Effect of Inflammatory Bowel Disease–Related Characteristics and Treatment Interventions on Cardiovascular Disease Incidence

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Abstract: *Background:* An association between inflammatory bowel disease (IBD) and cardiovascular diseases has been shown in multiple studies. However, little is known about the effect of IBD-related characteristics on cardiovascular events. *Methods:* The authors conducted a retrospective, nested case-control study of IBD patients who presented to the institution from 2000 to 2004, allowing for a 10-year follow-up period. One hundred eleven patients who developed cardiovascular events (cases) and 222 patients who did not develop cardiovascular events (cases) were included in the study after matching for Framingham cardiovascular risk score (2008). Relationships between predictor variables and cardiovascular outcome were assessed by conditional logistic regression. *Results:* The cases and controls were similar in age, gender, smoking and cholesterol level. There was no difference in disease subtype (ulcerative colitis or Crohn's disease). On conditional logistic regression, thiopurine treatment (odds ratio [OR]: 0.42, 95% confidence interval [CI]: 0.19–0.87; $P = 0.02$) was associated with decreased cardiovascular events and tumor necrosis factor alpha antagonist use (OR: 2.63, 95% CI: 1.49–4.63; $P = 0.001$) was associated with increased cardiovascular events. Although not statistically significant, disease-related surgery (OR: 0.57, 95% CI: 0.32–1.02; $P = 0.06$) was associated with decreased cardiovascular events and disease-related hospitalization (OR: 1.58, 95% CI: 0.96–2.57; $P = 0.07$) was associated with increased incidence of cardiovascular disorders. *Conclusions:* The authors observed decreased incidence of cardiovascular diseases in patients with IBD who were treated with thiopurines and increased incidence of cardiovascular outcomes among patients treated with tumor necrosis factor alpha antagonist.

Key Indexing Terms: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Coronary artery disease; Thiopurine; Biological agents. **[Am J Med Sci 2015;350(3):175–180.]**

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder associated with intestinal and extraintestinal manifestations. Cardiovascular disorders have increased incidence among patients suffering from chronic inflammatory diseases.[1] Among IBD patients, studies have been contradictory with some studies showing increased cardiovascular events,[1] whereas others have not shown increased risk.[2] Although the pathogenic link between IBD and cardiovascular disorders is not well known, inflammation is considered to be the general mechanism of pathogenesis in both disorders. In addition, inflammatory markers that are increased in patients with IBD have been associated with cardiovascular diseases[3] and multiple studies have shown IBD patients to be at increased risk of developing cardiovascular events.[1]

Furthermore, vascular alterations are common in IBD patients. Early arterial wall alterations have been observed in IBD patients, marked by increased carotid artery intima-media thickness which is a marker of atherogenesis.[4] Even children with IBD have early endothelial dysfunction based on increased intima-media thickness and reduced flow-mediated dilatation.[5] On the contrary, some studies in the past have not shown increased cardiovascular disease risk among IBD patients.[2,6] Therefore, the current evidence is not sufficient to definitively conclude that IBD patients are at increased risk of developing cardiovascular disorders.[6]

However, increased inflammation among IBD patients has been shown to increase the risk of cardiovascular diseases. A nationwide cohort study from Denmark showed increased risk of cardiovascular death during active IBD.[7] Another retrospective study by Yarur et al[8] showed increased risk of coronary artery disease in IBD patients compared with the general population despite having lower burden of traditional risk factors.

Despite the increasing knowledge that inflammation in IBD is associated with increased risk of cardiovascular diseases, the disease-related characteristics and the effect of anti-inflammatory medications used in IBD on cardiovascular disease incidence are poorly understood. Furthermore, most studies so far have focused on acute coronary events rather than the long-term evolution of cardiovascular diseases in IBD.

The aim of the present study was to explore the effect of disease-related characteristics, including disease activity, severity and treatment, on cardiovascular disease incidence among IBD patients over a 10-year follow-up period.

METHODS

This study was approved by the Henry Ford Hospital Institutional Review Board.

Subject Identification and Data Collection

The authors used Henry Ford Hospital medical record databases that contain medical and demographic information for patients evaluated at Henry Ford Health System. These databases were used to identify patients who presented with IBD from January 1, 2000, to December 31, 2004, to allow for a 10-year follow-up period. *International Classification of Diseases, Ninth Revision*, codes 555.x and 556.x were used to identify patients with IBD.

Cases and Controls

The inclusion criteria included the following: (1) age at presentation between 30 and 74 years, (2) histological evidence of IBD and (3) follow-up data available for greater than 5 years.

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Exclusion criterion was medical history of cardiovascular or cerebrovascular disease. Records for a cohort of 2,525 IBD cases who had been evaluated in the IBD clinic at Henry Ford Hospital from 2000 to 2004 were reviewed. A total of 1,188 patients were excluded because they did not meet the inclusion criteria or had history of cardiovascular or cerebrovascular disease. One thousand three hundred thirty-seven patients met the study criteria. There were 111 patients who subsequently developed cardiovascular diseases.

Framingham risk score (2008) was used to measure the baseline general cardiovascular disease risk for all patients included in the study. Patients between the age of 30 and 74 years were selected because the Framingham risk score (2008) applies to this age group. The Framingham risk score (2008) is a validated risk score that is used to calculate the risk of developing general cardiovascular disorders over a period of 10 years.[9] The score is based on age, gender, smoking status, total cholesterol level, high-density lipoprotein (HDL) level and systolic blood pressure.

