorders that are characterized by chronic and autoimmune inflammation and comprises mainly Crohn's disease (CD) and ulcerative colitis (UC). The prevalence and incidence of IBD have increased in time and across different regions of the world and is gradually becoming a global problem [1]. Various studies have demonstrated that chronic inflammatory conditions are associated with atherosclerosis and cardiovascular events [2,3]. In this context, there has been growing interest in the relationship between IBD and atherosclerosis.

Cardiovascular disease (CVD), a major consequence of atherosclerosis, is a leading cause of morbidity and mortality worldwide [4]. The main risk factors for CVD have been reported to include diabetes mellitus, hypercholesterolemia, obesity, high blood pressure (BP), and smoking [4]. However, the presence of atherosclerosis has been demonstrated in individuals without any conventional risk factors, in individuals who died due to non-cardiovascular reasons, and even in young subjects [5]. Therefore, early detection of subclinical atherosclerosis in addition to searching and defining CVD risk factors other than conventional factors has become important. In the detection of subclinical atherosclerosis, there are several invasive and non-invasive methods, including the measurements of carotid intima-media thickness (CIMT; a valid surrogate marker of atherosclerosis), flow-mediated dilatation (FMD; a marker of vascular aging and endothelial-dependent vasodilatation), nitroglycerine-mediated dilatation (NMD; a marker of endothelial-independent vasodilatation), von Willebrand factor antigen (VWF-Ag), lipoprotein (a) (Lp(a)), and D-dimer [6–10].

Although novel markers proposed to reflect subclinical atherosclerosis have been investigated in several studies, the results on the relationship between atherosclerosis and IBD are conflicting [11,12]. The present study aimed to investigate subclinical atherosclerosis in IBD patients using laboratory, functional, and morphological markers.

Material and Methods

Patients and controls

This prospective single-center study included 96 IBD patients (58 patients with UC and 36 patients with CD) and 65 healthy controls. The patients were enrolled consecutively from IBD patients who were admitted to the Gastroenterology Department of Ankara University Faculty of Medicine between March 2007 and October 2009. The healthy controls were selected from the hospital staff and from the patients with normal physical examination findings and laboratory values who were

followed-up in the outpatient clinics of our hospital. The diagnosis of IBD was established based on the clinical, radiological, endoscopic, and histological findings. Subjects who were previously diagnosed with other autoimmune diseases, CVDs, premature atherosclerosis, hypertension, diabetes mellitus, hyperlipidemia, renal failure, chronic lung diseases, liver dysfunction, and thyroid dysfunction and those having thromboembolic events were excluded. Approval of the local Ethics Committee was obtained and the study was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all subjects.

Procedure

The demographic data of each patient and control subject were recorded. The weight and height measurements were performed using an electronic balance and a stadiometer, respectively; the body mass index (BMI) was calculated in units of kg/m^2. The resting BP was measured on the right arm with a random-zero sphygmomanometer; the mean of the second and third measurements was used. During the testing period, all subjects were asked to maintain their regular diet and physical activity level. Lipid profiles, erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hsCRP), D-dimer, VWF-Ag, and Lp(a) levels were measured in all subjects. Active disease was defined using the Mayo score in the patients with UC and using the Crohn's Disease Activity Index (CDAI) in those with CD [13,14]. FMD and NMD of the brachial artery and CIMT measurements were performed.

Brachial flow-mediated dilatation (FMD) and nitroglycerine-mediated dilatation (NMD)

The measurements of brachial FMD and NMD were performed in all participants on their right arms using a high-resolution duplex ultrasound device (Vivid 7; Wipro General Electric Healthcare, General Electric Medical Systems Inc., Chicago, IL, USA) with a 13-MHz linear transducer and an electrocardiogram. A B-mode longitudinal section of the brachial artery was obtained 4–7 cm proximal to the antecubital fossa. To assess FMD, reactive hyperemia was induced by the release of a pneumatic cuff around the forearm after being inflated to 50 mmHg above the systolic BP for 5 min. The mean of 3 consecutive measurements, which were carried out synchronously with the R wave of the heart cycle, was determined as the mean diameter. FMD values are expressed as the percent change (increase or decrease) in the arterial diameter after flow from the resting value.

