Evaluation of Early Atherosclerosis Markers in Patients with Inflammatory Bowel Disease

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

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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/m². 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
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 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/m²           | 24.8±4.6            | 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±63.0          | 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        | –              | –       |
| 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.

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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 2. Laboratory, functional, and morphological parameters in patients with inflammatory bowel disease and controls. |
|--------------------------------------------------|--------------------------------------------------|------------------|
| **IBD (n=96) Mean ±SD** | **Controls (n=65) Mean ±SD** | **P** |
| **Median (Min–Max)** | **Median (Min–Max)** |  |
| VWF-Ag | 156.6±58.9 | 104.2±43.3 | <0.001 |
| D-dimer, ug/mL | 337.2±710.8 | 175.9±110.9 | <0.001 |
| Lipoprotein (a), U/L | 0.3±0.3 | 0.2±0.1 | 0.776 |
| FMD,% | 13.3±7.8 | 10.5±10.9 | 0.305 |
| NMD,% | 13.3±8.2 | 10.0±13.4 | 0.201 |
| CIMT, mm | 0.517±0.141 | 0.467±0.099 | 0.073 |

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

| **IBD patients** | **In active phase (n=38)** | **In remission (n=57)** | **P** |
|------------------|---------------------------|-------------------------|-----|
| **Mean ±SD** | **Median (Min–Max)** | **Mean ±SD** | **Median (Min–Max)** |  |
| VWF-Ag | 175.5±65.2 | 142.3±50.6 | 0.027 |
| D-dimer, ug/mL | 507±1080.3 | 215.9±132.8 | 0.002 |
| Lipoprotein (a), U/L | 0.2±0.1 | 0.3±0.3 | 0.229 |
| FMD,% | 13.8±8.7 | 13.0±7.1 | 0.633 |
| NMD,% | 12.2±7.8 | 14.7±8.4 | 0.153 |
| CIMT, mm | 0.546±0.174 | 0.500±0.112 | 0.297 |

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.
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.

| 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          |
| rho                  | −0.247           | −                 | −                 | −                 | −                 | −                 | −                 | −                 |
| P                    | 0.025            | −                 | −                 | −                 | −                 | −                 | −                 | −                 |
| N                    | 82               | −                 | −                 | −                 | −                 | −                 | −                 | −                 |
| rho                  | −0.169           | 0.459            | −                 | −                 | −                 | −                 | −                 | −                 |
| P                    | 0.134            | <0.001           | −                 | −                 | −                 | −                 | −                 | −                 |
| N                    | 80               | 81               | −                 | −                 | −                 | −                 | −                 | −                 |
| rho                  | 0.173            | −0.080           | −0.119           | −                 | −                 | −                 | −                 | −                 |
| P                    | 0.101            | 0.473            | 0.294            | −                 | −                 | −                 | −                 | −                 |
| N                    | 91               | 82               | 80               | −                 | −                 | −                 | −                 | −                 |
| rho                  | 0.215            | −0.114           | −0.128           | 0.485            | −                 | −                 | −                 | −                 |
| P                    | 0.041            | 0.306            | 0.255            | <0.001           | −                 | −                 | −                 | −                 |
| N                    | 83               | 83               | 81               | 94               | −                 | −                 | −                 | −                 |
| 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               | −                 | −                 | −                 |
| 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               | −                 | −                 |
| 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               | −                 |
| 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).
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 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 vasodilation 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 vasodilatation 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 [30,51]. 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.

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