A total of 111 cases with cardiovascular disorders were identified and matched for Framingham risk score with 2 controls for each case. Cases were defined as patients who developed incidental cardiovascular diseases, including coronary artery disease, heart failure, stroke or peripheral artery disease on objective testing. Some patients developed multiple cardiovascular conditions. Cases were identified by reviewing medical records for objective evidence of cardiovascular disease (ejection fraction less than 40% on echocardiography, computed tomography scan head or magnetic resonance imaging brain with evidence of stroke, carotid artery Doppler ultrasound with atherosclerotic narrowing, ankle-brachial index suggestive of peripheral artery disease, computed tomography angiography with coronary calcification, fixed wall motion abnormality on echocardiography, cardiac stress test suggestive of coronary artery disease). Controls were chosen from IBD patients in the cohort who did not develop cardiovascular diseases. Physician notes from the hospital and from outside health-care facilities were also reviewed when available for history of cardiovascular disease. None of the control patients had any history of cardiovascular disorders. Cases and controls were propensity matched for Framingham risk score (2008) by "nearest neighbor method."

Variables and Outcomes

Information regarding age at presentation, gender and race (white, black or other) was extracted. Lifetime history of smoking more than 1 pack year or current smoker was recorded. Colonoscopy results on extent of anatomical disease involvement were also collected. Histopathology results for intestinal tissue obtained during colonoscopy were reviewed for active inflammation during the follow-up period. The total cholesterol and HDL and low-density lipoprotein levels were collected during the initial clinic visit. Patient records were reviewed for blood pressure at initial presentation. All the recorded blood pressures, glycated hemoglobin levels and cholesterol levels during the follow-up period were also reviewed for the development of diabetes, hypertension and/or hyperlipidemia during the follow-up period. These data were used to calculate the Framingham risk score (2008) for cardiovascular risk prediction.

Disease characteristic was divided as follows: ulcerative colitis (UC) patients were divided into panulcerative colitis and non-panulcerative colitis. Crohn's disease (CD) patients were divided into inflammatory disease or fistulizing/stricturing disease. Age at onset of disease was also abstracted. Colonoscopy reports were reviewed for histological evidence of active inflammation during the follow-up period, and data regarding need for disease-related hospitalization were also reviewed from medical records for identifying patients with active inflammation during the follow-up period. Peak erythrocyte sedimentation rate (ESR) was also abstracted as a marker of inflammation.

Data regarding the use of IBD-related medications, including 5-aminosalicylates, corticosteroids, thiopurines (6-mercaptopurine and azathioprine) and antitumor necrosis factor agents (infliximab, adalimumab and certolizumab pegol), were collected. Only medications used before the development of cardiovascular events were included.

The primary outcome of this study was a composite of cardiovascular events, including coronary artery disease, heart failure, peripheral vascular disease and stroke. Composite outcomes are often used in studies with cardiovascular endpoint.

Statistical Analyses

R software, version 3.0.1, for all statistical analyses was used. Continuous variables were summarized using medians and interquartile range (IQR), and categorical variables were expressed as proportions. Categorical variables were analyzed using the χ^2 test and fisher's exact test, and continuous variables were analyzed using t test or Wilcoxon signed rank test for parametric and nonparametric data, respectively. Framingham risk score was used as a continuous variable. Cases and controls were matched for the Framingham risk score (2008) using the nearest neighbor method.

Variables with a P value less than 0.1 on univariate conditional logistic regression analysis were included in the multivariate conditional logistic regression model.

Secondary analysis comparing patients who developed hard cardiovascular endpoints (myocardial infarction, stroke and heart failure) with the control population was also conducted. Predictor variables were identified using univariate logistic regression. Variables with P value less than 0.1 in the univariate model were included in the multivariate logistic regression model.

The effect was expressed as odds ratio (OR) with 95% confidence interval (CI), along with P values.

RESULTS

The median age for the cases was 56 years (IQR, 47.5–64.5), and the median age of the controls was 54 years (IQR, 46–62). Data involving 3,410 patient years were reviewed for final analysis. The cases consisted of 64.86% Caucasian and 53.15% were men. The controls consisted of 58.5% Caucasians and 46.85% were men. The mean systolic blood pressures on initial presentation were 133.1 mm Hg for cases and 134 mm Hg for controls. The median Framingham risk score for general cardiovascular disease risk (2008) for cases was 14.54 (IQR, 6.66–24.58) and for controls was 13.41 (IQR, 6.62–20.44). The median follow-up period for cases was 9.53 years (IQR, 9.19–10.22). The median follow-up for controls was 9.82 years (IQR, 8.9–12.19) (Table 1). Of the cohort, 111 patients developed cardiovascular events. There were 67 cases of coronary artery disease, 23 cases of stroke, 25 cases of heart failure and 31 cases of peripheral vascular disease. Some patients had multiple cardiovascular events.

Cases and controls were matched for Framingham risk score (2008) for cardiovascular risk. Matching was done using the nearest neighbor method. There was no difference in the median Framingham score between the cases and controls (14.54 versus 13.41, $P = 0.27$).

The median age at IBD diagnosis for cases was 45 years (IQR, 32.5–53.5) and for controls was 44 years (IQR, 31.25–52).