All assessments were performed by a single trained technician, who was blinded to the clinical characteristics of the participants. The participants were not allowed to drink coffee and tea or to take antioxidant vitamins in the last 12 h before the

Table 1. Characteristics of patients with inflammatory bowel disease and controls.

	IBD (n=96)		Controls (n=65)		P
Age, year	43.7±13.3		41.2±10.7		0.271
Gender					
Male	41	(42.7)	22	(33.8)	0.258
Female	55	(57.3)	43	(66.2)	
BMI, kg/m^2	24.8±4.4		25.6±3.8		0.130
Smokers	10	(10.4)	17	(26.6)	**0.008**
Systolic BP, mmHg	115.6±20.6		118.2±23.3		0.280
Diastolic BP, mmHg	71.1±12.0		68.5±9.7		0.320
Total cholesterol, mg/dL	185.2±48.8		189.6±38.6		0.571
LDL, mg/dL	105.3±36.1		110±27.5		0.414
Triglycerides, mg/dL	133.6±63		131.8±69.2		0.545
ESR, mm/h	31.3±21.9		16.1±9.7		**<0.001**
	25	(2–110)	14	(1–37)	
hsCRP, mg/L	16.1±30.1		2.0±1.7		**<0.001**
	4.3	(0.1–145)	1.4	(0.2–7)	
Disease duration, months	76.9±73.9		–		–
	54	(2–332)			
In remission	57	(60.0)	–		–

Data are presented as mean ± standard deviation, mean ± standard deviation (minimum-maximum), or number (%), where appropriate. IBD – inflammatory bowel diseases; BMI – body mass index; BP – blood pressure; LDL – low density lipoprotein; ESR – erythrocyte sedimentation rate; hsCRP – high sensitivity C-reactive protein.

assessments. No vasoactive drugs were allowed within the 24 h of the assessments. NMD was assessed after sublingual administration of 400 µg nitroglycerine.

Carotid intima-media thickness (CIMT)

Carotid intima-media thickness was determined using a high-resolution duplex ultrasonography device (Philips HD-11, Best, The Netherlands) with a 7-MHz linear transducer. Briefly, longitudinal and transverse section images were obtained from the carotid system. According to the leading edge method, the distance between the first (lumen-intima border) and second (media-adventitia border) echogenic lines was recorded as the CIMT. An average of 10 measurements was performed on both sides and the mean of these 10 measurements was considered as the baseline value.

Statistical analysis

Statistical analyses were performed using the Predictive Analytics Software (PASW) version 18.0 (SPSS Inc., Chicago, USA). Descriptive statistics are expressed as mean, standard deviation, median, and minimum and maximum for numerical variables. Normal distribution of variables was tested using visual (histogram and probability graphics) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. For 2-group comparisons, Student's t-test was used for normally distributed numerical variables and the Mann-Whitney U test was used for non-normally distributed numerical variables. In 2-group comparisons for categorical variables, the chi-square test was performed when chi-square test assumption was met. Spearman's test was used to calculate correlation coefficients and statistical significances for the relations among variables, at least 1 of which was not normally distributed. A p value of <0.05 was considered statistically significant.

Results

The present study included 96 IBD patients (38 patients with CD and 58 patients with UC) and 65 healthy controls. The clinical characteristics of the IBD patients and controls are presented in Table 1.

Table 2. Laboratory, functional, and morphological parameters in patients with inflammatory bowel disease and controls.

