Evaluation of Endothelial Dysfunction via Flow-Mediated Dilation in Patients with Inflammatory Bowel Disease Referred to Medical Centers in Kerman

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Abstract

Background: By examining flow-mediated dilatation (FMD) as an index for indirect assessment of arterial endothelial function, this study aimed to investigate the relationship between inflammatory bowel disease (IBD) and early atherosclerosis.

Methods: This study was performed on 75 patients with ulcerative colitis, 15 patients with Crohn’s disease, and 75 healthy individuals as the control group. Vascular endothelial function was assessed by FMD and Doppler ultrasonography of the right brachial artery.

Results: The mean FMD in IBD patients (12.04 ± 3.8) was lower than that of the persons in the control group (16.68 ± 2.2). Besides, the mean FMD in Crohn’s patients was 12.02 ± 3.5 and the corresponding value in the patients with ulcerative colitis was 12.07 ± 4.2, showing no significant difference (P = 0.78). There was a significant opposite relationship between age and FMD in the control group, meaning that as age increased, FMD decreased (r = 0.6, P = 0.01). However, there was no association between age and FMD among IBD patients.

Conclusion: Given that this study focused on people without known risk factors for atherosclerosis, the results pointed to endothelial dysfunction in IBD patients, and IBD can be considered an independent factor in the development of atherosclerosis.

Keywords: Flow mediated dilatation, Inflammatory bowel disease, Atherosclerosis

Introduction

Inflammatory bowel disease (IBD), which includes Crohn’s disease (CD) and ulcerative colitis (UC), is a common disorder worldwide, with a prevalence rate of 0.1% to 0.4% among the general population (1). Due to changes in people’s lifestyles and industrialization outcomes, this disease is increasing in Iran like in Western countries (2,3).

The exact cause of IBD is unknown. However, risk factors such as family history, smoking, air pollution, oral contraceptive pills, and diet can all play a role in the development of the disease. Studies conducted in recent decades have shown that intestinal microvascular defects can play a role in IBD development. Structural changes in endothelial function are caused by a network of cytokines and inflammatory growth factors that also signal IBD activity. Besides, small intestinal arteries have been reported to have some degree of endothelial dysfunction, which is due to marked impairment of endothelium-dependent dilatation (due to acetylcholine) and a decrease in NO production by the endothelium (4-10). Patients with IBD show increased inflammatory cytokines (including TNF-α and interleukins 6 and 18) and CRP, which are known to play a role in endothelial dysfunction and atherosclerosis (11-15).

There are also some pieces of evidence indicating that inflammation plays an important role in the pathogenesis of heart disease and atherosclerosis, with IBD being one of the most common systemic inflammatory diseases (16-20). While the prevalence of dyslipidemia, obesity,
and hypertension is not higher in IBD patients, they have a higher risk for cardiovascular diseases (21-23).

In recent decades, some imaging techniques have made the diagnosis of atherosclerosis possible in the early stages. Vascular endothelial dysfunction in the brachial or femoral arteries (accessible arteries) appears to be associated with the coronary arteries (24-27). Therefore, the health of endothelial function in coronary arteries can be reliably predicted by examining the function of vascular endothelium in the brachial artery (28).

The flow-mediated dilatation (FMD) index indicates the percentage of arterial dilation in response to increased blood flow (29). This dilation depends on the function of the endothelium because the endothelium is stimulated in response to increased blood flow in the artery and releases vasodilators such as NO, which cause the artery to dilate and the better the endothelium functions, the higher the percentage of arterial dilation (30).

As has been shown by past studies from countries other than Iran, the FMD values are lower in IBD patients than in the healthy population (31-34). However, we have not found any study in this field in Iran; therefore, we decided to investigate endothelial dysfunction via FMD in patients with IBD in the Iranian population (particularly southeastern Iran) and examine the possible role of genetics and race on FMD.

**Methods**

This cross-sectional study employed a descriptive-analytical design. The study was conducted in Kerman, Iran, and participants consisted of 85 patients with IBD (75 patients with ulcerative colitis and 15 with Crohn’s disease) and 75 healthy individuals (control group).

The participants in the control group were selected from healthy people including students, employees, and nurses of the Afzalipour hospital. The IBD patients were diagnosed based on clinical, endoscopic, and pathologic (mucosal sampling) findings and they were receiving treatment at the time of the study.

