



Steroid Exposure, Acute Coronary Syndrome, and Inflammatory Bowel Disease: Insights into the Inflammatory Milieu

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ABSTRACT

BACKGROUND: Steroids are anti-inflammatory agents commonly used to treat inflammatory bowel disease. Inflammation plays a critical role in the pathophysiology of both inflammatory bowel disease and acute coronary syndrome. We examined the relationship between steroid use in patients with inflammatory bowel disease and acute coronary syndrome.

METHODS: In 177 patients with inflammatory bowel disease (mean age 67 years, 75% male, 44% Crohn's disease, 56% ulcerative colitis), we performed a 1:2 case-control study matched for age, sex, and inflammatory bowel disease type, and compared 59 patients with inflammatory bowel disease with acute coronary syndrome to 118 patients with inflammatory bowel disease without acute coronary syndrome. Steroid use was defined as current or prior exposure. Acute coronary syndrome was defined as myocardial infarction or unstable angina, confirmed by cardiac biomarkers and coronary angiography.

RESULTS: In patients with inflammatory bowel disease, 34% with acute coronary syndrome had exposure to steroids, vs 58% without acute coronary syndrome ($P < .01$). Steroid exposure reduced the adjusted odds of acute coronary syndrome by 82% (odds ratio [OR] 0.39; 95% confidence interval [CI], 0.20-0.74; adjusted OR 0.18; 95% CI, 0.06-0.51) in patients with inflammatory bowel disease, 77% in Crohn's disease (OR 0.36; 95% CI, 0.14-0.92; adjusted OR 0.23; 95% CI, 0.06-0.98), and 78% in ulcerative colitis (OR 0.41; 95% CI, 0.16-1.04; adjusted OR 0.22; 95% CI, 0.06-0.90). There was no association between other inflammatory bowel disease medications and acute coronary syndrome.

CONCLUSIONS: In patients with inflammatory bowel disease, steroid use significantly reduces the odds of acute coronary syndrome. These findings provide further mechanistic insight into the inflammatory processes involved in inflammatory bowel disease and acute coronary syndrome.

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KEYWORDS: Acute coronary syndrome; Crohn's disease; Inflammatory bowel disease; Ulcerative colitis; Steroids

Inflammation plays a critical role in the pathophysiology of inflammatory bowel disease, including Crohn's disease and ulcerative colitis, as well as coronary artery disease.^{1,2} The

pathogenesis of inflammatory bowel disease involves a cascade of dysfunctional immune-mediated processes in genetically predisposed individuals. Inflammation is

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involved in all stages of coronary atherosclerosis and acute coronary syndromes, from initiation and progression to eventual plaque rupture and thrombosis.¹ There is some evidence in the literature that supports a shared interaction between these 2 different diseases, with patients with inflammatory bowel disease, regardless of inflammatory bowel disease type, having a higher incidence of coronary artery disease compared with patients without inflammatory bowel disease.³⁻⁵

Steroids are anti-inflammatory agents, which are commonly used for the treatment of acute inflammatory bowel disease flares. Other medications for inflammatory bowel disease include biological agents such as infliximab and immunomodifiers such as azathioprine, 6-mercaptopurines, and methotrexate.⁶ Steroids are able to modulate the immune response via interactions with glucocorticoid receptors in the cell nucleus, leading to the inhibition of signaling and subsequent expression of inflammatory adhesion molecules.⁷ Although there is a relationship between inflammatory bowel disease and coronary artery disease regarding inflammation, there is controversy regarding the impact of steroids in patients with inflammatory bowel disease and the development of subsequent cardiovascular events.⁸⁻¹⁰ Furthermore, current inflammatory bowel disease management guidelines do not include any specific recommendations for primary prevention of coronary artery disease.⁶

Therefore, this case control study aims to: 1) investigate the relationship between steroid use in patients with inflammatory bowel disease and the development of acute coronary syndrome; and 2) examine the relationship between inflammatory bowel disease medications other than steroids and the development of acute coronary syndrome.

METHODS

Study Population

In this case-control study, patients with inflammatory bowel disease were identified using the Research Patient Data Registry (Partners HealthCare, Boston, MA), a centralized clinical data registry with medical information from Partners HealthCare. **Figure 1** summarizes the study schema and inclusion/exclusion of patients. Patients were initially screened for a diagnosis of inflammatory bowel disease (Crohn's disease or ulcerative colitis) and a first presentation of acute coronary syndrome (acute myocardial infarction or unstable angina) who also underwent

coronary angiography between January 2005 and July 2011. We determined if it was a first presentation of acute coronary syndrome by confirming in the patients' medical record from the Partners HealthCare network, which included all available clinical notes, electrocardiograms, noninvasive imaging studies, coronary angiography, and cardiothoracic surgical reports, to ensure that there was no previous documentation of acute coronary syndrome. For the inflammatory bowel disease diagnosis, both newly diagnosed and long-standing cases were included. Of the 430 patients screened, 59 patients with both inflammatory bowel disease and acute coronary syndrome were selected as "cases." A separate Research Patient Data Registry search was then conducted to identify "controls" with a diagnosis of inflammatory bowel disease but no previous history of coronary artery disease. Two control patients were matched to each case on the basis of age (± 3 years), sex, and inflammatory bowel disease type. The local Institutional Review Board approved the study protocol.

CLINICAL SIGNIFICANCE

- Acute coronary syndrome, an ominous sequelae of coronary artery disease, and inflammatory bowel disease may be precipitated by a heightened inflammatory state.
- Steroid exposure is associated with a reduction in acute coronary syndrome in patients with inflammatory bowel disease.
- Our findings support the inflammatory hypothesis in the atherosclerosis cascade and suggest that reducing inflammatory burden in patients with inflammatory bowel disease may reduce future incidence of acute coronary syndrome.

Definition of Inflammatory Bowel Disease

The diagnosis of inflammatory bowel disease, either Crohn's disease or ulcerative colitis, was established by a physician, as documented in the electronic medical records, and was confirmed using clinical, histological, endoscopic, or imaging studies. Such studies included colonoscopies, sigmoidoscopies, or gastrointestinal biopsies.

Definition of Steroid Use

The primary predictor of interest in this study was steroid use, which was determined by review of the medical record. We classified steroid use into the following 3 categories: current (taking steroids at the time of acute coronary syndrome for cases and at the corresponding time point for controls); former (use of steroids during any time before acute coronary syndrome for cases or corresponding time point for controls); and never (no steroids taken at any time or no mention of steroid use in the medical record before acute coronary syndrome for cases or at the corresponding time point for controls). Steroid use was indicated primarily for the treatment of acute inflammatory bowel disease flares. However, other reasons for steroid use such as allergic reactions and asthma also were included. Steroid use included oral prednisone and intravenous methylprednisolone, budesonide, or

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