	IBD (n=96) Mean ±SD Median (Min-Max)	Controls (n=65) Mean ±SD Median (Min-Max)	P
VWF-Ag	156.6±58.9	104.2±43.3	**<0.001**
	151.2 (35.8–314)	96.4 (28.1–213.8)	
D-dimer, ug/mL	337.2±710.8	175.9±110.9	**<0.001**
	210.9 (56.6–6855.4)	147.8 (32.7–762.7)	
Lipoprotein (a), U/L	0.3±0.3	0.2±0.1	0.776
	0.1 (0.1–1.6)	0.1 (0.1–0.7)	
FMD,%	13.3±7.8	10.5±10.9	0.305
	13.3 (–6.8–35.7)	12.0 (–12.4–28.2)	
NMD,%	13.6±8.2	10.0±13.4	0.201
	13.3 (–5.7–42.9)	12.2 (–23.7–41.6)	
CIMT, mm	0.517±0.141	0.467±0.099	0.073
	0.490 (0.325–1.178)	0.450 (0.285–0.700)	

IBD – inflammatory bowel diseases; SD – standard deviation; Min–Max – Minimum–Maximum; VWF-Ag – von Willebrand factor antigen; FMD – flow-mediated dilatation; NMD – nitroglycerine-mediated dilatation; CIMT – carotid intima-media thickness.

Table 3. Laboratory, functional, and morphological parameters in patients with inflammatory bowel disease and controls.

	IBD patients		P
	In active phase (n=38) Mean ±SD Median (Min–Max)	In remission (n=57) Mean ±SD Median (Min–Max)	
VWF-Ag	175.5±65.2	142.3±50.6	**0.027**
	179.9 (69.5–314)	130.7 (35.8–244.6)	
D-dimer, ug/mL	507±1080.3	215.9±132.8	**0.002**
	286 (70.5–6855.4)	188.3 (56.6–701.4)	
Lipoprotein (a), U/L	0.2±0.1	0.3±0.3	0.229
	0.1 (0.1–0.7)	0.1 (0.1–1.6)	
FMD,%	13.8±8.7	13.0±7.1	0.633
	14.1 (–4.4–35.7)	13.3 (–6.8–33.3)	
NMD,%	12.2±7.8	14.7±8.4	0.153
	12 (–5.7–31.3)	14.5 (–4–42.9)	
CIMT, mm	0.546±0.174	0.500±0.112	0.297
	0.495 (0.345–1.178)	0.490 (0.325–0.835)	

IBD – inflammatory bowel diseases; SD – standard deviation; Min–Max – Minimum–Maximum; VWF-Ag – von Willebrand factor antigen; FMD – flow-mediated dilatation; NMD – nitroglycerine-mediated dilatation; CIMT – carotid intima-media thickness.

There were no significant differences between the IBD patients and controls in terms of age, sex, BMI, systolic and diastolic BPs, serum levels of total cholesterol, low-density lipoprotein, or triglycerides. The proportion of smokers was higher in the control group. The patients with IBD had significantly higher ESR and higher hsCRP level as compared with the controls. The mean duration of disease was 76.9±73.9 months (range, 2–332 months). Based on the CDAI and Mayo scores, 57 (60%) IBD patients were in remission.

Table 4. Correlation of carotid intima-media thickness with other parameters in the patients with inflammatory bowel disease.

		CIMT	FMD	NMD	ESR	hsCRP	VWF-Ag	Lp(a)	D-dimer
FMD	rho	−0.247	–	–	–	–	–	–	–
	P	0.025	–	–	–	–	–	–	–
	N	82	–	–	–	–	–	–	–
NMD	rho	−0.169	0.459	–	–	–	–	–	–
	P	0.134	<0.001	–	–	–	–	–	–
	N	80	81	–	–	–	–	–	–
ESR	rho	0.173	−0.080	−0.119	–	–	–	–	–
	P	0.101	0.473	0.294	–	–	–	–	–
	N	91	82	80	–	–	–	–	–
hsCRP	rho	0.215	−0.114	−0.128	0.485	–	–	–	–
	P	0.041	0.306	0.255	<0.001	–	–	–	–
	N	91	83	81	94	–	–	–	–
VWF Ag	rho	0.225	−0.040	−0.176	0.209	0.270	–	–	–
	P	0.041	0.729	0.128	0.055	0.013	–	–	–
	N	83	76	76	85	85	–	–	–
Lp(a)	rho	−0.127	0.185	0.105	0.045	0.100	0.087	–	–
	P	0.241	0.105	0.368	0.677	0.354	0.442	–	–
	N	87	78	76	87	88	80	–	–
D-dimer	rho	0.221	−0.111	−0.221	0.367	0.379	0.342	0.008	–
	P	0.037	0.323	0.049	<0.001	<0.001	0.001	0.942	–
	N	89	82	80	91	91	84	85	–
Disease duration	rho	0.038	0.118	0.100	0.036	0.012	−0.078	0.066	0.086
	P	0.717	0.287	0.376	0.732	0.909	0.475	0.543	0.416
	N	92	83	81	95	95	86	88	92