Crohn’s disease activity was assessed based on the Crohn’s Disease Activity Index (CDAI) and ulcerative colitis activity based on the Ulcerative Colitis Activity Index as mild, moderate, and severe (35,36). The patients were treated with steroids, 5-aminosaliclyate (5-ASA), azathioprine, and anti-TNF-a based on the severity of the disease.

The exclusion criteria were known risk factors for atherosclerosis and cardiovascular disease such as smoking, diabetes, BMI above 30 (obesity), dyslipidemia (TG>250 and cholesterol above 220), hypertension (systolic pressure greater than 140 mmHg or diastole pressure greater than 90 mm Hg), and having a family history of premature cardiovascular disease. Besides, persons with thromboembolic diseases, cardiovascular or cerebrovascular accidents, and pregnant women were excluded from the study. Given that age is a confounding factor at the onset of atherosclerosis and considering that age over 55 years is a risk factor for atherosclerosis, the study was performed on people aged from 18 to 50 years.

First, before entering the study, informed consent was obtained from all patients. After entering the study, a checklist including required information such as age, duration of the disease, sex, current status of the patient, comorbidities, disease activity, and the medications taken by the IBD patients was completed for all patients. Besides, all participants underwent the right brachial Doppler ultrasound by a radiologist at 10-12 in the morning, and their FMD was measured.

To measure FMD, consuming vasoactive drugs (beta-blockers and calcium channel blockers) was stopped 24 hours before measurement. Patients were fasting and required not to take caffeine for at least 12 hours before the test (37). They rested for 10 minutes in the supine position on the bed. The anterior-posterior diameter of the right brachial artery was measured 5-10 cm above the elbow cavity using a linear probe (5-7 MHz) by Philips Affiniti 50 Ultrasound Machine. The sphygmomanometer cuff was fastened for 5 minutes at a pressure of 250 mm Hg around the forearm (below the arterial scan site) to cause ischemia at the end of the limb. The anterior-posterior diameter of the brachial artery was measured again at 45-60 seconds after emptying the cuff. In response to the ischemia caused by the cuff inflation, the brachial artery dilates as a mechanism to increase blood flow. This dilation is dependent on the function of the endothelial cells lining the artery. A higher percentage of dilation indicates healthier endothelial function, as the endothelium is better able to promote vasodilation in response to the ischemic stimulus. The percentage of FMD was measured using the following formula (31,32).

\[
\text{FMD(%) = \frac{\text{Artery diameter at rest} - \text{Artery diameter at 45 – 50 s after emptying the cuff}}{\text{Artery diameter at rest}} \times 100}
\]

Then, FMD numbers were calculated for each participant and recorded in a special data collection form. The collected data were analyzed using SPSS software version 20 through inferential statistics including Pearson correlation and the Student’s t-test and descriptive statistics including frequency, relative frequency, and central measures of tendency. All statistical procedures were performed at the significance level of 0.05 (P=0.05) (38).

**Results**

The initial sample in this study included more than 172 people, of whom 165 people with complete information were selected as the participants in the study. However, no significant difference was observed between the three groups in terms of gender and age (P > 0.05) (Table 1).

According to clinical criteria, IBD activity was divided.
into three categories: mild, moderate, and severe. The severity and duration of illness are shown in Table 2. There was no significant difference between ulcerative colitis and Crohn’s disease patient groups in terms of the duration of illness and distribution of patients based on disease severity (Table 2). Seventy-three patients in the ulcerative colitis group were in mild condition and two were moderate. In the Crohn’s group, the severity of the disease was mild for all people. Considering that the patients were being treated and were referred from the IBD clinic, the above-said results were expected. Concerning comorbidities, one case of sickle cell anemia, one case of ischemic heart disease, two cases of primary biliary cirrhosis, ten cases with diabetes mellitus and hypertension, and two cases of autoimmune hepatitis were found in the ulcerative colitis group and all were excluded from the study.

There was a significant difference found between the control group and the ulcerative colitis group (P=0.017) and the Crohn’s disease group (P=0.04) in terms of the mean FMD, and the mean FMD was higher in the control group. However, there was no significant difference between ulcerative colitis and Crohn’s disease groups in terms of the mean FMD (P=0.78) (Figure 1).

The results also showed a negative significant relationship between FMD and age in the control group, implying that with increasing age, the FMD value decreased (r = -0.6, P=0.01). However, there was no association between FMD and age in the IBD group (Figure 2).