CIMT – carotid intima-media thickness; FMD – flow-mediated dilatation; NMD – nitroglycerine-mediated dilatation; ESR – erythrocyte sedimentation rate; hsCRP – high sensitivity C-reactive protein; VWF-Ag – von Willebrand factor antigen; Lp(a) – lipoprotein (a).

The comparisons of laboratory, functional, and morphological parameters, which are the markers of atherosclerosis, between the IBD patients and controls are presented in Table 2. The patients with IBD had significantly higher VWF-Ag and D-dimer levels than the controls. There were no significant differences between the IBD patients and controls in terms of Lp(a) levels and FMD and NMD values. Although statistically not significant, the CIMT values were higher in the IBD patients than in the controls.

The comparisons of laboratory, functional, and morphological parameters between IBD patients in remission and those in active disease are presented in Table 3. The levels of VWF-Ag and D-dimer were significantly higher in IBD patients in active disease than in those in remission. The level of Lp(a) and the values of FMD, NMD, and CIMT did not differ according to the disease activity status.

The correlation of CIMT, which is the main marker of atherosclerosis, with other parameters in IBD patients are presented in Table 4. In the correlation analysis, CIMT was found to be correlated negatively with FMD and positively with hsCRP, VWF-Ag, and D-dimer.

Discussion

Inflammatory bowel disease has been implicated in the development of atherosclerosis over the last decade due to its chronic inflammatory nature [15–17]. Traditional cardiovascular risk factors are not overrepresented in IBD patients compared to in the general population [18]. However, cardiovascular morbidity and mortality and the risk of cardiovascular events are higher in IBD patients [19–24]. This higher risk may be attributable to inflammation-mediated atherosclerosis [18]. It is now well known that inflammation may have an independent role or act synergistically with traditional risk factors in the pathogenesis of atherosclerosis [25]. Atherosclerosis and inflammation have been proposed to share similar pathogenesis, such as CD40-CD40 ligand couple [26]. High levels of inflammatory markers are known to be the predictors of cardiovascular events [27,28]. It has been reported that there is a complex association between inflammatory markers, such as hsCRP and fibrinogen, and CIMT, an early atherosclerosis marker, and that inflammatory markers play a role in the pathogenesis of CVD [29].

In IBD patients, regardless of conventional cardiovascular risk factors, an increase in arterial stiffness has been reported [30]. Arterial stiffness in IBD patients is decreased by immunomodulatory therapy and this emphasizes the role of chronic inflammation in the pathophysiology [31]. In the present study, we investigated the surrogate markers of different aspects of atherosclerosis in a group of IBD patients based on the hypothesis that IBD patients have laboratory, functional, and morphological evidence of subclinical atherosclerosis.

In the present study, no significant differences were found between the IBD patients and controls in terms of BMI, lipid profile, and BP among conventional risk factors. The proportion of smokers was higher in the control group. The subjects with diabetes mellitus were already excluded from the study. Based on these findings, the patient and control groups were comparable in terms of other parameters. The levels of hsCRP and ESR, which are acute-phase reactants and inflammatory markers, were found to be significantly higher in the IBD patients than in the controls, as was expected.

D-dimer and VWF have been reported to be associated with atherosclerosis [32]. It has been suggested that there is a relationship between elevated levels of VWF and enhanced risk of arterial thrombosis, including myocardial infarction and ischemic stroke [33]. Elevated D-dimer levels indicate hypercoagulable state and have a role in atherothrombogenesis. High D-dimer levels have been demonstrated to be associated with coronary artery disease [34]. VWF has also been defined as an important feature of and a good marker for UC. Moreover, it has been reported that it is useful to evaluate VWF together with D-dimer

for distinguishing disease activity in UC patients [35]. In the present study, IBD patients had significantly higher levels of VWF-Ag (156.6±58.9 *vs.* 104.2±43.3, $P<0.001$) and D-dimer (337.2±710.8 *vs.* 175.9±110.9, $P<0.001$) compared with the controls.

Studies have demonstrated that Lp(a) elevation is associated with impairment of endothelial function and increased risk of cardiovascular events [36,37]. In the long-term follow-up of patients undergoing percutaneous coronary intervention, Kardys et al. [38] observed that Lp(a) was associated with a higher 1-year risk of cardiovascular events. In their study, Momiyama et al. [39] reported that elevated Lp(a) levels were associated with aortic and coronary atherosclerosis. In the present study, Lp(a) levels were not significantly different between the IBD patients and controls.

Flow-mediated dilatation is expressed as the capacity of endothelium-dependent relaxation of smooth muscle cells and vasodilatation in case of stimulation of blood vessels by a physical or chemical stimulus [40]. Measurement of FMD is a useful non-invasive method for evaluating endothelial dysfunction and cardiovascular risks [41]. FMD is inversely correlated with the degree of arteriosclerosis [42]. In one of the earliest reports on the relationship between IBD and atherosclerosis, Kocaman et al. [43] evaluated FMD and NMD in patients with mild, moderate, and severe UC and compared their findings with those of healthy subjects. They concluded that endothelial dysfunction was significant in severe and moderate UC patients as compared with mild UC patients and healthy subjects. Kayahan et al. [44] found that FMD and NMD values were significantly impaired in the patients with IBD compared to the healthy subjects; however, CIMT values were not different between the groups. This suggested that functional changes occurred before structural changes in the vessels of IBD patients. In the present study, no significant difference was found between the patients with IBD and controls (13.3±7.8 *vs.* 10.5±10.9, p=0.305) and FMD did not significantly differ according to the disease activity status (13.8±8.7 for IBD patients in active disease and 13.0±7.1 for the patients in remission, p=0.633).

Nitroglycerine-induced vasodilation measures endothelium-independent smooth muscle relaxation (vascular dilatation) induced by administration of nitroglycerine [42]. It was demonstrated that not only FMD but also NMD is impaired in individuals with CVDs, including coronary heart disease, and it can be used as a marker of the progression of atherosclerosis [45,46]. In the present study, no significant difference was found between the IBD patients and controls in terms of NMD (13.6±8.2 *vs.* 10.0±14.4, p=0.201) and NMD did not significantly differ according to the disease activity status (12.2±7.8 for IBD patients in active disease and 14.7±8.4 for the patients in remission, p=0.153).