Furthermore, no association was found between FMD, sex, duration of illness, or medications used in any of the Crohn’s disease and ulcerative colitis groups. Given that the severity of the disease was mild in most of the patients in this study, no correlation was found between the IBD severity and FMD.

Table 1. The characteristics of the participants in the three groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
<th>Gender</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>75</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>15</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Control</td>
<td>75</td>
<td>39</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 2. Descriptive results of duration and severity of illness in the study groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Duration of illness (year)</th>
<th>Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative colitis</td>
<td>6.09 ± 3.34</td>
<td>73</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>6.43 ± 0.5</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Inflammatory bowel disease plays an important role in reducing FMD and endothelial dysfunction (39,40). Measuring FMD is a useful and non-invasive method for assessing endothelial dysfunction. FMD is inversely related to the degree of atherosclerosis. Besides, studies have shown that this method is sensitive and its results are similar to ones obtained via invasive methods (39-41).

The results of the present study indicated that FMD in patients with inflammatory bowel disease was significantly lower than in healthy individuals. Since the individuals without known risk factors for atherosclerosis were examined in this study, it can be suggested that endothelial dysfunction in inflammatory bowel and IBD patients can be considered an independent factor in the development of atherosclerosis.

Principi et al (33) showed that FMD was significantly lower in IBD patients (6.1 ± 3 vs. 8.2 ± 3.2) (P=0.003). Another study by Kayahan (34) showed that the mean FMD in a group of 39 patients was 11.9 ± 6.12, and the corresponding value was 18.7 ± 9.2 among 31 healthy individuals, confirming endothelial dysfunction in IBD patients.

Andreozzi et al (31) examined the association between
FMD and IBD in children and showed that FMD was significantly lower in the patients with IBD than in the healthy group, as was evident in the present study. It was also shown that despite taking drugs and suppressing the disease, the FMD level was still decreasing, indicating the continuation of endothelial inflammation independent of the disease itself (31). Although Andreozzi et al showed that FMD was associated with the duration of the disease, this association was not observed in the present study. This discrepancy may be due to the fact that in the present study, most of the patients were known cases of IBD with active treatment, except for a few patients who have been diagnosed and treated most recently; and it was because of the paucity of new known cases in our center. In Andreozzi’s study, the patients were followed from the beginning of the diagnosis and as a result, the course of the disease and the treatment affected the results (31). However, as shown by Dorta Cibor, endothelial dysfunction has a chronic pathogenicity in IBD patients, so we appreciated the impaired FMD even if they were known cases with active ongoing treatments (42).

Ozturk et al. showed that the FMD rate in patients with IBD was significantly lower than in healthy individuals (32). Besides, the present study showed no significant difference between the two groups of patients (Crohn’s disease and ulcerative colitis).

It seems that systemic inflammation via the proinflammatory cytokines has a pivotal role in endothelial dysfunction in IBD patients (43).

Our study had limitations in terms of the selection of patients; they should have no atherosclerosis risk factors. Also, the non-cooperation of patients was another limitation. Therefore, a larger study by examining patients from the time of diagnosis, following them over several years, and examining the changing trend of FMD is needed.

Conclusion

This study indicated that IBD plays an important role in reducing FMD and endothelial dysfunction. The FMD rate in IBD patients was significantly lower than in healthy individuals, and FMD can be used as a non-invasive screening tool to assess atherosclerosis in IBD patients and to diagnose cardiovascular diseases at an early stage.

Authors’ Contribution

Conceptualization: Bizhan Ahmadi.

Data curation: Ahmad Enhesari, Alireza Raji-Amirhasani, Zahra Heidari.

Formal analysis: Alireza Raji-Amirhasani.

Funding acquisition: Ahmad Enhesari.

Investigation: Zahra Heidari.

Methodology: Bizhan Ahmadi, Ahmad Enhesari.

Project administration: Bizhan Ahmadi, Ahmad Enhesari.

Resources: Zahra Heidari, Motahareh Zaherara.

Software: Alireza Raji-Amirhasani.

Supervision: Bizhan Ahmadi.

Validation: Motahareh Zaherara.

Visualization: Ahmad Enhesari, Bizhan Ahmadi.

Writing-original draft: Zahra Heidari.

Writing-review & editing: Motahareh Zaherara.

Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences with the ethical code IR.KMU. IR.KMU.AH.REC.1398.066.

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References