Carotid intima-media thickness is the most commonly used and the best-validated ultrasonographic measure for the assessment of early atherosclerosis and the degree of arteriosclerosis. CIMT is an indicator of generalized atherosclerosis and a strong predictor of cardiovascular events independently of conventional vascular risk factors [47, 48]. It has been suggested that morphological parameters (CIMT) are more important than functional parameters (NMD and FMD) for the prediction of the extent and severity of coronary artery disease [49]. Therefore, it has been suggested that the measurement of CIMT may be used to identify individuals at high risk for future cardiovascular events among IBD patients. Many studies have examined the relationship between CIMT measurement and IBD. Some studies have reported that the CIMT values of IBD patients are similar to those of controls and that IBD patients are not at an increased risk for accelerated atherosclerosis [50,51]. On the other hand, in the study by Akdoğan et al. [52], UC patients were found to be at increased risk for atherosclerosis and higher CIMT was found to be associated with disease activity and its extensive involvement. In another study, Dagli et al. [15] compared IBD patients and healthy controls in terms of CIMT and carotid arterial stiffness and found that CIMT was significantly higher in the patients with IBD than in the controls (0.74±0.08 mm *vs.* 0.70±0.05 mm). They concluded that IBD was a risk factor for early atherosclerosis. In their study on subclinical atherosclerosis in IBD patients, Papa et al. [53] found the CIMT was significantly higher in the IBD patients than in the controls (0.63±0.15 mm *vs.* 0.53±0.08 mm). Theocharidou et al. [54] reported the CIMT to be significantly higher in patients with IBD than in healthy controls (0.62±0.08 *vs.* 0.52±0.06 mm). As compared with the controls, Aloi et al. [55] demonstrated high CIMT and low FMD values as premature subclinical atherosclerosis markers in pediatric IBD patients. In the present study, there was no statistically

significant difference between the IBD patients and controls in terms of CIMT values (0.517±0.141 mm *vs.* 0.467±0.099 mm, p=0.073); however, the higher CIMT values in the IBD patients compared to the controls was thought to be clinically remarkable. No significant difference was determined between the CIMT values of IBD patients in active disease and in remission (0.546±0.174 mm *vs.* 0.500±0.112, p=0.297). In the correlation analysis, the CIMT was found to be correlated negatively with FMD and positively with hsCRP, VWF-Ag, and D-dimer.

The major limitations of the present study are the data being limited by the single-center study design and the absence of longitudinal follow-up of the patients. On the other hand, having a large number of patients among the studies evaluating the atherosclerotic markers in IBD and simultaneous assessment of vascular and serologic early atherosclerotic markers were the strengths of our study.

Conclusions

Although statistically not significant, the CIMT values were higher in the IBD patients than in the controls. Long-term follow-up of IBD patients may provide clearer evidence on the subject. The significantly higher levels of VWF-Ag and D-dimer in the IBD patients than in the controls and in the patients in active disease than in those in remission, and both parameters being positively correlated with CIMT suggest that VWF-Ag and D-dimer are useful parameters to determine early atherosclerosis in IBD patients.

Conflict-of-interest statement

There are no conflicts of interest.

References:

1. Molodecky NA, Soon IS, Rabi DM et al: Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology, 2012; 142: 46–54

2. Mason JC, Libby P: Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. Eur Heart J, 2015; 36: 482–89c.

3. Amaya-Amaya J, Montoya-Sánchez L, Rojas-Villarraga A: Cardiovascular involvement in autoimmune diseases. Biomed Res Int, 2014; 2014: 367359

4. Levenson JW, Skerrett PJ, Gaziano JM: Reducing the global burden of cardiovascular disease: the role of risk factors. Prev Cardiol, 2002; 5: 188–99

5. Rodríguez-Saldaña J, Rodriguez-Flores M, Cantú-Brito C, Aguirre-Garcia J: A pathological study of the epidemiology of atherosclerosis in Mexico city. Cardiol Res Pract, 2014; 2014: 264205

6. Theilmeier G, Michiels C, Spaepen E et al: Endothelial von Willebrand factor recruits platelets to atherosclerosis-prone sites in response to hypercholesterolemia. Blood, 2002; 99: 4486–93

7. Schreiner PJ, Morrisett JD, Sharrett AR et al: Lipoprotein[a] as a risk factor for preclinical atherosclerosis. Arterioscler Thromb, 1993; 13: 826–33

8. Salomaa V, Stinson V, Kark JD et al: Association of fibrinolytic parameters with early atherosclerosis. The ARIC Study. Atherosclerosis Risk in Communities Study. Circulation, 1995; 91: 284–90

9. Chua SK, Kilung A, Ong TK et al: Carotid intima media thickness and high sensitivity C-reactive protein as markers of cardiovascular risk in a malaysian population. Med J Malaysia, 2014; 69: 166–74

10. Patel S, Celermajer DS: Assessment of vascular disease using arterial flow mediated dilatation. Pharmacol Rep, 2006; 58(Suppl.): 3–7

11. Zanoli L, Inserra G, Castellino P: Increased cardiovascular risk in subjects with a low prevalence of classic cardiovascular risk factors: The inflammatory bowel disease paradox. Trends Cardiovasc Med, 2015; 25: 705–6

12. Rungoe C, Nyboe Andersen N, Jess T: Inflammatory bowel disease and risk of coronary heart disease. Trends Cardiovasc Med, 2015; 25: 699–704

13. Schroeder KW, Tremaine WJ, Ilstrup DM: Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med, 1987; 317: 1625–29

14. 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: 439–44

15. Dagli N, Poyrazoglu OK, Dagli AF et al: Is inflammatory bowel disease a risk factor for early atherosclerosis? Angiology, 2010; 61: 198–204

16. Roifman I, Sun YC, Fedwick JP et al: Evidence of endothelial dysfunction in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol, 2009; 7: 175–82

17. Rachapalli SM: Inflammatory bowel diseases and atherosclerosis: do we need more studies? Inflamm Bowel Dis, 2005; 11: 705

18. Singh S, Kullo IJ, Pardi DS, Loftus EV Jr: Epidemiology, risk factors and management of cardiovascular diseases in IBD. Nat Rev Gastroenterol Hepatol, 2015; 12: 26–35

19. 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: 41–45

20. Ha C, Magowan S, Accortt NA et al: Risk of arterial thrombotic events in inflammatory bowel disease. Am J Gastroenterol, 2009; 104: 1445–51

21. Yarur AJ, Deshpande AR, Pechman DM et al: Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. Am J Gastroenterol, 2011; 106: 741–47

22. Kristensen SL, Ahlehoff O, Lindhardsen J et al: Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death – a Danish nationwide cohort study. PLoS One, 2013; 8: e56944

23. Rungoe C, Basit S, Ranthe MF et al: Risk of ischaemic heart disease in patients with inflammatory bowel disease: A nationwide Danish cohort study. Gut, 2013; 62: 689–94

24. Singh S, Singh H, Loftus EV Jr., Pardi DS: 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: 382–93

25. Libby P: Inflammation in atherosclerosis. Nature, 2002; 420: 868–74

26. Phipps RP: Atherosclerosis: the emerging role of inflammation and the CD40-CD40 ligand system. Proc Natl Acad Sci USA, 2000; 97: 6930–32

27. Pearson TA, Mensah GA, Alexander RW et al: Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation, 2003; 107: 499–511

28. Danesh J, Wheeler JG, Hirschfield GM et al: C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med, 2004; 350: 1387–97

29. Corrado E, Rizzo M, Coppola G et al: An update on the role of markers of inflammation in atherosclerosis. J Atheroscler Thromb, 2010; 17: 1–11

30. Zanoli L, Cannavò M, Rastelli S et al: Arterial stiffness is increased in patients with inflammatory bowel disease. J Hypertens, 2012; 30: 1775–81

31. Zanoli L, Rastelli S, Inserra G et al: Increased arterial stiffness in inflammatory bowel diseases is dependent upon inflammation and reduced by immunomodulatory drugs. Atherosclerosis, 2014; 234: 346–51

32. Azuma RW, Kadowaki T, El-Saed A et al: Associations of D-dimer and von Willebrand factor with atherosclerosis in Japanese and white men. Acta Cardiol, 2010; 65: 449–56

33. van Schie MC, van Loon JE, de Maat MP, Leebeek FW: Genetic determinants of von Willebrand factor levels and activity in relation to the risk of cardiovascular disease: A review. J Thromb Haemost, 2011; 9: 899–908

34. Koenig W, Rothenbacher D, Hoffmeister A et al: Plasma fibrin D-dimer levels and risk of stable coronary artery disease: Results of a large case-control study. Arterioscler Thromb Vasc Biol, 2001; 21: 1701–5

35. Xu G, Tian KL, Liu GP et al: Clinical significance of plasma D-dimer and von Willebrand factor levels in patients with ulcer colitis. World J Gastroenterol, 2002; 8: 575–76

36. Schlaich MP, John S, Langenfeld MR et al: Does lipoprotein(a) impair endothelial function? J Am Coll Cardiol, 1998; 31: 359–65

37. Cai A, Li L, Zhang Y et al: Lipoprotein(a): A promising marker for residual cardiovascular risk assessment. Dis Markers, 2013; 35: 551–59

38. Kardys I, Oemrawsingh RM, Kay IP et al: Lipoprotein(a), interleukin-10, C-reactive protein, and 8-year outcome after percutaneous coronary intervention. Clin Cardiol, 2012; 35: 482–89

39. Momiyama Y, Ohmori R, Fayad ZA et al: Associations between serum lipoprotein(a) levels and the severity of coronary and aortic atherosclerosis. Atherosclerosis, 2012; 222: 241–44

40. Raitakari OT, Celermajer DS: Flow-mediated dilatation. Br J Clin Pharmacol, 2000; 50: 397–404

41. Frolow M, Drozdz A, Kowalewska A et al: Comprehensive assessment of vascular health in patients; towards endothelium-guided therapy. Pharmacol Rep, 2015; 67: 786–92

42. Akamatsu D, Satou A, Watanabe T et al: Smooth muscle dysfunction in patients older than 54 years of age with objective evidence of arteriosclerosis. Eur J Vasc Endovasc Surg, 2007; 34: 639–45

43. Kocaman O, Sahin T, Aygun C et al: Endothelial dysfunction in patients with ulcerative colitis. Inflamm Bowel Dis, 2006; 12: 166–71

44. Kayahan H, Sari I, Cullu N et al: Evaluation of early atherosclerosis in patients with inflammatory bowel disease. Dig Dis Sci, 2012; 57: 2137–43

45. Maruhashi T, Soga J, Fujimura N et al: Nitroglycerine-induced vasodilation for assessment of vascular function: A comparison with flow-mediated vasodilation. Arterioscler Thromb Vasc Biol, 2013; 33: 1401–8

46. Raitakari OT, Seale JP, Celermajer DS: Impaired vascular responses to nitroglycerin in subjects with coronary atherosclerosis. Am J Cardiol, 2001; 87: 217–19

47. Grobbee DE, Bots ML: Carotid artery intima-media thickness as an indicator of generalized atherosclerosis. J Intern Med, 1994; 236: 567–73

48. Eikendal AL, Groenewegen KA, Anderson TJ et al: Common carotid intima-media thickness relates to cardiovascular events in adults aged <45 years. Hypertension, 2015; 65: 707–13

49. Rohani M, Jogestrand T, Källner G et al: Morphological changes rather than flow-mediated dilatation in the brachial artery are better indicators of the extent and severity of coronary artery disease. J Hypertens, 2005; 23: 1397–402

50. 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: 197–202

51. Maharshak N, Arbel Y, Bornstein NM et al: Inflammatory bowel disease is not associated with increased intimal media thickening. Am J Gastroenterol, 2007; 102: 1050–55

52. Akdoğan RA, Durakoğlugil ME, Kocaman SA et al: Increased pulse wave velocity and carotid intima-media thickness in patients with ulcerative colitis. Dig Dis Sci, 2013; 58: 2293–300

53. Papa A, Santoliquido A, Danese S et al: Increased carotid intima-media thickness in patients with inflammatory bowel disease. Aliment Pharmacol Ther, 2005; 22: 839–46

54. 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: 543–50

55. Aloi M, Tromba L, Di Nardo G et al: Premature subclinical atherosclerosis in pediatric inflammatory bowel disease. J Pediatr, 2012; 161: 589–94